Vitamin D supplementation for prevention of mortality in adults (Review)

Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 8

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[Intervention Review]

Vitamin D supplementation for prevention of mortality in adults

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Editorial group: Cochrane Metabolic and Endocrine Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 8, 2011.
Review content assessed as up-to-date: 30 January 2011.

Citation: Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD007470. DOI: 10.1002/14651858.CD007470.pub2.

ABSTRACT

Background

The available evidence on vitamin D and mortality is inconclusive.

Objectives

To assess the beneficial and harmful effects of vitamin D for prevention of mortality in adults.

Search strategy

We searched *The Cochrane Library*, MEDLINE, EMBASE, LILACS, the Science Citation Index Expanded, and Conference Proceedings Citation Index-Science (to January 2011). We scanned bibliographies of relevant publications and asked experts and pharmaceutical companies for additional trials.

Selection criteria

We included randomised trials that compared vitamin D at any dose, duration, and route of administration versus placebo or no intervention. Vitamin D could have been administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)) or an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol) or 1,25-dihydroxyvitamin D (calcitriol)).

Data collection and analysis

Six authors extracted data independently. Random-effects and fixed-effect model meta-analyses were conducted. For dichotomous outcomes, we calculated the risk ratios (RR). To account for trials with zero events, meta-analyses of dichotomous data were repeated using risk differences (RD) and empirical continuity corrections. Risk of bias was considered in order to minimise risk of systematic errors. Trial sequential analyses were conducted to minimise the risk of random errors.

Main results

Fifty randomised trials with 94,148 participants provided data for the mortality analyses. Most trials included elderly women (older than 70 years). Vitamin D was administered for a median of two years. More than one half of the trials had a low risk of bias. Overall, vitamin D decreased mortality (RR 0.97, 95% confidence interval (CI) 0.94 to 1.00, I^2 = 0%). When the different forms of vitamin D were assessed separately, only vitamin D_3 decreased mortality significantly (RR 0.94, 95% CI 0.91 to 0.98, I^2 = 0%; 74,789 participants, 32 trials) whereas vitamin D_2, alfacalcidol, or calcitriol did not. Trial sequential analysis supported our finding regarding vitamin D_3, corresponding to 161 individuals treated to prevent one additional death. Vitamin D_3 combined with calcium increased the risk of nephrolithiasis (RR 1.17, 95% CI 1.02 to 1.34, I^2 = 0%). Alfacalcidol and calcitriol increased the risk of hypercalcaemia (RR 3.18, 95% CI 1.17 to 8.68, I^2 = 17%). Data on health-related quality of life and health economics were inconclusive.

Authors' conclusions

Vitamin D in the form of vitamin D_3 seems to decrease mortality in predominantly elderly women who are mainly in institutions and dependent care. Vitamin D_2, alfacalcidol, and calcitriol had no statistically significant effect on mortality. Vitamin D_3 combined with calcium significantly increased nephrolithiasis. Both alfacalcidol and calcitriol significantly increased hypercalcaemia.

PLAIN LANGUAGE SUMMARY

Vitamin D supplementation for prevention of mortality in adults

Numerous observational studies and randomised trials have observed that optimal vitamin D status has a positive effect on our health and may reduce cancers and cardiovascular diseases. However, a number of systematic reviews and meta-analyses on vitamin D for prevention of mortality have reported variable results.

This systematic review analysed the influence of different forms of vitamin D on mortality. In the 50 trials that provided data for our analyses a total of 94,148 participants were randomly assigned to either vitamin D or no treatment or a placebo. All trials came from high-income countries. The mean age of participants was 74 years. The mean proportion of women was 79%. The median duration of vitamin D administration was two years. Our analyses suggested that vitamin D_3 reduces mortality by about 6%, which corresponds to 200 participants that need to be treated over a median of two years to save one additional life. Another supplemental form of vitamin D, vitamin D_2 (ergocalciferol), as well as the active forms of vitamin D (alfacalcidol and calcitriol) had no significant effect on mortality. We also found evidence of adverse effects including renal stone formation (seen for vitamin D_3 combined with calcium) and elevated blood levels of calcium (seen for both alfacalcidol and calcitriol). In conclusion, we found evidence that vitamin D_3 decreases mortality in predominantly elderly women who are mainly in institutions and dependent care.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Vitamin D supplementation for prevention of mortality in adults

Patient or population: adults
Settings: any
Intervention: Vitamin D
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no intervention	Vitamin D				
All-cause mortality in trials using vitamin D3 (cholecalciferol)	Study population		RR 0.94 (0.91 to 0.98)	74789 (32 studies)	⊕⊕⊕⊕ high	
	104 per 1000	98 per 1000 (95 to 102)				
	Moderate risk					
	46 per 1000	43 per 1000 (42 to 45)				
Cardiovascular mortality	Study population		RR 1.01 (0.91 to 1.13)	42589 (10 studies)	⊕⊕⊕⊕ high	
	29 per 1000	29 per 1000 (26 to 32)				
	Moderate risk					
	13 per 1000	13 per 1000 (12 to 15)				

Cancer mortality	**Study population**		**RR 0.89** (0.78 to 1.02)	39200 (3 studies)	⊕⊕⊕⊕ **high**	
	23 per 1000	**21 per 1000** (18 to 24)				
	Moderate risk					
	21 per 1000	**19 per 1000** (16 to 21)				
Adverse events - Nephrolithiasis in trials using vitamin D3 combined with calcium	**Study population**		**RR 1.17** (1.02 to 1.34)	42876 (4 studies)	⊕⊕⊕⊕ **high**	
	18 per 1000	**21 per 1000** (18 to 24)				
	Moderate risk					
	9 per 1000	**11 per 1000** (9 to 12)				
Adverse events - Hypercalciuria	**Study population**		**RR 4.64** (0.99 to 21.76)	695 (3 studies)	⊕⊕◯◯ **low**[1]	
	3 per 1000	**13 per 1000** (3 to 61)				
	Moderate risk					
	0 per 1000	**0 per 1000** (0 to 0)				
Health-related quality of life	See comment	See comment	Not estimable	-	See comment	Insufficient information as only one included study reported on health-related quality of life.

Health economics	See comment	See comment	Not estimable	-	See comment	Insufficient information as only one included study reported on health economics.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable harm. Additionally, total number of events is rather low.

BACKGROUND

Description of the condition

Vitamin D is synthesised in the skin as vitamin D_3 (cholecalciferol) or obtained from dietary sources or supplements as vitamin D_3 or vitamin D_2 (ergocalciferol). Vitamins D_3 and D_2 are metabolised in the liver to a 25-hydroxyvitamin D and in the kidneys to the biologically active 1,25-dihydroxyvitamin D (calcitriol), which functions as a steroid-like hormone (Horst 2005; Lips 2006). The effects of vitamin D are mediated by its binding to vitamin D receptors (Wesley Pike 2005). The renal production of 1,25-dihydroxyvitamin D is regulated by parathyroid hormone levels and serum calcium and phosphorus levels.

Under conditions of hypocalcaemia, the synthesis of the biologically active form of vitamin D (1,25-dihydroxyvitamin D or calcitriol) is stimulated. This in turn stimulates the transport of calcium out of the intestine, kidneys, and bones into the blood (Lips 2006). Therefore, homeostasis of vitamin D and calcium levels is essential for bone health (Holick 2007a; Horst 2005; Lips 2006). Current interest in vitamin D has been provoked by the discovery that most cells and tissues in our body contain vitamin D receptors (Holick 2006). In the last decades, a number of observational studies have suggested that vitamin D is effective for prevention of malignant, cardiovascular, autoimmune, and infectious diseases (Holick 2007a; Nnoaham 2008; Rosen 2011; Souberbielle 2010).

Vitamin D status

Vitamin D status is determined by the measurement of the serum 25-hydroxyvitamin D level, which is a functional indicator of vitamin D status (Bischoff-Ferrar 2009c; Dawson-Hughes 2005; Lips 2004). The Institute of Medicine recently recommended a target serum 25-hydroxyvitamin D level of 20 ng/ml (50 nmol/L) (IOM 2011). The worldwide prevalence of suboptimal vitamin D status is estimated to be high (Holick 2007a; Mithal 2009). The major causes of vitamin D deficiency are insufficient exposure to sunlight, decreased dietary intake, skin pigmentation, obesity, and advanced age (Lips 2006). Vitamin D deficiency in adults precipitates or exacerbates osteopenia and osteoporosis, and induces osteomalacia (Holick 2007a). Vitamin D insufficiency is linked to increased risk of malignant, cardiovascular, autoimmune, and infectious diseases (Holick 2007a; Rosen 2011; Souberbielle 2010). An opposing hypothesis that vitamin D insufficiency is a consequence of disease but not the cause has been postulated by Marshall et al (Marshall 2008).

How the intervention might work

Vitamin D supplementation (vitamin D_3 (cholecalciferol), vitamin D_2 (ergocalciferol), 1α-hydroxyvitamin D (alfacalcidol), or 1,25-dihydroxyvitamin D (calcitriol)) prevents osteoporosis, osteomalacia, and fractures (Holick 2007a; Lamberg-Allardt 2006). It has been speculated that vitamin D may have benefits beyond the skeletal system (Davis 2007). The evidence on whether vitamin D may prevent cancer, cardiovascular diseases, and mortality is contradictory (Davis 2007; Giovannucci 2005; Michos 2008; Pittas 2010; Wang 2010; Zittermann 2006).

Adverse effects of the intervention

Excessive vitamin D intake for a prolonged period of time may lead to vitamin D toxicity. The evidence that ingestion of high quantities of vitamin D is harmful is sparse. Most trials reported hypercalcaemia, hypercalciuria, or nephrocalcinosis when vitamin D was administered to patients with renal failure (Cranney 2007). Excessive exposure to sunlight does not lead to vitamin D intoxication (Holick 2007b).

Why it is important to do this review

The available evidence on vitamin D and mortality is intriguing but inconclusive. Most observational studies have associated increased vitamin D intake with decreased risk of cancer (Garland 2007; Gorham 2007; Schwartz 2007) while the results of recently completed randomised clinical trials are contradictory (Lappe 2007; Wactawski-Wende 2006). A number of systematic reviews or meta-analyses found beneficial effects, in vitamin deficient elderly persons, of vitamin D supplementation as monotherapy or in combination with calcium for the prevention of osteoporosis (Richy 2005; Tang 2007), fractures, and falls (Bischoff-Ferrar 2005; Bischoff-Ferrar 2009a; Jackson 2007; Latham 2003b). Vitamin D supplementation revealed positive effects in maintaining glucose homeostasis (Pittas 2007a) and the prevention of tuberculosis (Nnoaham 2008). However, Izaks et al (Izaks 2007) and Boonen et al (Boonen 2006) found no significant effects of vitamin D supplementation in the general population. A meta-analysis by Autier and Gandini (Autier 2007) of 18 randomised clinical trials found significantly lower mortality in vitamin D supplemented participants. A Cochrane systematic review of 16 randomised trials on the prevention of fractures found only a non-significant tendency to reduce mortality (Avenell 2009). Results of a number of new randomised trials testing the influence of vitamin D supplementation on mortality have recently become available.

OBJECTIVES

To assess the beneficial and harmful effects of vitamin D supplementation for prevention of mortality in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials, irrespective of blinding, publication status, or language, that assessed supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)) or an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol) or 1,25-dihydroxyvitamin D (calcitriol)). We included primary prevention trials (defined as trials that deal with prevention of disease before it occurs) and secondary prevention trials (defined as trials that deal with prevention of recurrences or exacerbations of a disease that already has been diagnosed) (Starfield 2008).

Types of participants

We included adult participants (aged 18 years or over) who were:

- healthy or were recruited from the general population (primary prevention);
- diagnosed with a specific disease and were in a stable phase (secondary prevention);
- diagnosed with vitamin D deficiency (secondary prevention).

We excluded trials that included:

- patients with secondary induced osteoporosis (e.g., glucocorticoid-induced osteoporosis, thyroidectomy, primary hyperparathyroidism, chronic kidney disease, liver cirrhosis, Crohn's disease, and gastrointestinal by-pass surgery);
- pregnant or lactating women (as they usually are in need of vitamin D);
- patients with cancer.

Types of interventions

Intervention

Vitamin D at any dose, for any duration, and by any route of administration. Vitamin D could have been administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)) or an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol) or 1,25-dihydroxyvitamin D (calcitriol)). Vitamin D could have been administered:

- as monotherapy; or
- in combination with calcium.

Control

Identical placebo or no intervention. Calcium in the control group was allowed if used equally in the vitamin D group(s) of the trial.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Adverse events

Depending on the availability of data, we attempted to classify adverse events as serious or non-serious. Serious adverse events were defined as any untoward medical occurrence that was life threatening; resulted in death, or persistent or significant disability; or any medical event which might have jeopardised the patient, or required intervention to prevent it (ICH-GCP 1997). All other adverse events (that is, any medical occurrence not necessarily having a causal relationship with the treatment but did, however, cause a dose reduction or discontinuation of the treatment) were considered as non-serious.

Secondary outcomes

- Cancer-related mortality
- Cardiovascular mortality
- Fracture-related mortality
- Other causes of mortality
- Health-related quality of life
- Health economics

Covariates, effect modifiers, and confounders

We noted and recorded any possible covariates, effect modifiers, and confounders (dosage and form of vitamin D, dosing schedule, duration of supplementation, duration of follow-up, mean age, risk of bias, calcium co-administration, other medications, compliance, attrition).

Timing of outcome measurement

We did not apply any restrictions regarding the length of intervention or length of follow-up. We calculated outcomes at the end of the follow-up period.

Search methods for identification of studies

Electronic searches

We used the following sources for the identification of trials:

- *The Cochrane Library* (Issue 1, January 2011);
- MEDLINE (until January 2011);
- EMBASE (until January 2011);
- LILACS (until January 2011);
- Science Citation Index Expanded (until January 2011);
- Conference Proceedings Citation Index-Science (until January 2011).

We also searched databases of ongoing trials: Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials).

The described search strategy was used for MEDLINE. We slightly adapted this strategy for searches of EMBASE, *The Cochrane Library*, and the other databases (see Appendix 1 for a detailed search strategy).

Searching other resources

We identified additional trials by searching the reference lists of included trials and systematic reviews, meta-analyses, and health technology assessment reports. We also contacted experts and the main manufacturers of vitamin D to ask for unpublished randomised trials.

Data collection and analysis

Selection of studies

One author (GB) performed the electronic searches. Six authors (GB, LLG, DN, KW, RGS, MB) participated in the manual searches, identified trials eligible for inclusion from the search results, and extracted data from included trials. GB listed the excluded studies with the reason for exclusion. When a discrepancy occurred in the trial selection or data extraction, CG was consulted in order to reach consensus. We contacted authors of the trials for missing information. Interrater agreement for trial selection was measured using the kappa statistic (Cohen 1960). Agreement between authors was very good (kappa statistic 0.85). An adapted PRISMA flow diagram of study selection is included in the review (Moher 2009).

Data extraction and management

For studies that fulfilled the inclusion criteria, six authors (GB, LLG, DN, KW, RGS, MB) independently extracted the relevant population, intervention characteristics, and risk of bias components using standard data extraction templates. We looked out for duplicate publications. Disagreements were resolved by discussion or, when required, by CG.

Assessment of risk of bias in included studies

Due to the risk of overestimation of beneficial intervention effects in randomised trials with unclear or inadequate methodological quality (Kjaergard 2001; Moher 1998; Schulz 1995; Wood 2008), we assessed the influence of the risk of bias on our results. We used the following domains: allocation sequence generation, allocation concealment, blinding, complete outcome data reporting, selective outcome reporting, and other apparent biases (Higgins 2008). The following definitions were used:

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer generated random numbers or a random number table, or similar.
- Uncertain risk of bias: the trial was described as randomised but the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients, were inadequate and were excluded for the assessment of benefits but not for harms.

Allocation concealment

- Low risk of bias: allocation was controlled by a central and independent randomisation unit; sequentially numbered, opaque and sealed envelopes; or similar so that intervention allocations could not have been foreseen, i.e., in advance of or during enrolment.
- Uncertain risk of bias: the trial was described as randomised but the method used to conceal the allocation was not described so that intervention allocations may have been foreseen, i.e., in advance of or during enrolment.
- High risk of bias: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised studies were excluded for the assessment of benefits but not for harms.

Blinding

- Low risk of bias: the trial was described as blinded, the parties that were blinded and the method of blinding were described, so that knowledge of allocation was adequately prevented during the trial.
- Uncertain risk of bias: the trial was described as blind but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
- High risk of bias: the trial was not blinded, so that the allocation was known during the trial.

Incomplete outcome data

- Low risk of bias: the numbers and reasons for dropouts and withdrawals in all intervention groups were described, or it was specified that there were no dropouts or withdrawals.
- Uncertain risk of bias: the report gave the impression that there had been no dropouts or withdrawals but this was not specifically stated.
- High risk of bias: the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting

- Low risk of bias: pre-defined, or clinically relevant and reasonably expected outcomes were reported on.
- Uncertain risk of bias: not all pre-defined or clinically relevant and reasonably expected outcomes were reported on, or were not reported on fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on, and data on these outcomes were likely to have been recorded.

Other bias

- Low risk of bias: the trial appeared to be free of other components that could put it at risk of bias.
- Uncertain risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias, e.g., for-profit involvement, authors have conducted trials on the same topic, etc.

Trials with adequate assessments in all of the above mentioned bias risks domains were considered as having low risk of bias.

Dealing with missing data

We tried to obtain relevant missing data from authors of the included trials. We performed an evaluation of important numerical data such as screened, eligible, and randomised participants as well as intention-to-treat (ITT) and per protocol (PP) populations. We investigated attrition (that is, dropouts, losses to follow-up, and withdrawals).

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary trial, we tried to maximise the yield of information by simultaneous evaluation of all available data. Where there were doubts, the publication that reported the longest follow-up (usually the most recent version) obtained priority.

Assessment of heterogeneity

We identified heterogeneity by visual inspection of the forest plots by using a standard χ^2-test and a significance level of $\alpha = 0.1$. In view of the low power of such tests, we also examined heterogeneity with the I^2 statistic (Higgins 2002), where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity was found, we attempted to determine potential reasons for it by examining individual trial characteristics and subgroups of the main body of evidence.

Assessment of reporting biases

Funnel plots were used to assess the potential existence of bias (Lau 2006). There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect, with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We performed adjusted rank correlation (Begg 1994) and a regression asymmetry test for detection of bias (Egger 1997).

Data synthesis

We performed this review and meta-analyses according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).
For the statistical analyses we used Review Manager 5 (RevMan 2008), Trial Sequential Analysis version 0.8 (TSA 2008), STATA 8.2 (STATA Corp, College Station, Tex), and Sigma Stat 3.0 (SPSS Inc, Chicago, Ill). For dichotomous outcomes, we calculated the Mantel-Haenszel risk ratios (RR) (Gluud 2008). For all association measures, 95% confidence intervals (CI) were used. We analysed the data with both fixed-effect (DeMets 1987) and random-effects (DerSimonian 1986) model meta-analyses. In case there was no difference in statistical significance between the results obtained with the two models, we presented the results of the random-effects model analyses. Otherwise, we presented the results of both analyses.
The analyses were performed using the ITT principle, including all randomised participants irrespective of completeness of data. Patients with missing data were included in the analyses using a carry forward of the last observed response. Accordingly, patients who had been lost to follow-up were counted as being alive.
Review Manager 5.0 (RevMan 2008) does not include trials with zero events in both arms when calculating RR. To account for trials with zero events, meta-analyses of dichotomous data were repeated using risk differences (RD) (Friedrich 2007; Keus 2009). The influence of trials with zero events in the treatment, control, or both groups was also assessed by re-calculating the random-effects model meta-analyses with 0.5 and 0.01 continuity corrections (Bradburn 2007; Sweeting 2004) using Trial Sequential Analysis version 0.8 (TSA 2008).
For trials using a factorial design that tested vitamin D parallel to any other intervention (that is, hormone replacement therapy, other vitamins, etc), we used 'inside the table' analysis in which we compared only the vitamin D intervention group with the placebo or no intervention group. Otherwise, we used 'at margins' analysis (McAlister 2003). In the trials with parallel group design with more than two intervention groups and additional therapy, we compared the vitamin D only group with the placebo or no intervention group.
We included in the analyses individually randomised trials as well as cluster-randomised trials. The data of cluster-randomised trials were incorporated using the generic inverse variance method. We

explored the association between intervention effects of vitamin D and subgrouping of individually randomised and cluster-randomised trials. The influence of cluster-randomised trials on our results was also explored in sensitivity analyses, either including or excluding them.
We compared the intervention effects in subgroups of trials with the test of interaction in the fixed-effect model meta-analysis (Altman 2003).

Trial sequential analyses

We conducted trial sequential analyses to reduce the risk of random error and prevent premature statements of superiority of the experimental or control intervention (Wetterslev 2008). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009). We assumed an event proportion of 10% of deaths in the vitamin D group (Autier 2007) and an anticipated intervention effect of 5% relative risk reduction.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses mainly if one of the primary outcome measures demonstrated statistically significant differences between the intervention groups.
We performed the following subgroup analyses:

- trials with a low risk of bias compared to trials with a high risk of bias;
- placebo-controlled trials compared to trials with no intervention in the control group;
- individually randomised trials compared to cluster-randomised trials;
- primary prevention trials compared to secondary prevention trials;
- vitamin D_3 compared to placebo or no intervention;
- trials that applied vitamin D_3 singly compared to trials that applied vitamin D_3 combined with calcium;
- trials that applied low-dose vitamin D_3 compared to trials that applied high-dose vitamin D_3;
- trials that applied vitamin D_3 daily compared to trials that applied vitamin D_3 intermittently;
- trials that applied vitamin D_3 in vitamin D sufficient participants compared to trials that applied vitamin D_3 in vitamin D insufficient participants;
- vitamin D_2 compared to placebo or no intervention;
- trials that applied vitamin D_2 singly compared to trials that applied vitamin D_2 combined with calcium;
- trials that applied low-dose vitamin D_2 compared to trials that applied high-dose vitamin D_2;
- trials that applied vitamin D_2 daily compared to trials that applied vitamin D_2 intermittently;
- trials that applied vitamin D_2 in vitamin D sufficient participants compared to trials that applied vitamin D_2 in vitamin D insufficient participants;
- alfacalcidol compared to placebo or no intervention;
- trials that applied alfacalcidol in vitamin D sufficient participants compared to trials that applied alfacalcidol in vitamin D insufficient participants;
- calcitriol compared to placebo or no intervention;
- trials that applied calcitriol in vitamin D sufficient participants compared to trials that applied calcitriol in vitamin D insufficient participants.

Sensitivity analysis

We performed the following sensitivity analyses in order to explore the influence of these factors on the intervention effect size:

- repeating the analysis excluding cluster-randomised trials;
- repeating the analysis including trials with zero mortality in both arms;
- repeating the analyses taking attrition bias into consideration.

RESULTS

Description of studies

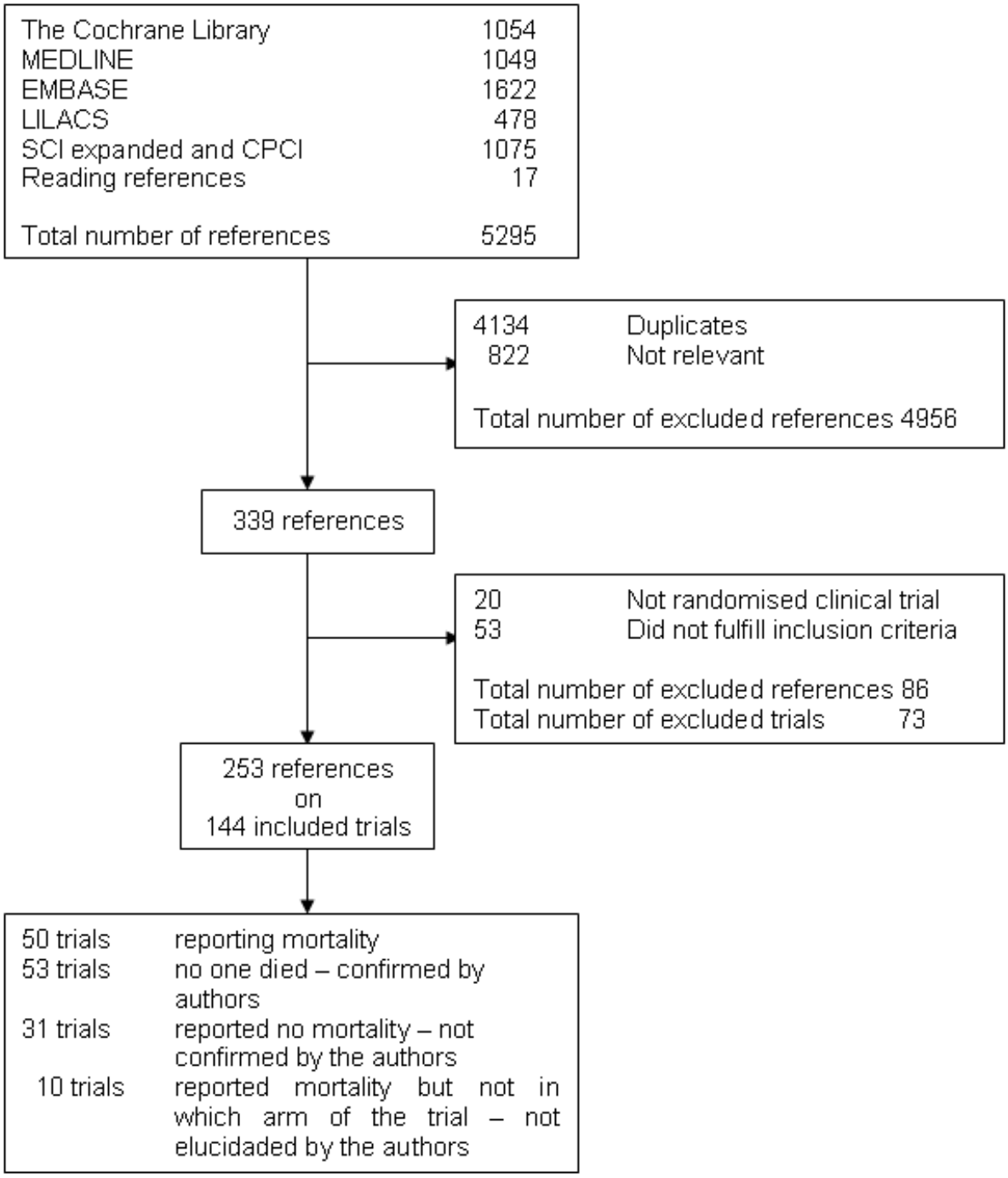
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

We identified a total of 5295 references of possible interest through searching *The Cochrane Library* (n = 1054), MEDLINE (n = 1049), EMBASE (n = 1622), LILACS (n = 478), Science Citation Index Expanded (n = 1061), Conference Proceedings Citation Index-Science (n = 14), and reference lists (n = 17). We excluded 4134 duplicates and 822 clearly irrelevant references through reading the abstracts. Accordingly, 339 references were retrieved for further assessment. Of these, we excluded 86 references describing 73 studies because they were not randomised trials or did not fulfil our inclusion criteria. Reasons for exclusion are listed in the table Characteristics of excluded studies.
In total, 144 randomised trials described in 254 references fulfilled our inclusion criteria (Figure 1). They included a total of 108,496 participants. In total, 84 trials reported no deaths. All participants of five trials completed the follow-up period. We contacted the authors of the remaining 79 trials and the authors of 48 trials confirmed that mortality was indeed zero. For 31 trials we did not

obtain such confirmation. In 10 trials there were deaths reported ($n \simeq 50$), but the authors did not report in which group of the trial. The authors of these trials did not respond to our requests for additional information (Cashman 2009; Chapuy 1987; Doetsch 2004; Fedirko 2010; Gallagher 1989; Janssen 2010; Keane 1998; Moreira-Pfrimer 2009; Orwoll 1990; Peacock 2000).

Figure 1. PRISMA flow diagram of identification of randomised trials for inclusion



In total 50 trials described in 139 references, with 94,148 participants, were able to provide data for our analyses of mortality (1). A further 53 trials with zero mortality in both the experimental and the control groups were included in our sensitivity analyses.
We contacted 127 authors for the missing information and received answer from authors of 87 trials (68%).
We identified an additional 20 ongoing trials through searching databases of ongoing trials. Data from these trials will be included in future updates of this review.

Included studies

The included trials are described in detail in the table Characteristics of included studies, in Table 1, Table 2, Table 3, and Appendix 2.

Table 1. Characteristics of included trials (1)

Trial	Design	Arms	Bias risk	Blinding	Participants [n]	Women [%]	Mean age [years]
Aloia 2005	Parallel	2	Low	PL	208	100	60
Avenell 2004	2x2	4	High	NI	134	83	77
Baeksgaard 1998	Parallel	3	High	PL	240	100	62.5
Bischoff 2003	Parallel	2	High	PL	122	100	85.3
Bjorkman 2007	Parallel	3	Low	PL	218	82	84.5
Bolton-Smith 2007	2x2	4	Low	PL	244	100	68
Brazier 2005	Parallel	2	High	PL	192	100	74.6
Broe 2007	Parallel	5	Low	PL	124	73	89
Burleigh 2007	Parallel	2	Low	PL	205	59	83
Campbell 2005	2x2	4	High	NI	391	68	83.6
Chapuy 1992	Parallel	2	High	PL	3270	100	84
Chapuy 2002	Parallel	3	High	PL	610	100	85
Chel 2008	Parallel	6	High	PL	338	77	84

Table 1. Characteristics of included trials (1) (*Continued*)

Cooper 2003	Parallel	2	Low	PL	187	100	56
Corless 1985	Parallel	2	High	PL	65	78	82.4
Daly 2008	Parallel	2	High	NI	167	0	61.9
Dawson-Hughes 1997	Parallel	2	Low	PL	389	55	71
Dukas 2004	Parallel	2	Low	PL	378	51	71
Flicker 2005	Parallel	2	Low	PL	625	95	83.4
Gallagher 2001	2x2	4	Low	PL	489	100	71.5
Grady 1991	Parallel	2	High	PL	98	54	79.1
Grant 2005	2x2	4	Low	PL	5292	85	77
Harwood 2004	Parallel	4	High	NI	150	100	81.2
Jackson 2006	Parallel	2	Low	PL	36282	100	62.4
Komulainen 1999	2x2	4	Low	PL	464	100	52.7
Krieg 1999	Parallel	2	High	NI	248	100	84.5
Kärkkäinen 2010	Parallel	2	High	NI	3139	100	67
Lappe 2007	Parallel	3	High	PL	1179	100	66.7
Larsen 2004	2x2	4	High	NI	9605	60	75
Latham 2003	2x2	4	Low	PL	243	53	79.5
Law 2006	Parallel	2	High	NI	3717	76	85
Lips 1996	Parallel	2	Low	PL	2578	74	80
Lips 2010	Parallel	2	Low	PL	226	n/a	78
Lyons 2007	Parallel	2	Low	PL	3440	76	84
Meier 2004	Parallel	2	High	NI	55	65	56.5

Table 1. Characteristics of included trials (1) (*Continued*)

Mochonis 2006	Parallel	3	High	NI	112	100	60.3
Ooms 1995	Parallel	2	Low	PL	348	100	80.3
Ott 1989	Parallel	2	High	PL	86	100	67.5
Porthouse 2005	Parallel	2	High	NI	3314	100	76.8
Prince 2008	Parallel	2	Low	PL	302	100	77.2
Sanders 2010	Parallel	2	Low	PL	2258	100	76.0
Sato 1997	Parallel	2	High	PL	64	45	68.5
Sato 1999a	Parallel	2	High	PL	86	78	70.6
Sato 1999b	Parallel	3	High	NI	103	56	70.7
Sato 2005a	Parallel	2	Low	PL	96	100	74.1
Schleithoff 2006	Parallel	2	Low	PL	123	17	51
Smith 2007	Parallel	2	Low	PL	9440	54	79.1
Trivedi 2003	Parallel	2	Low	PL	2686	24	74.7
Witham 2010	Parallel	2	Low	PL	105	34	79.7
Zhu 2008	Parallel	3	Low	PL	120	100	75

NI: no intervention; PL: placebo

Table 2. Characteristics of included trials (2)

Trial	Participants	Outcome Measures	Country	Sponsor
Aloia 2005	Black postmenopausal African American women	Bone mineral density	United States	No
Avenell 2004	Elderly people with an osteoporotic fracture within the last 10 years	Recruitment, compliance, and retention within a randomised trial	United Kingdom	Yes

Table 2. Characteristics of included trials (2) (*Continued*)

Baeksgaard 1998	Postmenopausal women	Bone mineral density	Denmark	Yes
Bischoff 2003	Elderly women living in institutional care	Falls	Switzerland	Yes
Bjorkman 2007	Chronically bedridden patients	Parathyroid function and bone mineral density	Finland	Yes
Bolton-Smith 2007	Elderly nonosteoporotic women	Bone mineral density	United Kingdom	Yes
Brazier 2005	Elderly vitamin D insufficient women	Bone mineral density	France	Yes
Broe 2007	Nursing home residents	Falls	United States	Yes
Burleigh 2007	Older geriatric inpatients	Falls	United Kingdom	Yes
Campbell 2005	Elderly people with visual impairment	Fractures	New Zealand	No
Chapuy 1992	Healthy ambulatory women	Fractures	France	Yes
Chapuy 2002	Older people living in institutional care	Bone mineral density	France	Yes
Chel 2008	Nursing home residents	Vitamin D status	Netherlands	Yes
Cooper 2003	Postmenopausal women	Bone mineral density	Australia	Yes
Corless 1985	Elderly patients from the geriatric wards	Abilities to carry out basic activities of daily life	United Kingdom	Yes
Daly 2008	Healthy ambulatory men	Bone mineral density	Australia	Yes
Dawson-Hughes 1997	Healthy, ambulatory participants	Bone mineral density	United States	Yes
Dukas 2004	Elderly people	Falls	Switzerland	Yes
Flicker 2005	Older people living in institutional care	Falls and fractures	Australia	No
Gallagher 2001	Elderly women	Bone mineral density	United States	No
Grady 1991	Elderly people	Muscle strength	United States	Yes

Table 2. Characteristics of included trials (2) (*Continued*)

Grant 2005	Elderly people with low-trauma, osteoporotic fracture in the previous 10 years	Fractures	United Kingdom	Yes
Harwood 2004	Elderly women following surgery for hip fracture	Bone mineral density, falls and fractures	United Kingdom	Yes
Jackson 2006	Postmenopausal women	Fractures	United States	Yes
Komulainen 1999	Postmenopausal women	Bone mineral density	Finland	Yes
Krieg 1999	Elderly institutionalised women	Bone mineral density	Switzerland	Yes
Kärkkäinen 2010	Postmenopausal women	Falls	Finland	Yes
Lappe 2007	Healthy postmenopausal white women	Fractures	United States	Yes
Larsen 2004	Older community-dwelling residents	Fractures	Denmark	Yes
Latham 2003	Frail elderly people	Self-rated physical health and falls	New Zealand	No
Law 2006	Nursing home residents	Falls and fractures	United Kingdom	No
Lips 1996	Elderly people	Fractures	Netherlands	Yes
Lips 2010	Elderly people with vitamin D insufficiency	Postural stability, muscle strength, and safety	Netherlands	No
Lyons 2007	Older people living in institutional care	Fractures	United Kingdom	No
Meier 2004	Healthy volunteers	Bone mineral density	Germany	No
Mochonis 2006	Postmenopausal women	Bone mineral density	Greece	Yes
Ooms 1995	Elderly people	Bone mineral density	Netherlands	Yes
Ott 1989	Postmenopausal women	Bone mass	United States	Yes
Porthouse 2005	Elderly women with one or more risk factors for hip fracture	Fractures	United Kingdom	Yes

Table 2. Characteristics of included trials (2) (*Continued*)

Prince 2008	Elderly women with a history of falling and vitamin D insufficiency	Falls	Australia	Yes
Sanders 2010	Elderly women at high risk of fracture	Falls and fractures	Australia	Yes
Sato 1997	Outpatients with hemiplegia after stroke	Bone mineral density and fractures	Japan	No
Sato 1999a	Elderly patients with Parkinson's disease	Fractures	Japan	No
Sato 1999b	Outpatients with hemiplegia after stroke	Bone mineral density	Japan	Yes
Sato 2005a	Hospitalised elderly women with post stroke hemiplegia	Falls	Japan	No
Schleithoff 2006	Patients with congestive heart failure	Mortality	Germany	Yes
Smith 2007	Elderly people	Fractures	United Kingdom	No
Trivedi 2003	Elderly people	Mortality, fractures	United Kingdom	No
Witham 2010	Patients with systolic heart failure	Exercise capacity	United Kingdom	No
Zhu 2008	Elderly women	Bone mineral density	Australia	No

Table 3. Characteristics of included trials (3)

Trial	**D_3 [IU]**	**D_2 [IU]**	**1α(OH) D [µg]**	**1,25(OH) $_2$D [µg]**	**Ca [mg]**	**Regimen**	**Route**	**Treatment [years]**	**Follow-up [years]**
Aloia 2005	800 2000				1200 1500*	daily	orally	3	3
Avenell 2004	800				1000**	daily	orally	1	1
Baeksgaard 1998	560				1000	daily	orally	2	2

Table 3. Characteristics of included trials (3) (*Continued*)

Bischoff 2003	800				1200*	daily	orally	0.25	0.25
Bjorkman 2007	400 1200				500*	daily	orally	0.5	0.5
Bolton-Smith 2007	400				1000	daily	orally	2	2
Brazier 2005	800				1000	daily	orally	1	1
Broe 2007		200 400 600 800				daily	orally	0.42	0.42
Burleigh 2007	800				1200*	daily	orally	0.08	0.08
Campbell 2005	50,000 100,000					monthly	orally	1	1
Chapuy 1992	800				1200	daily	orally	1.5	4
Chapuy 2002	800				1200	daily	orally	2	2
Chel 2008	600 4200 18.000				800 1600	daily weekly monthly	orally	0.33	0.33
Cooper 2003		10,000			1000*	weekly	orally	2	2
Corless 1985		9000				daily	orally	0.75	0.75
Daly 2008	800				1000	daily	orally	2	3.5
Dawson-Hughes 1997	700				500	daily	orally	3	3
Dukas 2004			1			daily	orally	0.75	0.75

Table 3. Characteristics of included trials (3) (*Continued*)

Flicker 2005		1000 10,000			600*	daily weekly	orally	2	2
Gallagher 2001				0.5		daily	orally	3	5
Grady 1991				0.5		daily	orally	0.5	0.5
Grant 2005	800				500**	daily	orally	3.75	3.75
Harwood 2004	800	300,000			1000	single dose daily	im orally	1	1
Jackson 2006	400				1000	daily	orally	7	7
Komu-lainen 1999	300				500	daily	orally	5	5
Krieg 1999	880				1000	daily	orally	2	2
Kärkkäinen 2010	800				1000	daily	orally	3	3
Lappe 2007	1000				1400 1500**	daily	orally	4	4
Larsen 2004	400				1000	daily	orally	3.5	3.5
Latham 2003	300,000					single dose	orally	0.003	0.5
Law 2006		100,000				four-monthly	orally	0.83	0.83
Lips 1996	400					daily	orally	3.5	3.5
Lips 2010	8400				500*	weekly	orally	0.31	0.31
Lyons 2007		100,000				four-monthly	orally	3	3
Meier 2004	500				500	daily	orally	0.5	1

Table 3. Characteristics of included trials (3) (*Continued*)

Mochonis 2006	300				1200**	daily	orally	1	1
Ooms 1995	400					daily	orally	2	2
Ott 1989				0.5 2	1000*	daily	orally	2	2
Porthouse 2005	800				1000	daily	orally	2	2
Prince 2008		1000			1000*	daily	orally	1	1
Sanders 2010	500,000					yearly	orally	2.96	2.96
Sato 1997			1		300*	daily	orally	0.5	0.5
Sato 1999a			1			daily	orally	1.5	1.5
Sato 1999b			1			daily	orally	1	1
Sato 2005a		1000				daily	orally	2	2
Schleithoff 2006	2000				500*	daily	orally	0.75	1.25
Smith 2007		300,000				yearly	im	3	3
Trivedi 2003	100,000					four-monthly	orally	5	5
Witham 2010	100,000					10-weekly	orally	0.38	0.38
Zhu 2008		1000			1200**	daily	orally	5	5

* Equal dose of calcium was administered to a control group

** Calcium was tested singly in one arm of the trial as well as combined with vitamin D. Placebo or no intervention group of the trial was not supplemented with calcium.

1α(OH)D: alfacalcidol; 1,25$(OH)_2$D: calcitriol; im: intramuscular injection; IU: international units; µg: microgram

Trial characteristics

Out of the 50 trials reporting mortality, 48 trials randomised participants individually, and two were cluster-randomised (Larsen 2004; Law 2006). Forty-two trials used a parallel-group design, and eight trials (Avenell 2004; Bolton-Smith 2007; Campbell 2005; Gallagher 2001; Grant 2005; Komulainen 1999; Larsen 2004; Latham 2003) used the 2 x 2 factorial design (Pocock 2004). The trials were published from 1980 to 2010.

In 34 trials (68%), the vitamin D was provided free of charge from pharmaceutical companies. In the rest of the trials, funding was not reported.

The trials were conducted in Europe (n = 30), North America (n = 8), Oceania (n = 8), and Asia (n = 4). All 50 trials came from high-income countries.

The 53 trials reporting no mortality included a total of 10,292 participants. These trials were mostly phase I or phase II short-term clinical trials assessing the pharmacokinetic or pharmacodynamic properties of vitamin D. These trials had typical outcome measures that are non-validated potential surrogates for participant-relevant outcomes (Gluud 2006).

Participants

A total of 94,148 participants were randomly assigned in the 50 trials reporting mortality (Table 4). The number of participants in each trial ranged from 55 to 36,282 (median 243). The mean age of participants was 74 years (range 18 to 103 years). The mean proportion of women was 79% (Table 1).

Table 4. Overview of study populations

study ID	intervention	[n] screened	[n] randomised	[n] safety	[n] ITT	[n] finishing study
Aloia 2005	Intervention 1 (I1): vitamin D3 (800 IU) plus calcium (1200 to 1500 mg) daily; Control 1 (C1): matched placebo plus calcium (1200 to 1500 mg daily).	322	208	I1: 17 C1: 11 Total: 28	I1:104 C1: 104 Total: 208	I1: 74 C1:74 Total: 148
Avenell 2004	Intervention 1 (I1): vitamin D_3 (800 IU) daily; Intervention 2 (I2): calcium (1000 mg) daily; Intervention 3 (I3): vitamin D_3 (800 IU) plus calcium (1000 mg) daily; Control 1 (C1): no tablets.	180	I1: 35 I2: 29 I3: 35 C1: 35 Total: 134	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a	I1: 35 I2: 29 I3: 35 C1: 35 Total: 134	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a
Baeksgaard 1998	Intervention 1 (I1): vitamin D3 (560 IU) plus calcium (1000 mg) daily;	n/a	I1: 80 I2: 80 C1: 80 Total: 240	I1: 15 I2: 10 C1: 16 Total: 41	I1: 80 I2: 80 C1: 80 Total: 240	I1: 65 I2: 70 C1: 64 Total: 199

Table 4. Overview of study populations (*Continued*)

	Intervention 2 (I2): vitamin D3 (560 IU) plus calcium (1000 mg) plus multivitamin containing retinol 800 μg; thiamine 1.4 mg; riboflavine 1.6 mg; pyridoxine 2 mg; cyanocobalamin 1 μg; folic acid 100 μg; niacine 18 mg; patothenic acid 6 mg; biotin 150 μg; ascorbic acid 60 mg; D-alpha tocopherol 10 mg; and phylloquinone 70 μg; daily; Control 1 (C1): matched placebo tablets daily.					
Bischoff 2003	Intervention 1 (I1): vitamin D_3 (800 IU) plus calcium 1200 mg daily; Control 1 (C1) : calcium 1200 mg daily.	130	I1: 62 C1: 60 Total: 122	I1: 2 C1: 0 Total: 2	I1: 62 C1: 60 Total: 122	I1: n/a C1: n/a Total: 89
Bjorkman 2007	Intervention 1 (I1): vitamin D3 (1200 IU) plus calcium (500 mg) daily; Intervention 2 (I2): vitamin D3 (400 IU) plus calcium (500 mg) daily; Control 1 (C1) : calcium (500 mg) daily.	1215	I1: 73 I2: 77 C1: 68 Total: 218	I1: 1 I2: 0 C1: 0 Total: 1	I1: 73 I2: 77 C1: 68 Total: 218	I1: 63 I2: 60 C1: 59 Total: 182

Table 4. Overview of study populations (*Continued*)

Bolton-Smith 2007	Intervention 1 (I1): vitamin D_3 (400 IU) plus calcium 1000 mg daily; Intervention 2 (I2): vitamin D_3 (400 IU) plus calcium 1000 mg plus vitamin K_1 200 μg daily; Intervention 3 (I3): vitamin K_1 200 μg daily; Control (C1): matched placebo daily;	n/a	I1: 62 I2: 61 I3: 60 C1: 61 Total: 218	I1: n/a I2: n/a I3: n/a C1: n/a Total: n/a	I1: 62 I2: 61 I3: 60 C1: 61 Total: 218	I1: 50 I2: 49 I3: 54 C1: 56 Total: 209
Brazier 2005	Intervention 1 (I1): vitamin D_3 (800 IU) plus calcium (1000 mg) daily; Control 1 (C1): matched placebo tablets daily.	360	I1: 95 C1: 97 Total: 192	I1: 15 C1: 17 Total: 32	I1: 95 C1: 97 Total: 192	I1: 74 C1: 68 Total: 192
Broe 2007	Intervention 1 (I1): vitamin D_2 (800 IU) daily; Intervention 2 (I2): vitamin D_2 (600 IU) daily; Intervention 3: vitamin D_2 (400 IU) daily; Intervention 4: vitamin D_2 (200 IU) daily; Control 1 (C1): matched placebo tablet.	126	I1: 23 I2: 25 I3: 25 I4: 26 C1: 25 Total: 124	I1: 1 I2: 1 I3: 0 I4: 1 C1: 0 Total: 3	I1: 23 I2: 25 I3: 25 I4: 26 C1: 25 Total: 124	I1: 22 I2: 23 I3: 23 I4: 23 C1: 23 Total: 114
Burleigh 2007	Intervention 1 (I1): vitamin D_3 (800 IU) plus calcium (1200 mg) daily;	515	I1: 101 C1: 104 Total: 205	I1: 2 C1: 2 Total: 4	I1: 101 C1: 104 Total: 205	I1: 98 C1: 101 Total: 199

Table 4. Overview of study populations (*Continued*)

	Control 1 (C1) : calcium (1200 mg) daily.					
Campbell 2005	Intervention 1 (I1): home safety assessment and modification programme delivered by an occupational therapist (n = 100); Intervention 2 (I2): an exercise programme prescribed at home by a physiotherapist plus vitamin D_3 100,000 IU initially and then 50,000 IU monthly (n = 97) ; Intervention 3 (I3) : both interventions (intervention 1 plus intervention 2) (n = 98); Control 1 (C1): social visits (n = 96)	391	I1: 100 I2: 97 I3: 98 C1: 96	I1: n/a I2: n/a I3: n/a C1: n/a	I1: 100 I2: 97 I3: 98 C1: 96	I1: 97 I2: 90 I3: 87 C1: 87 Total: 361
Chapuy 1992	Intervention 1 (I1): vitamin D_3 (800 IU) plus calcium (1200 mg) daily; Control 1 (C1) : double placebo daily.	n/a	I1: 1634 C1: 1636 Total: 3270	I1: 40 C1: 28 Total: 3270	I1: 1634 C1: 1636 Total: 3270	I1: 1590 C1: 1573 Total: 3163
Chapuy 2002	Intervention 1 (I1): vitamin D_3 (800 IU) plus calcium (1200 mg) (fixed combination)	639	I1: 199 I2: 194 C1: 190 Total: 583	I1: I2: C1: Total:	I1: 199 I2: 194 C1: 190 Total: 583	I1: n/a I2: n/a C1: n/a Total: n/a

Table 4. Overview of study populations (*Continued*)

	daily; Intervention 2 (I2): vitamin D_3 (800 IU) plus calcium (1200 mg), (separate combination) daily; Control 1 (C1) : double placebo daily.					
Chel 2008	Intervention 1 (I1): vitamin D_3 (600 IU) daily; Intervention 2 (I2): vitamin D_3 (4200 IU) weekly; Intervention 3 (I3): vitamin D_3 (18000 IU) monthly; Control 1 (C1): matched placebo tablet daily; Control 2 (C2): matched placebo tablets weekly; Control 3 (C3): matched placebo powder monthly.	1006	I1: 55 I2: 54 I3: 57 C1: 57 C2: 58 C3: 57 Total: 338	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a	I1: 55 I2: 54 I3: 57 C1: 57 C2: 58 C3: 57 Total: 338	I1: 46 I2: 48 I3:45 C1: 45 C2: 44 C3: 48 Total: 276
Cooper 2003	Intervention 1 (I1): vitamin D_2 (10000 IU) weekly plus calcium (1000 mg) daily; Control 1 (C1) : calcium (1000 mg) daily;	n/a	I1: 93 C1: 94 Total: 187	I1: 8 C1: 1 Total: 9	I1: 93 C1: 94 Total: 187	I1: 73 C1: 80 Total: 153
Coreless 1985	Intervention 1 (I1): vitamin D_2 (9000 IU) daily; Control 1 (C1): placebo daily.	320	I1: 32 C1: 33 Total: 65	I1: 1 C1: 0 Total: 1	I1: 32 C1: 33 Total: 65	I1: 8 C1: 17 Total: 25

Table 4. Overview of study populations (*Continued*)

Daly 2006	Intervention 1 (I1): calcium-vitamin D_3-fortified milk containing vitamin D_3 (800 IU) plus calcium (1000 mg) daily Control 1 (C1): no intervention.	422	I1: 85 C1: 82 Total: 167	I1: n/a C1: n/a Total: n/a	I1: 85 C1: 82 Total: 167	I1: 76 C1: 73 Total: 149
Dawson-Hughes 1997	Intervention 1 (I1): vitamin D_3 (700 IU) plus calcium (500 mg) daily; Control 1 (C1): double placebo daily.	545	I1: 187 C1: 202 Total: 389	I1: n/a C1: n/a Total: n/a	I1: 187 C1: 202 Total: 389	I1: 148 C1: 170 Total: 318
Dukas 2004	Intervention 1 (I1): alfacalcidol (1μg) daily; Control 1 (C1): placebo daily.	410	I1: 192 C1: 186 Total: 378	I1: n/a C1: n/a Total: n/a	I1: 192 C1: 186 Total: 378	I1: n/a C1: n/a Total: n/a
Flicker 2005	Intervention 1 (I1): vitamin D_3 (10000 IU) weekly until November 1998 and thereafter vitamin $D_3$1000 IU daily plus calcium (600 mg) daily; Control 1 (C1): calcium (600 mg).	1767	I1: 313 C1: 312 Total: 625	I1: n/a C1: n/a Total: n/a	I1: 313 C1: 312 Total: 625	I1: 269 C1: 271 Total: 540
Gallagher 2001	Intervention 1 (I1): calcitriol (0.5 μg) daily; Intervention 2 (I2): conjugated estrogens (Premarin) 0.625 mg/daily plus	1905	I1: 123 I2: 121 I3: 122 C1: 123 Total: 489	I1: n/a I2: n/a I3: n/a C1: n/a Total: n/a	I1: 123 I2: 121 I3: 122 C1: 123 Total: 489	I1: 101 I2: 101 I3: 102 C1: 112 Total: 416

Table 4. Overview of study populations (*Continued*)

	medroxyprogesterone acetate (Provera) 2.5 mg daily; Intervention 3 (I3): calcitriol (0.5 μg daily) plus conjugated estrogens (Premarin) 0.625 mg/daily plus medroxyprogesterone acetate (Provera) 2.5 mg daily; Control 1 (C1): matched placebo pills.					
Grady 1991	Intervention 1 (I1): calcitriol (0.5 μg) daily; Control 1 (C1) : placebo vitamin D daily	98	I1: 50 C1: 48 Total: 98	I1: 1 C1: 1 Total: 2	I1: 50 C1: 48 Total: 98	I1: 49 C1: 47 Total: 96
Grant 2005	Intervention 1 (I1): vitamin D_3 (800 IU) daily; Intervention 2 (I2): calcium (1000 mg) daily; Intervention 3 (I3): vitamin D_3 (800 IU) plus calcium (1000 mg) daily; Control 1 (C1): matched placebo tablets daily;	15024	I1: 1343 I2: 1311 I3: 1306 C1: 1332 Total: 5292	I1: I2: I3: C1:	I1: 1343 I2: 1311 I3: 1306 C1: 1332 Total: 5292	I1: 9 I2: 13 I3: 15 C1: 16 Total: 50
Harwood 2004	Intervention 1 (I1) : single injection of 300,000 IU of vitamin D_2; Intervention 2	208	I1: 38 I2: 36 I3: 39 C1: 37 Total: 150	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a	I1: 38 I2: 36 I3: 39 C1: 37 Total: 150	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a

Table 4. Overview of study populations (*Continued*)

	(I2): single injection of 300,000 IU of vitamin D_2 plus oral calcium (1000 mg) daily; Intervention 3 (I3): oral vitamin D_3 (800 IU) plus calcium (1000 mg) daily; Control 1 (C1): no intervention.					
Jackson 2006	Intervention 1 (I1): vitamin D_3 (400 IU) plus calcium (1000 mg) Control 1 (C1): matched placebo daily	68132	I1: 18176 C1: 18106 Total: 36282	I1: 449 C1: 381 Total: 830	I1: 18176 C1: 18106 Total: 36282	I1: 16936 C1: 16815 Total: 33751
Janssen 2010	Intervention 1 (I1): vitamin D_3 (400 IU) plus calcium (500 mg); Control 1 (C!): matched placebo vitamin D_3 plus calcium (500 mg)	91	I1: 36 C1: 34 Total: 70	I1: n/a C1: n/a Total: n/a	I1: 36 C1: 34 Total: 70	I1: 28 C1: 31 Total: 59
Komulainen 1999	Intervention 1 (I1) : sequential combination of 2 mg estradiol valerate (E_2Val; days 1 to 21) and 1 mg cyproterone acetate (days 12 to 21) and a treatment-free interval (days 22 to 28); Intervention 2 (I2): vitamin D_3 (300 IU)	13100	I1: 116 I2: 116 I3: 116 C1: 116 Total: 464	I1: 6 I2: 5 C1: 6 C2: 4 Total: 21	I1: 116 I2: 116 I3: 116 C1: 116 Total: 464	I1: n/a I2: n/a C1: n/a C2: n/a Total: 435

Table 4. Overview of study populations (*Continued*)

	plus calcium (500 mg) daily, no intake during June-August, the Vit D_3 dosage was lowered to 100 IU/day after 4 years of treatment because of adverse lipid changes noticed during the first years of the trial; Intervention 3 (I3): sequential combination of 2 mg estradiol valerate (E_2Val; days 1 to 21) and 1 mg cyproterone acetate (days 12 to 21) and a treatment-free interval (days 22 to 28) plus vitamin D_3 (300 IU) and calcium (500 mg) daily; Control 1 (C1): placebo.					
Krieg 1999	Intervention 1 (I1): vitamin D_3 (880 IU) plus calcium (1000 mg; Control 1 (C1): no treatment	n/a	I1: 124 C1: 124 Total: 248	I1:10 C1: 2 Total: 12	I1: 124 C1: 124 Total: 248	I1: 50 C1: 53 Total: 103
Kärkkäinen 2010	Intervention group 1: vitamin D_3 800 IU plus calcium (calcium carbonate) 1000 mg daily (n = 1718); Inter-	5407	I1: 1718 C1: 1714 Total: 3432	I1: 113 C1: 0 Total: 113	I1: 1718 C1: 1714 Total: 3432	I1: 1566 C1: 1573 Total: 3139

Table 4. Overview of study populations (*Continued*)

	vention group 2 (Control group) : no intervention (n = 1714)					
Lappe 2007	Intervention 1 (I1): vitamin D_3 (1000 IU) plus calcium (1400 to 1500 mg) daily; Intervention 2 (I2): calcium (1400 to 1500 mg) plus a vitamin D placebo daily; Control 1 (C1): placebo, consisting of both a vitamin D placebo and a brand-specific calcium placebo daily.	1180	I1: 446 I2: 445 C1: 288 Total: 1179	I1: 1 I2: 3 C1: 1 Total: 5	I1: 446 I2: 445 C1: 288 Total: 1179	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a
Larsen 2004	Intervention 1 (I1): home safety inspection by a community nurse to participants in the first block to identify and remedy possible hazards and identification and correction of potential health or dietary problems. The nurse evaluated the resident's prescribed medication to identify possible errors or necessary dose adjustments. Those who accepted a home visit in this area were given	62000	I1: 2532 I2: 2426 I3: 2531 C1: 2116 Total: 9605	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a	I1: 2532 I2: 2426 I3: 2531 C1: 2116 Total: 9605	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a

Table 4. Overview of study populations (*Continued*)

	leaflets with information of different ways to avoid falling; Intervention 2 (I2): vitamin D_3 (400 IU) plus calcium (1000 mg). Furthermore, these participants were offered an evaluation of their prescribed medication. This revision also ensured that the elderly took no other types of calcium and vitamin D products. If the elderly used cardiovascular medicine (digoxin or calcium antagonists) that may interact with calcium, they were referred to their general practitioner. Those who accepted a home visit were given leaflets with information of different ways to avoid osteoporosis; Intervention 3 (I3): a combination of the intervention 1 and intervention 2; Control 1 (C1): no intervention.					

Table 4. Overview of study populations (*Continued*)

Latham 2003	Intervention 1: resistance exercise; Intervention 2: attention control; Intervention 3: vitamin D_3 (300,000 IU) single dose; Control: matched placebo tablets.	3028	I1: 121 C1: 122 Total: 243	I1: n/a C1: n/a Total: n/a	I1: 121 C1: 122 Total: 243	I1: 108 C1: 114 Total: 222
Law 2006	Intervention 1 (I1): vitamin D_2 100,000 IU every 3 months (equivalent to 1100 IU daily); Control 1 (C1): no intervention.	n/a	I1: 1762 C1: 1955 Total: 3717	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a	I1: 1762 C1: 1955 Total: 3717	I1: 1366 C1: 1569 Total: 2935
Lips 1996	Intervention 1 (I1): vitamin D_3 400 IU; Control 1 (C1): matched placebo.	n/a	I1: 1291 C1: 1287 Total: 2578	I1: n/a C1: n/a Total: n/a	I1: 1291 C1: 1287 Total: 2578	I1: 1061 C1: 1029 Total: 2090
Lips 2010	Intervention 1 (I1): vitamin D_3 8400 IU weekly; Control 1 (C1): matched placebo weekly.	593	I1: 114 C1: 112 Total: 226	I1: 24 C1: 26 Total: 50	I1: 114 C1: 112 Total: 226	I1: 105 C1: 97 Total: 202
Lyons 2007	Intervention 1 (I1): vitamin D_2 100,000 IU three times a year (four-monthly); Control 1 (C1): matched placebo tablet three times a year (four-monthly.	5745	1: 1725 C1: 1715 Total: 3440	I1: n/a C1: n/a Total: n/a	I1: 1725 C1: 1715 Total: 3440	I1: 1639 C1: 1623 Total: 3262

Table 4. Overview of study populations (*Continued*)

Meier 2004	Intervention 1 (I1): vitamin D_3 (500 IU); Control 1 (C1): no intervention.	n/a	I1: 30 C1: 25 Total: 55	I1: 0 C1: 3 Total: 1	I1: 30 C1: 25 Total: 55	I1: 27 C1: 16 Total: 43
Mochonis 2006	Intervention 1 (I1) : vitamin D_3 300 IU plus calcium 1200 mg daily; Intervention 2 (I2): calcium 1200 mg; Control group (C1): no intervention	n/a	I1: 42 I2: 30 C1: 40 Total: 112	I1: 0 I2: 4 C1: 0 Total: 4	I1: 42 I2: 30 C1: 40 Total: 112	I1: 39 I2: 26 C1: 36 Total:
Ooms 1995	Intervention 1 (I1): vitamin D_3 400 IU daily; Control 1 (C1): matched placebo daily.	n/a	I1: 177 C1: 171 Total: 348	I1: 1 C1: 0 Total: 1	I1: 177 C1: 171 Total: 348	I1: 126 C1: 118 Total: 244
Ott 1989	Intervention 1 (I1): vitamin D_3 17.2 IU plus calcium 1000 mg daily; Control 1 (C1): matched placebo plus calcium 1000 mg daily.	n/a	I1: 43 C1: 43 Total: 86	I1: 6 C1: 0 Total: 80	I1: 43 C1: 43 Total: 86	I1: 39 C1: 37 Total: 76
Porthouse 2005	Intervention 1 (I1): vitamin D_3 (800 IU) plus calcium (1000 mg); Control 1 (C1): information leaflet on dietary calcium intake and prevention of falls, or leaflet only.	11022	I1: 1321 C1: 1993 Total: 3454	I1: n/a I2: n/a C1: n/a C2: n/a Total: n/a	I1: 1321 C1: 1993 Total: 3454	I1: 1212 C1: 1862 Total: 3074

Table 4. Overview of study populations (*Continued*)

Prince 2008	Intervention 1 (I1): vitamin D_2 1000 IU plus calcium 1000 mg daily; Control 1 (C1): matched placebo tablet of vitamin D plus calcium 1000 mg daily.	827	I1: 151 C1: 151 Total: 302	I1: 1 C1: 0 Total: 1	I1: 151 C1: 151 Total: 302	I1: 144 C1: 145 Total: 289
Sanders 2010	Intervention 1 (I1): vitamin D_3 500,000 IU yearly (n = 1131); Control group 1 (C1): matched placebo tablet of vitamin D yearly (n = 1127)	7204	I1: 1131 C1: 1127 Total: 2258	I1: 223 C1: 201 Total: 424	I1: 1131 C1: 1127 Total: 2258	I1: 1015 C1: 1017 Total: 1032
Sato 1997	Intervention 1 (I1): vitamin D (alfacalcidol) (1 μg) plus calcium 300 mg daily; Control 1 (C1): matched placebo tablets of vitamin D and calcium daily.	Not reported	I1: 45 C1: 39 Total: 84	I1: n/a C1: n/a Total: n/a	I1: 45 C1: 39 Total: 84	I1: 30 C1: 34 Total: 64
Sato 1999a	Intervention 1 (I1): vitamin D (alfacalcidol) (1 μg) daily; Control 1 (C1): matched placebo tablet of vitamin D daily.	n/a	I1: 43 C1: 43 Total: 86	I1: 0 C1: 1 Total: 1	I1: 43 C1: 43 Total: 86	I1: 40 C1: 40 Total: 80
Sato 1999b	Intervention 1 (I1): vitamin D in a form of 1-α hydroxyvitamin D_3 (alfacalcidol) (1 μg)	n/a	I1: 34 I2: 34 C1: 35 Total: 103	I1: 0 I2: 0 C1: 0 Total: 0	I1: 34 I2: 34 C1: 35 Total: 103	I1: 32 I2: 30 C1: 32 Total: 94

Table 4. Overview of study populations (*Continued*)

	daily (n = 34); Intervention 2 (I2): ipriflavone 600 mg daily; Control 1 (C1): no treatment					
Sato 2005a	Intervention 1 (I1): vitamin D_2 (1000 IU) daily; Control 1 (C1): matched placebo tablet of vitamin D daily.	n/a	I1: 48 C1: 48 Total: 96	I1: n/a C1: n/a Total: n/a	I1: 48 C1: 48 Total: 96	I1: 43 C1: 42 Total: 85
Schleithoff 2006	Intervention 1 (I1): vitamin D_3 2000 IU plus calcium 500 mg daily; Control 1 (C1): matched placebo vitamin D plus calcium 500 mg daily.	n/a	I1: 61 C1: 62 Total: 103	I1: 0 C1: 1 Total: 1	I1: 61 C1: 62 Total: 103	I1:42 C1: 51 Total: 93
Smith 2007	Intervention 1 (I1): vitamin D_2 300000 IU intramuscular injection yearly; Control 1 (C1): matched placebo intramuscular injection yearly..	13487	I1: 4727 C1: 4713 Total: 9440	I1: n/a C1: n/a Total: n/a	I1: 4727 C1: 4713 Total: 9440	I1: 2304 C1: 2266 Total: 4570
Trivedi 2003	Intervention 1 (I1): vitamin D_3 100000 IU every four months orally; Control 1 (C1): matched placebo vitamin D every four months orally.	n/a	I1: 1345 C1: 1341 Total: 2696	I1: 665 C1: 676 Total: 1341	I1: 1345 C1: 1341 Total: 2696	I1: 1262 C1: 1264 Total: 2526

Table 4. Overview of study populations (*Continued*)

Witham 2010	Intervention 1 (I1): vitamin D_2 (10,000 IU); Control 1 (C1): matched placebo tablet	173	I1: 53 C1: 52 Total: 105	I1: 20 C1: 25 Total: 45	I1: 53 C1: 52 Total: 105	I1: 48 C1: 48 Total: 96
Zhu 2008	Intervention 1: vitamin D_2 (1000 IU) plus calcium (1200 mg) daily; Intervention group 2: calcium 1200 mg plus placebo vitamin D daily; Control 1 (C1): matched placebo vitamin D and placebo calcium daily	n/a	I1: 39 I2: 40 C1: 41 Total: 120	I1: 1 I2: 3 C1: 2 Total: 6	I1: 39 I2: 40 C1: 41 Total: 120	I1: 33 I2: 38 C1: 36 Total: 107

Forty-four trials were primary prevention trials that included 93,585 participants. There were three trials in healthy volunteers, nine trials in postmenopausal women, and 32 trials in older people living independently, or in institutional care.

Six trials with 563 participants were secondary prevention trials including participants with neurological (Sato 1997; Sato 1999a; Sato 1999b; Sato 2005a) and cardiovascular diseases (Schleithoff 2006; Witham 2010) (Table 2).

Of the 50 trials reporting mortality, 40 trials (80%) reported the baseline vitamin D status of participants based on serum 25-hydroxyvitamin D levels. Participants in 18 trials (Bjorkman 2007; Bolton-Smith 2007; Broe 2007; Burleigh 2007; Chel 2008; Cooper 2003; Daly 2008; Dawson-Hughes 1997; Dukas 2004; Flicker 2005; Gallagher 2001; Grady 1991; Meier 2004; Moschonis 2006; Ott 1989; Smith 2007; Trivedi 2003; Zhu 2008) had baseline 25-hydroxyvitamin D levels at or above vitamin D adequacy (20 ng/ml). Participants in the remaining 22 trials had baseline 25-hydroxyvitamin D levels in a range of vitamin D insufficiency (< 20 ng/ml). Ten trials did not report the baseline vitamin D status of participants (Avenell 2004; Baeksgaard 1998; Campbell 2005; Komulainen 1999; Lappe 2007; Larsen 2004; Law 2006; Lyons 2007; Porthouse 2005; Sato 1997).

The main outcome measures in the trials were bone mineral density, number of falls and fractures, and mortality (Table 2).

Experimental interventions

Vitamin D_3 - cholecalciferol

Vitamin D was administered as vitamin D_3 (cholecalciferol) in 32 trials (74,789 participants; 81% women; mean age 73.2 years). Vitamin D_3 was tested singly in seven trials, and combined with calcium in 23 trials. Two trials tested vitamin D_3 singly and combined with calcium (Avenell 2004; Grant 2005). Vitamin D_3 was tested orally in all trials. Vitamin D_3 was tested daily in 27 trials, and intermittently in five trials (daily, weekly, or monthly (Chel 2008); weekly (Lips 2010); monthly (Campbell 2005); four-monthly (Trivedi 2003); yearly (Sanders 2010)). The dose of the vitamin D_3 was 300 IU to 500,000 IU (mean daily dose 804 IU; median daily dose 800 IU). The duration of supplementation in trials using vitamin D_3 was one day to seven years (mean 2 years; median 2 years), and the duration of the follow-up period was one month to seven years (mean 2.1 years; median 2 years) (Table 3).

Vitamin D_2 - ergocalciferol

Vitamin D was administered as vitamin D_2 (ergocalciferol) in 12 trials (18,349 participants; 82% women; mean age 78.8 years). Vitamin D_2 was tested singly in seven trials, and combined with calcium in four trials. One trial (Harwood 2004) tested vitamin D_2 singly and combined with calcium. Vitamin D_2 was administered orally in 10 trials. One trial (Harwood 2004) tested vitamin D_2 orally and parenterally (single intramuscular injection), and one trial (Smith 2007) tested vitamin D_2 parenterally (single intramuscular injection yearly). The dosing schedule for vitamin D_2 was daily in six trials, and intermittently in five trials (weekly (Cooper 2003), 10-weekly (Witham 2010), three-monthly (Law 2006), four-monthly (Lyons 2007); and yearly (Smith 2007)). One trial tested vitamin D_2 first weekly and then daily (Flicker 2005). The dose of vitamin D_2 was 200 IU to 300,000 IU (mean daily dose 1661 IU; median daily dose 1000 IU). The duration of supplementation and follow-up in trials using vitamin D_2 was one day to seven years (mean 1.78 years; median 1.5 years) (Table 3).

Alfacalcidol - 1-alfahydroxyvitamin D

Vitamin D was administered as alfacalcidol in four trials (617 participants; 57% women; mean age 70.2 years). Alfacalcidol was tested singly in three trials, and combined with calcium in one trial (Sato 1997). Alfacalcidol was tested orally and daily in all trials. The dose of alfacalcidol was 1 μg in all four trials. The duration of supplementation and follow-up in trials using alfacalcidol was six months to one year (mean 0.94 years; median 0.87 years) (Table 3).

Calcitriol - 1,25-dihydroxyvitamin D

Vitamin D was administered as calcitriol in three trials (430 participants; 85% women; mean age 72.7 years). Calcitriol was tested singly in two trials, and combined with calcium in one trial (Ott 1989). Calcitriol was tested orally and daily in all trials. The dose of calcitriol was 0.5 μg in two trials; while one trial tested two doses of calcitriol, 0.5 μg and 2 μg (Ott 1989). The duration of supplementation in trials using calcitriol was two to five years (mean 3.33 years; median 3 years) and the duration of the follow-up period was two to five years (mean 4 years; median 5 years) (Table 3).

Control interventions

Thirty-eight trials used placebo vitamin D and 12 trials used no intervention in the control group (Table 1).

Co-interventions

Thirty-two trials used calcium combined with vitamin D in the experimental intervention groups. Five trials tested calcium separately in one of the intervention groups (Avenell 2004; Grant 2005; Lappe 2007; Moschonis 2006; Zhu 2008). Calcium was administered orally and daily in all trials. The dose of calcium was 300 mg to 1600 mg (mean 929 mg; median 1000 mg) (Table 3). Ten trials used calcium in the control group, combined with vitamin D placebo, in a dose of 300 mg to 1500 mg (mean 865 mg; median 1000 mg). These trials used an equal dose of calcium in the experimental intervention groups (Table 3). One trial with a 2 x 2 factorial design tested a combination of vitamin D_3, vitamin K_1, and calcium in one group (Bolton-Smith 2007). The factorial design of this trial allowed us to compare only the vitamin D_3 plus calcium group with the placebo group of this trial. Another two trials with parallel group design and three arms tested, in one group, the combination of calcium and multivitamins (Baeksgaard 1998) or ipriflavone (Sato 1999b). The parallel group design allowed us to compare the vitamin D group with the placebo group of these trials. Two trials with a 2 x 2 factorial design tested vitamin D and hormone replacement (Gallagher 2001; Komulainen 1999). We have compared only the vitamin D group with the placebo group of these trials.

Risk of bias in included studies

Twenty-six trials (52%) reporting mortality were considered as having low risk of bias. The remaining 24 trials had unclear bias control in one or more of the components assessed (Table 1; Figure 2; Figure 3). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 4). The adjusted-rank correlation test (P = 0.47) and regression asymmetry test (P = 0.1) found no significant evidence of bias.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

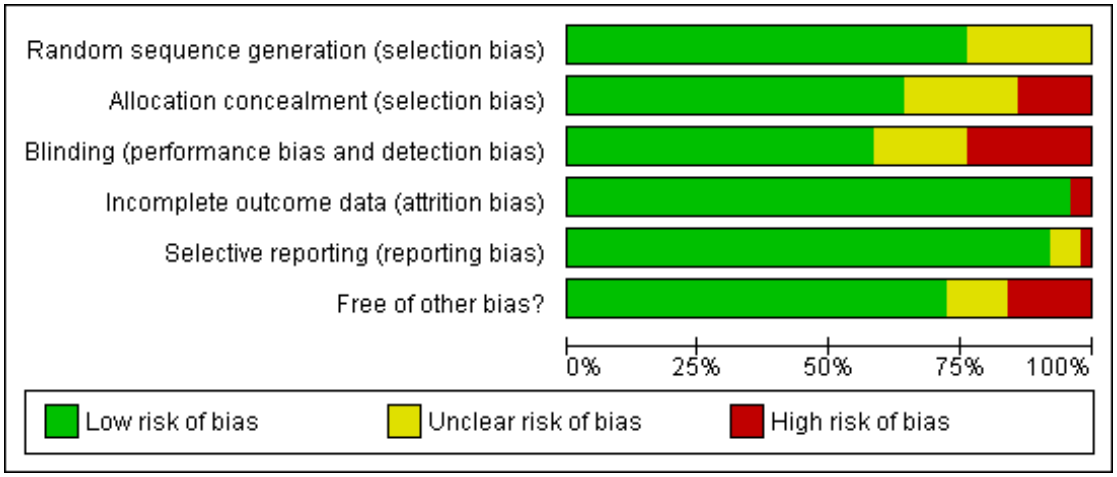


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

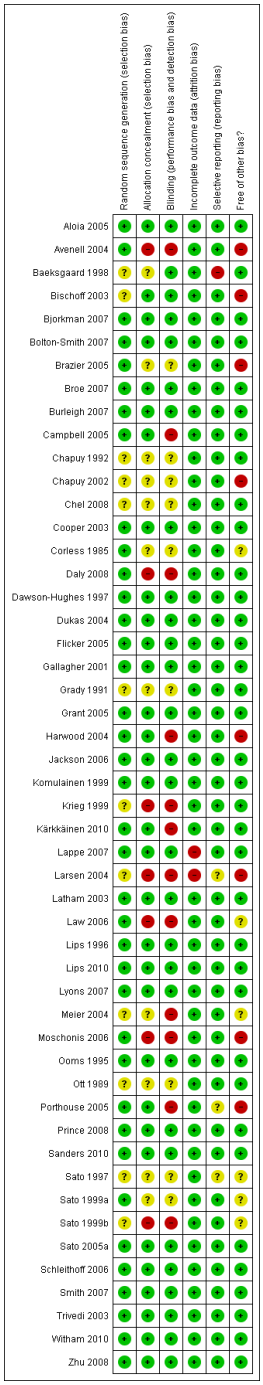
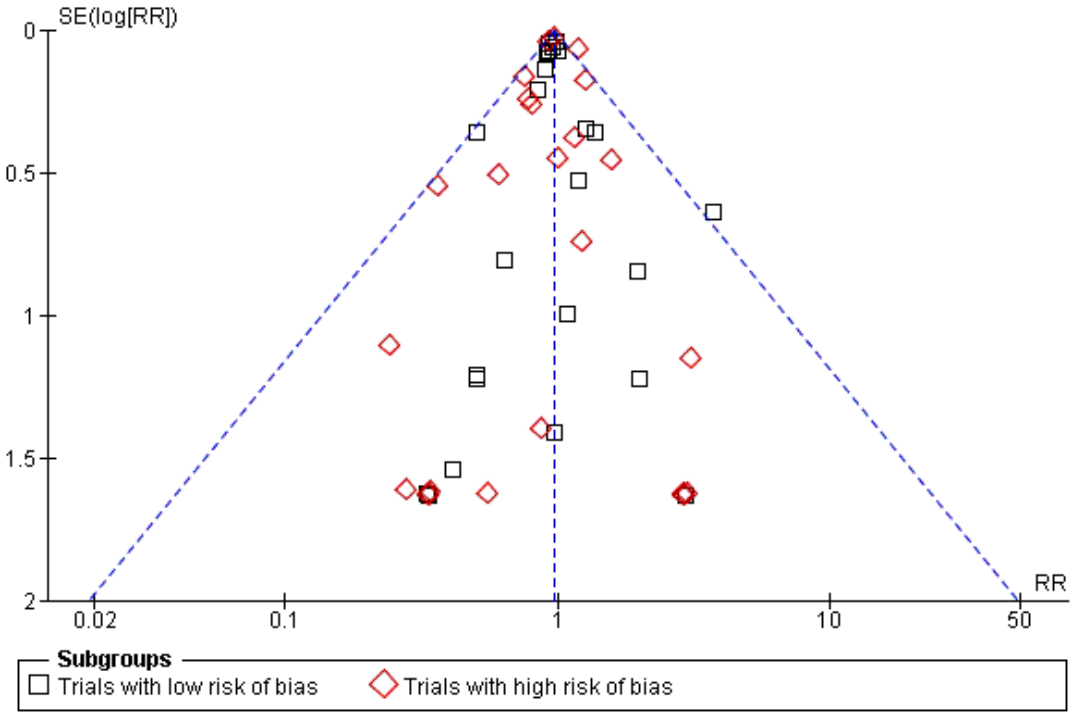


Figure 4. Funnel plot of comparison 1.1 Vitamin D versus placebo/no intervention, outcome: 1.1 All-cause mortality in trials with a low or high risk of bias.



Effects of interventions

See: **Summary of findings for the main comparison** Vitamin D supplementation for prevention of mortality in adults

All-cause mortality in all trials

Overall, vitamin D significantly decreased all-cause mortality (RR 0.97, 95% CI 0.94 to 1.00, P = 0.03, I^2 = 0%). A total of 5275 of 46,893 participants (11.2%) randomised to the vitamin D group and 5410 of 47,255 participants (11.4%) randomised to the placebo or no intervention group died. A sensitivity analysis excluding cluster-randomised trials had no noticeable effect on the result (RR 0.96, 95% CI 0.92 to 0.99, P = 0.02, I^2 = 0%) (Analysis 1.1). The difference between the effect estimate of vitamin D on mortality in individually randomised and cluster-randomised trials was not statistically significant (Z = 1.21; P = 0.23) (Analysis 1.2).

Intervention effects according to bias risk of trials (Analysis 1.1)

In trials with low risk of bias, mortality was significantly decreased in the vitamin D group (RR 0.95, 95% CI 0.91 to 1.00, P = 0.03, I^2 = 0%). In trials with a high risk of bias, mortality was not significantly changed (RR 0.99, 95% CI 0.91 to 1.06, P = 0.71, I^2 = 14%). The difference between the effect estimate of vitamin D on mortality in low- and high-bias risk trials was not statistically significant by the test of interaction (Z = 0.98, P = 0.33).

Placebo-controlled trials compared to no intervention trials (Analysis 1.3)

Vitamin D significantly decreased mortality in the placebo-controlled trials (RR 0.96, 95% CI 0.92 to 0.99, P = 0.01, I^2 = 0%). Vitamin D had no significant effect on mortality in trials with no intervention in the control group (RR 1.05, 95% CI 0.91 to 1.21,

P = 0.51, I^2 = 29%). The difference between the effect estimate of vitamin D on mortality in placebo-controlled trials and trials with no intervention in the control group was not statistically significant by the test of interaction (Z = 1.53, P = 0.13).

Sensitivity analyses taking attrition into consideration

Out of 50 trials reporting mortality, 47 trials reported the exact number of participants with missing outcomes in the intervention and the control groups. Two trials did not report losses to follow-up (Larsen 2004; Sato 1997), and one trial did not report losses to follow-up for each intervention group separately (Lappe 2007). There were 3588 out of 46,893 participants (7.7%) with missing outcomes in the vitamin D group and 3473 out of 47,255 participants (7.3%) with missing outcomes in the control group.

'Best-worst-case' scenario

If we assume that all participants lost to follow-up in the experimental intervention group had survived, and all those with missing outcomes in the control intervention group had died, vitamin D significantly decreased mortality (RR 0.41, 95% CI 0.32 to 0.53, P < 0.00001, I^2 = 96%).

'Worst-best-case' scenario

If we assume that all participants lost to follow-up in the experimental intervention group had died, and all those lost to follow-up in the control intervention group had survived, vitamin D significantly increased mortality (RR 2.73, 95% CI 2.04 to 3.65, P < 0.00001, I^2 = 98%).

Sensitivity analyses taking trials with zero events into account

In addition to the 50 trials reporting mortality, 53 trials with 10,292 participants had zero mortality in both the experimental and control groups. We assessed the influence of these trials by re-calculating the RR with 0.5, 0.01, and 0.001 as empirical continuity corrections. The random-effects model RR for the three continuity corrections were not noticeably influenced (RR 0.97, 95% CI 0.94 to 1.00, P = 0.033; RR 0.97, 95% CI 0.94 to 1.00, P = 0.0376; RR 0.97, 95% CI 0.94 to 1.00, P = 0.0378; respectively). We also tested the influence of zero event trials using a risk difference as the association measure. Vitamin D significantly decreased all-cause mortality using the fixed-effect model meta-analysis (RD 0.0039, 95% CI -0.016 to -0.008, P = 0.02). Heterogenity was significant (I^2 = 37%). The random-effects model revealed no statistically significant effect of vitamin D on all-cause mortality (RD -0.0022, 95% CI -0.005 to 0.001, P = 0.18).

Primary prevention compared to secondary prevention (Analysis 1.4)

Vitamin D significantly decreased mortality in primary prevention trials (RR 0.97, 95% CI 0.94 to 1.00, P = 0.03, I^2 = 0%). Vitamin D had no significant effect on mortality in secondary prevention trials (RR 1.16, 95% CI 0.55 to 2.43, P = 0.70, I^2 = 0%). The difference between the estimates of vitamin D on mortality in primary prevention and secondary prevention trials was not statistically significant (Z = 0.49, P = 0.62).

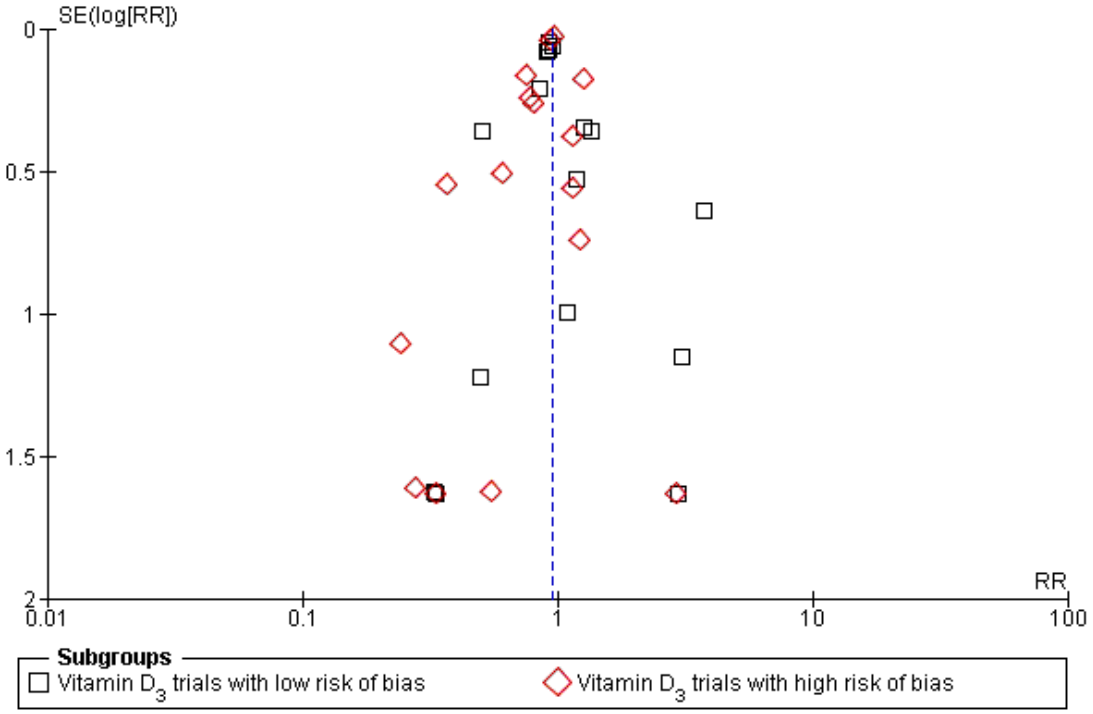
Intervention effects according to vitamin D status (Analysis 1.5)

Vitamin D significantly decreased mortality in participants with vitamin D insufficiency (RR 0.95, 95% CI 0.91 to 0.99, P = 0.02, I^2 = 0%). Vitamin D had no statistically significant effect on mortality in trials including participants with vitamin D adequacy (RR 0.95, 95% CI 0.86 to 1.04, P = 0.29, I^2 = 0%). The difference between the estimates of vitamin D on mortality in trials including participants with vitamin D adequacy and trials including participants with vitamin D insufficiency was not significant (Z = -0.20, P = 0.84).

Vitamin D_3 (cholecalciferol) (Analysis 1.6)

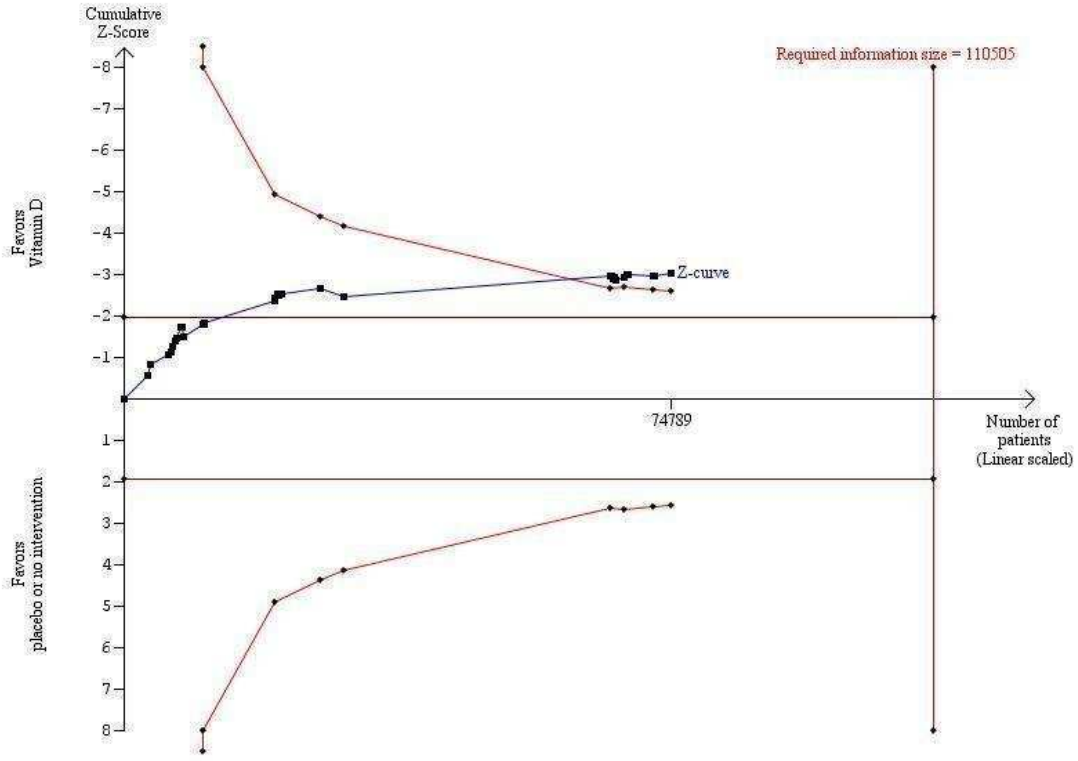
Vitamin D_3 was tested in 32 trials (74,789 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 5). The adjusted-rank correlation test (P = 0.98) and regression asymmetry test (P = 0.87) found no significant evidence of publication bias. Overall, vitamin D_3 significantly decreased mortality (RR 0.94, 95% CI 0.91 to 0.98, P = 0.003, I^2 = 0%). Vitamin D_3 significantly decreased mortality in trials with low risk of bias (RR 0.93, 95% CI 0.87 to 0.99, P = 0.01, I^2 = 0%). Vitamin D_3 had no significant effect on mortality in trials with a high risk of bias (RR 0.95, 95% CI 0.91 to 1.00, P = 0.06, I^2 = 0%). The difference between the estimates of vitamin D_3 on mortality in trials with low risk of bias and trials with a high risk of bias was not significant (Z = 0.52, P = 0.60).

Figure 5. Funnel plot of comparison: 1 Vitamin D versus placebo or no intervention, outcome: 1.6 All-cause mortality in trials using vitamin D_3 (cholecalciferol)).



Trial sequential analysis of all vitamin D_3 trials was constructed based on a mortality of 10% in the control group, a relative risk reduction of 5% with vitamin D_3, a type I error of 5%, and a type II error of 20% (80% power). There was no diversity. The trial sequential analysis revealed that the cumulative Z-curve crossed the trial sequential monitoring boundary in 2006 during the 21st trial. Subsequently, 11 trials have been published (Bjorkman 2007; Bolton-Smith 2007; Burleigh 2007; Chel 2008; Daly 2008; Jackson 2006; Kärkkäinen 2010; Lappe 2007; Lips 2010; Moschonis 2006; Sanders 2010) (Figure 6).

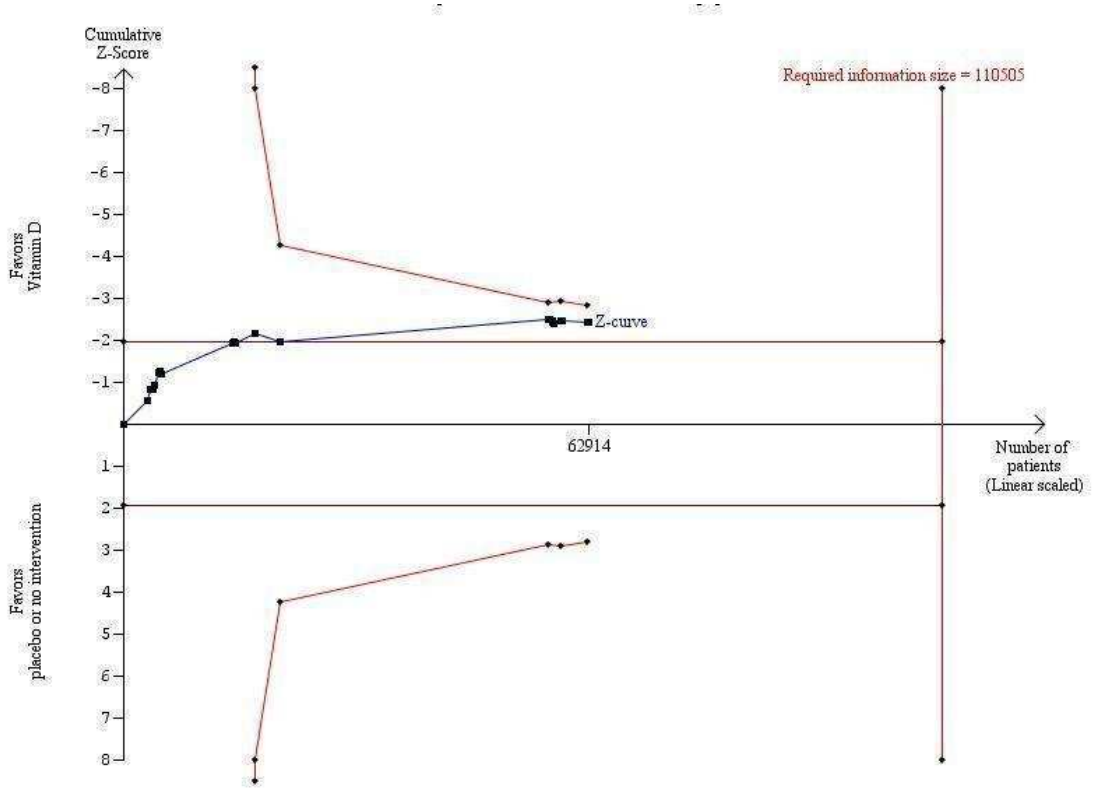
Figure 6. Trial sequential analysis on mortality in the 32 vitamin D_3 trials. Trial sequential analysis was performed based on a mortality in the control group of 10%, a relative risk reduction of 5% in the experimental group, a type I error of 5%, and type II error of 20% (80% power). There was no diversity. The required information size was 110,505 participants. The cumulative Z-curve (blue line) crossed the monitoring boundary (red line) after 21st trial. Subsequently, 11 trials have been published.



Vitamin D_3 and calcium (Analysis 1.7)

Vitamin D_3 administered singly versus placebo or no intervention had no statistically significant effect on mortality (RR 0.91, 95% CI 0.82 to 1.02, P = 0.10, I^2 = 19%). Vitamin D_3 combined with calcium versus placebo or no intervention significantly decreased mortality (RR 0.95, 95% CI 0.91 to 0.99, P = 0.02, I^2 = 0%). The difference between the estimate of vitamin D_3 on mortality in trials using vitamin D_3 singly and trials using vitamin D_3 combined with calcium was not significant (Z = 0.43, P = 0.67). The trial sequential analysis on mortality in the 23 trials that administered vitamin D_3 combined with calcium revealed that the cumulative Z-curve did not cross the monitoring boundary after the 24th trial (Figure 7).

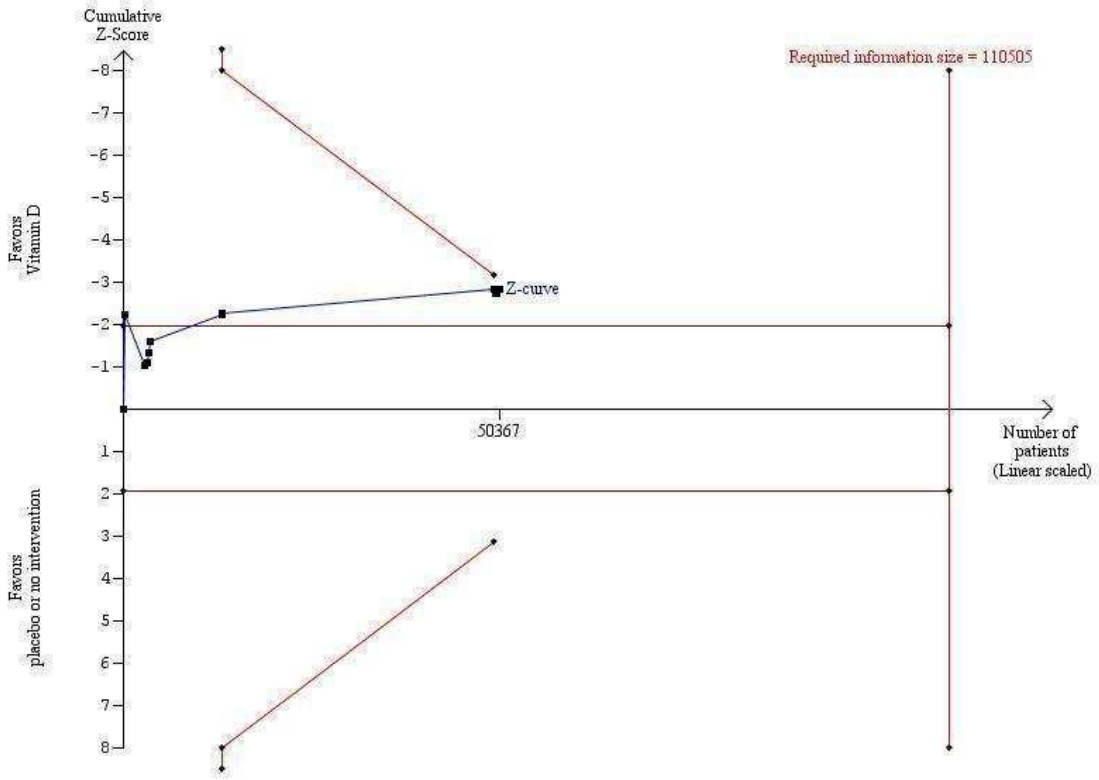
Figure 7. Trial sequential analysis on mortality in the 24 trials that administered vitamin D_3 combined with calcium. Trial sequential analysis was performed based on a mortality in the control group of 10%, a relative risk reduction of 5% in the experimental group, a type I error of 5%, and type II error of 20% (80% power). There was no diversity. The required information size was 110,505 participants. The cumulative Z-curve (blue line) did not cross the monitoring boundary (red line) after 24th trial.



Dose of vitamin D_3 (Analysis 1.8)

A dose of vitamin D_3 below 800 IU a day significantly decreased mortality (RR 0.92, 95% CI 0.87 to 0.97, P = 0.005, I^2 = 0%). A dose of vitamin $D_3 \geq$ 800 IU a day had no significant effect on mortality (RR 0.96, 95% CI 0.92 to 1.01, P = 0.13, I^2 = 0%). The difference between the estimate of vitamin D_3 on mortality in trials using a low dose of vitamin D_3 and trials using a high dose of vitamin D_3 was not significant (Z = 1.11, P = 0.27). The trial sequential analysis on mortality in the 12 trials that administered a low dose of vitamin D_3 revealed that the cumulative Z-curve did not cross the monitoring boundary after the 12th trial (Figure 8).

Figure 8. Trial sequential analysis on mortality in the 12 trials that administered low dose of vitamin D_3. Trial sequential analysis was performed based on a mortality in the control group of 10%, a relative risk reduction of 5% in the experimental group, a type I error of 5%, and type II error of 20% (80% power). There was no diversity. The required information size was 110,505 participants. The cumulative Z-curve (blue line) did not cross the monitoring boundary (red line) after 12th trial.



Dosing schedule of vitamin D_3 (Analysis 1.9)

Vitamin D_3 administered daily significantly decreased mortality (RR 0.95, 95% CI 0.91 to 0.99, P = 0.007, I^2 = 0%). Vitamin D_3 administered intermittently had no significant effect on mortality (RR 0.88, 95% CI 0.76 to 1.02, P = 0.08, I^2 = 0%). The difference between the estimate of vitamin D_3 on mortality in trials that administered vitamin D_3 daily and trials that administered vitamin D_3 intermittently was not significant (Z = -0.87, P = 0.38).

Intervention effect of vitamin D_3 according to vitamin D status (Analysis 1.10)

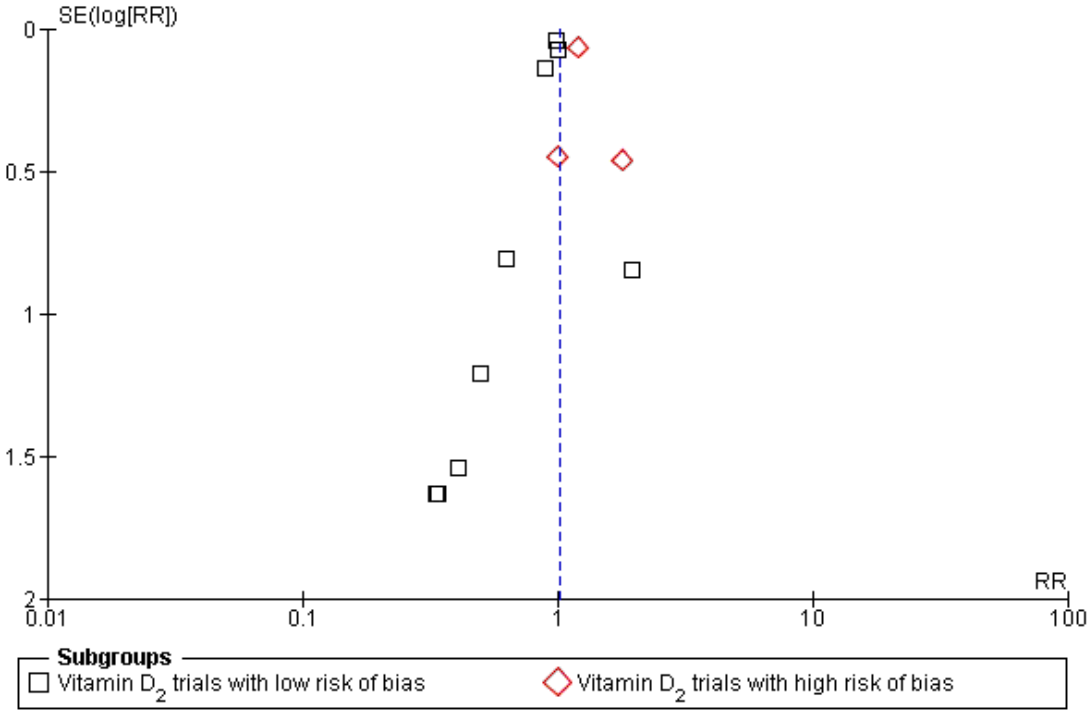
Vitamin D_3 significantly decreased mortality in trials including participants with vitamin D insufficiency (RR 0.94, 95% CI 0.90 to 0.99, P = 0.02, I^2 = 3%). Vitamin D_3 had no significant effect on mortality in trials including participants with vitamin D adequacy (RR 0.92, 95% CI 0.79 to 1.07, P = 0.27, I^2 = 0%). The difference between the estimate of vitamin D_3 on mortality in trials including participants with vitamin D insufficiency and trials including participants with vitamin D adequacy was not statistically significant (Z = 0.28; P = 0.78).

Vitamin D_2 (ergocalciferol) (Analysis 1.11)

Vitamin D_2 was tested in 12 trials (18,349 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 9). The adjusted-rank correlation test (P = 0.60) and regression asymmetry test (P = 0.55) found no significant evidence of bias. Overall, vitamin D_2 had no significant effect on mortality (RR 1.02, 95% CI 0.97 to 1.09, P = 0.42, I^2 = 0%). Vitamin D_2 had no significant effect on mortality in trials with a low risk of bias (RR 0.99, 95% CI 0.92 to 1.05, P = 0.66, I^2 = 0%). Vitamin D_2 significantly increased mortality in trials with a high risk of bias (RR 1.20, 95% CI 1.05 to 1.37, P = 0.007, I^2 = 0%). The

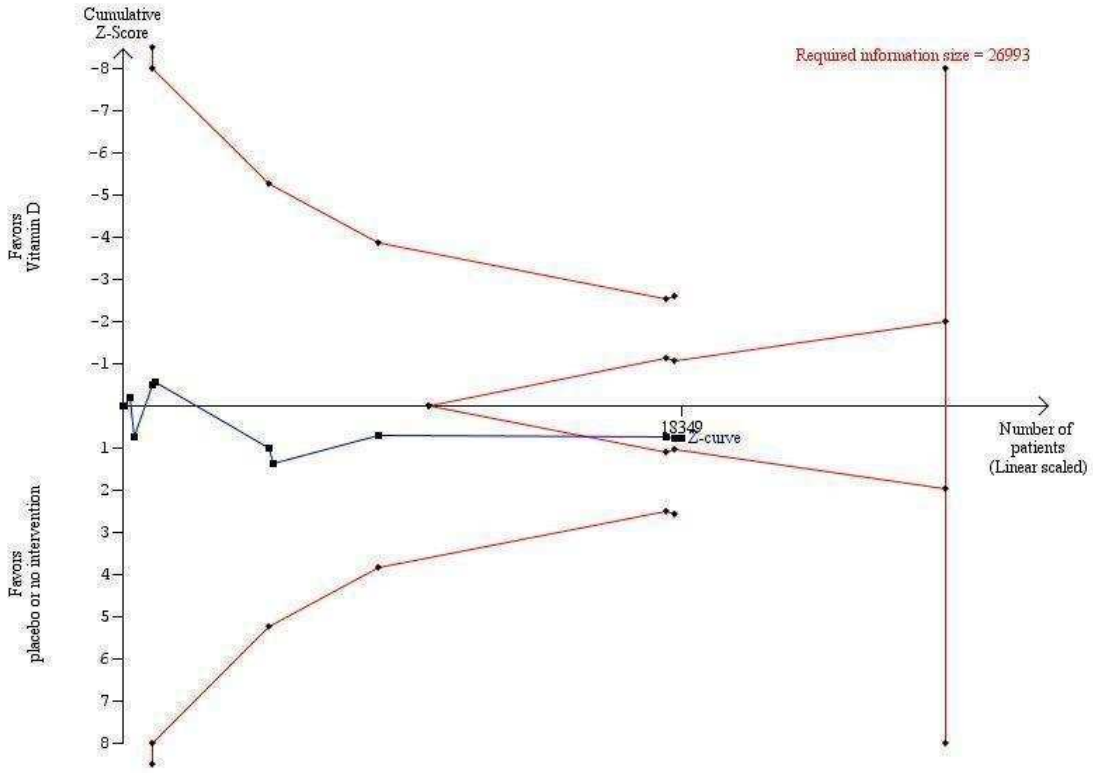
difference between the estimate of vitamin D_2 on mortality in trials with a low risk of bias and trials with a high risk of bias was significant (Z = 2.62, P = 0.009).

Figure 9. Funnel plot of comparison: 1 Vitamin D versus placebo or no intervention, outcome: 1.11 All-cause mortality in trials using vitamin D_2 (ergocalciferol).



Trial sequential analysis of all vitamin D_2 trials suggests that we reached the futility area after the eighth trial (Figure 10) allowing us to conclude that any possible intervention effect is lower than a 5% relative risk reduction or that the number needed to treat (NNT) is greater than 200.

Figure 10. Trial sequential analysis of mortality in the 12 vitamin D_2 trials. Trial sequential analysis was conducted based on 10% mortality in the control group, a relative risk reduction of 10% in the experimental group, a type I error of 5%, and type II error of 20% (80% power). There was no diversity. The required information size was 26993 participants. The cumulative Z-curve (blue line) crossed the futility boundary (red line) after the 8^{th} trial.



Vitamin D_2 and calcium (Analysis 1.12)

Vitamin D_2 administered singly had no significant effect on mortality (RR 1.04, 95% CI 0.97 to 1.11, P = 0.30, I^2 = 3%). Vitamin D_2 combined with calcium had no significant effect on mortality (RR 1.00, 95% CI 0.64 to 1.57, P = 1.00, I^2 = 11%). The difference between the estimates of vitamin D_2 on mortality in trials using vitamin D_2 singly and trials using vitamin D_2 combined with calcium was not significant (Z = -0.76, P = 0.45).

Dose of vitamin D_2 (Analysis 1.13)

A dose of vitamin D_2 below 800 IU a day, tested in one trial, had no significant effect on mortality (RR 0.82, 95% CI 0.17 to 3.98). A dose of vitamin $D_2 \geq$ 800 IU a day had no significant effect on mortality (RR 1.03, 95% CI 0.96 to 1.10, P = 0.42, I^2 = 4%). The difference between the estimate of vitamin D_2 on mortality in trials using a high dose of vitamin D_2 and the trial using low-dose vitamin D_2 was not significant (Z = 0.28, P = 0.78).

Dosing schedule of vitamin D_2 (Analysis 1.14)

Vitamin D_2 administered daily had no significant effect on mortality (RR 0.88, 95% CI 0.68 to 1.12, P = 0.30, I^2 = 0%). Vitamin D_2 administered intermittently had no significant effect on mortality (RR 1.06, 95% CI 0.95 to 1.18, P = 0.30, I^2 = 39%). The difference between the estimates of vitamin D_2 on mortality in trials that administered vitamin D_2 daily and trials that administered vitamin D_2 intermittently was not significant (Z = 1.38, P = 0.17).

Intervention effect of vitamin D_2 according to vitamin D status (Analysis 1.15)

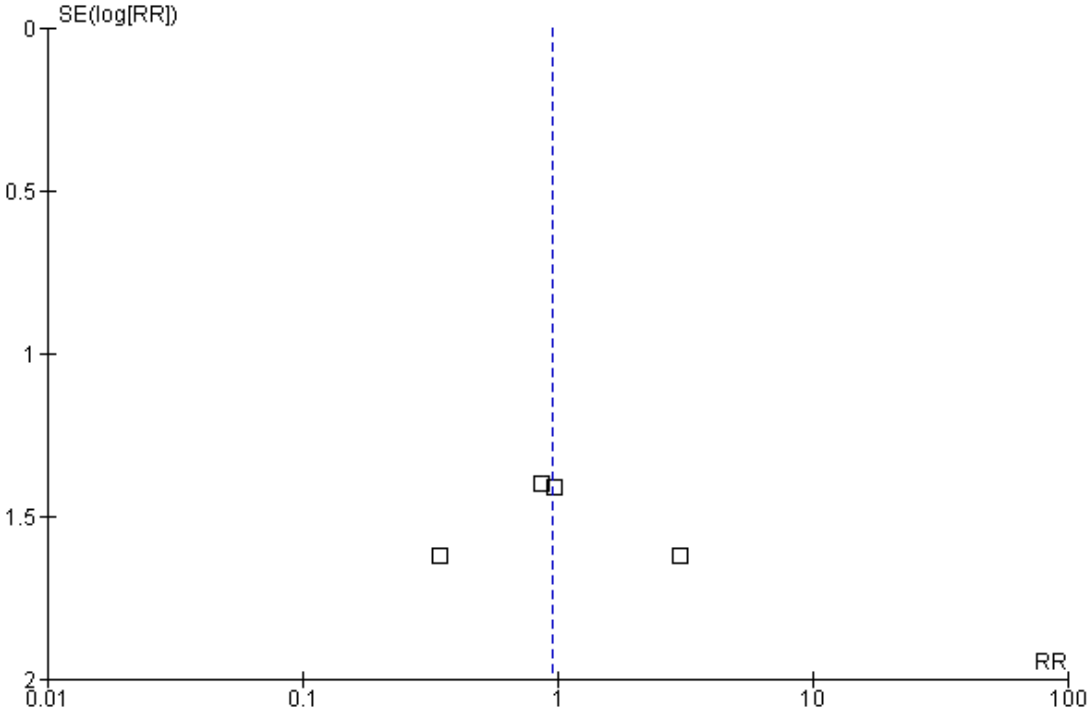
Vitamin D_2 significantly increased mortality in trials including participants with vitamin D insufficiency (RR 1.20, 95% CI 1.05 to 1.37, P = 0.008, I^2 = 0%). Vitamin D_2 had no statistically significant effect on mortality in trials including participants with

vitamin D adequacy (RR 0.97, 95% CI 0.86 to 1.10, P = 0.62, I^2 = 0%). The difference between the estimates of vitamin D_2 on mortality in trials including participants with vitamin D insufficiency and trials including participants with vitamin D adequacy was statistically significant (Z = 2.30; P = 0.02).

Alfacalcidol (1α hydroxyvitamin D) (Analysis 1.16)

Alfacalcidol was tested in four trials (617 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 11). The adjusted-rank correlation test (P = 1.00) found no significant evidence of bias. Alfacalcidol had no significant effect on mortality (RR 0.96, 95% CI 0.22 to 4.15, P = 0.95, I^2 = 0%). The effect of alfacalcidol on mortality was not dependant on vitamin D status (Analysis 1.17).

Figure 11. Funnel plot of comparison: 1 Vitamin D versus placebo or no intervention, outcome: 1.16 All-cause mortality in trials using alfacalcidol (1-α hydroxyvitamin D).

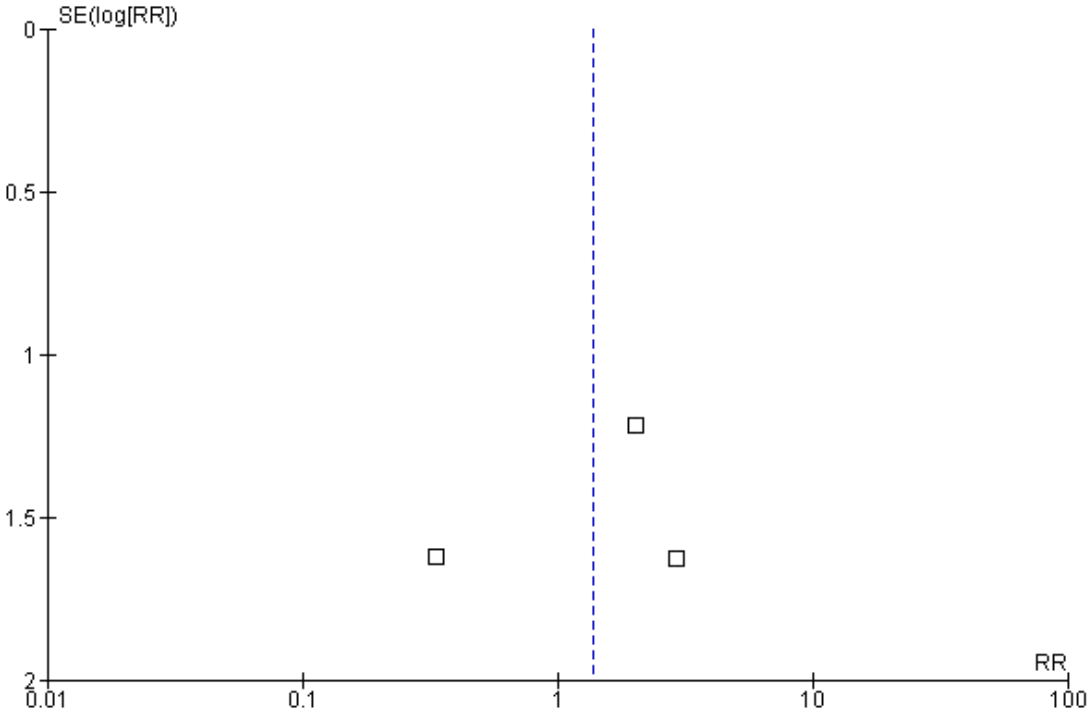


Calcitriol (1,25-dihydroxyvitamin D) (Analysis 1.18)

Calcitriol was tested in three trials (430 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 12). Calcitriol had no significant effect on mortality (RR 1.37, 95% CI 0.27 to 7.03, P = 0.71, I^2 = 0%). The effect of

calcitriol on mortality was not dependant on vitamin D status (Analysis 1.19).

Figure 12. Funnel plot of comparison: 1 Vitamin D versus placebo or no intervention, outcome: 1.18 All-cause mortality in trials using calcitriol (1,25-dihydroxyvitamin D).



Cause-specific mortality (Analysis 1.20; Analysis 1.21)

Vitamin D_3 had no significant effect on cardiovascular mortality (RR 1.02, 95% CI 0.91 to 1.13, I^2 = 0%; 7 trials) (Analysis 1.20), or cancer mortality (RR 0.89, 95% CI 0.78 to 1.02, I^2 = 0%; 3 trials). We were not able to extract relevant data on the other causes of mortality from the included trials (Analysis 1.21).

Adverse events (Analysis 1.22)

Several adverse events were reported (for example, hypercalcaemia, nephrolithiasis, hypercalciuria, renal insufficiency, gastrointestinal disorders, cardiovascular disorders, psychiatric disorders, skin disorders, cancer). The supplemental forms of vitamin D (D_3 and D_2) had no significant effect on the risk of hypercalcaemia (RR 1.26, 95% CI 0.78 to 2.05, P = 0.34, I^2 = 0%). Active forms of vitamin D (alfacalcidol and calcitriol) significantly increased the risk of hypercalcaemia (RR 3.18, 95% CI 1.17 to 8.68, P = 0.02, I^2 = 17%). The difference between the estimate of vitamin D on hypercalcaemia in trials that administered supplemental forms of vitamin D (D_3 and D_2) and trials that administered active forms of vitamin D (alfacalcidol or calcitriol) was not significant (Z = 1.63, P = 0.10).

Vitamin D_3 combined with calcium significantly increased nephrolithiasis (RR 1.17, 95% CI 1.02 to 1.34, P = 0.02, I^2 = 0%). The effect of vitamin D on the other adverse events was not statistically significant (hypercalciuria, RR 4.64, 95% CI 0.99 to 21.76, P = 0.05, I^2 = 0%; renal insufficiency, RR 1.70, 95% CI 0.27 to 10.70, P = 0.57, I^2 = 53%; cardiovascular disorders, RR 0.95, 95% CI 0.86 to 1.05, P = 0.31, I^2 = 0%; gastrointestinal disorders, RR 1.35, 95% CI 0.85 to 2.14, P = 0.20, I^2 = 59%; psychiatric disorders, RR 1.44, 95% CI 0.56 to 3.73, P = 0.45, I^2

= 0%; skin disorders, RR 3.27, 95% CI 0.17 to 62.47, P = 0.43, I^2 = 77%; cancer, RR 1.06, 95% CI 0.89 to 1.27, P = 0.49, I^2 = 0%).

Health-related quality of life

One trial published data on health-related quality of life (Witham 2010). Authors reported significant worsening in disease-specific quality of life (Minnesota score) in the vitamin D_2 group compared with the placebo group (Witham 2010).

Health economics

We found only one randomised trial (Chapuy 1992) that reported a cost-effectiveness analysis (Lilliu 2003). The authors found that vitamin D_3 and calcium supplementation prevented 46 hip fractures in every 1000 women treated and concluded that vitamin D_3 and calcium supplementation is cost-effective (Lilliu 2003). Mortality was not addressed.

DISCUSSION

Our systematic review contains a number of important findings. We found evidence that vitamin D_3 significantly benefits survival of mainly elderly, female participants living independently or in institutional care, who were likely to be vitamin D deficient with a significant risk of falls and fractures. Vitamin D_2, alfacalcidol, and calcitriol had no statistically significant effect on mortality, but these estimates are at risk of type II errors due to the fact that much smaller groups of participants were examined compared with the studies using vitamin D_3. A subgroup analysis of trials with high risk of bias suggests that vitamin D_2 may increase mortality, but trial sequential analysis opens the possibility that this could be a random error. Alfacalcidol and calcitriol significantly increased the risk of hypercalcaemia, and vitamin D_3 combined with calcium significantly increased nephrolithiasis. Vitamin D had no clear effect on other adverse events including cancer.

There has been a great debate in the literature about the possible beneficial health effects of vitamin D supplementation. A lot of evidence indicates that vitamin D has beneficial effects in addition to that on bones (Cavalier 2009; Stechschulte 2009; Wang 2009). It has been speculated that optimal vitamin D status is related to prevention of a spectrum of chronic diseases, including malignant and cardiovascular diseases (Fleet 2008; Ingraham 2008; Judd 2009; Zittermann 2010). Vitamin D insufficiency has been associated with increased mortality (Hutchinson 2010; Melamed 2008; Pilz 2009a; Zittermann 2009). Two recently published evidence reports, prepared for The Agency for Healthcare Research and Quality, have assessed the influence of vitamin D and calcium on different health outcomes (Chung 2009; Cranney 2007). The majority of the findings on bone health and different health outcomes were inconsistent (Chung 2009; Cranney 2007). The Institute of Medicine recently reported that available evidence supports a role of vitamin D and calcium in skeletal health (IOM 2011). The evidence was, however, considered insufficient and inconclusive for extraskeletal outcomes including mortality (IOM 2011).

Strengths

Our review offers a number of strengths. It follows the overall plan of a published, peer-reviewed Cochrane protocol (Bjelakovic 2008). It represents a comprehensive review of the topic, including 144 randomised trials with more than 108,000 participants. A total of 50 trials including more than 94,000 participants reported on mortality. This increases the precision and power of our analyses (Higgins 2008). Previous meta-analyses of preventive trials of vitamin D supplements have included substantially less information and have not examined the separate influence of different forms of vitamin D on mortality. We conducted a thorough review with our methodology following the recommendations of The Cochrane Collaboration (Higgins 2008) and findings of methodological studies (Kjaergard 2001; Moher 1998; Schulz 1995; Wood 2008). Our meta-analyses had almost no trial heterogeneity. This emphasises the consistency of our findings. Furthermore, all-cause mortality should generally be connected with unbiased estimates (Wood 2008). We also performed trial sequential analysis to avoid an undue risk of random errors in cumulative meta-analysis and to prevent premature statements of superiority of vitamin D, based on estimation of the diversity-adjusted required information size (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009).

Limitations

Certain potential limitations of this review warrant consideration. The number of participants lost to follow-up was approximately 8% in both groups. Our 'best-worst-case' and 'worst-best-case' scenarios revealed much more extreme confidence limits (95% CI 0.32 to 3.65) compared to our 'complete-case' scenario (95% CI 0.94 to 1.00) and convey a noticeable degree of uncertainty to our results. However, we have abstained from conducting 'uncertainty analyses' (Gamble 2005). This analysis accepts the point estimate from the complete-case analysis, assuming that the distribution of deaths among the participants lost to follow-up is equal to the distribution of deaths among the complete cases. But the distribution of dead participants among the lost to follow-up participants may indeed be different from the distribution of dead participants among participants actually followed through the whole observation period, making the 'uncertainty' analysis itself uncertain. The duration of supplementation and duration of follow-up was short in some of included trials. This may make it difficult to detect any effects, beneficial or harmful.

We found that vitamin D_3 had a significant beneficial effect on mortality in participants with vitamin D insufficiency (25-hydroxyvitamin D level less than 20 ng/ml). The optimal vitamin D status, reached by using the blood level of 25-hydroxyvitamin D that maximally suppresses serum parathyroid hormone, varies widely (8 ng/ml to 44 ng/ml) (Dawson-Hughes 2005; Lips 2004; Vieth 2006). The level of 25-hydroxyvitamin D depends much on the laboratory methods used (Binkley 2009; Holick 2009; Lips 1999). Many external factors (latitude, season, time of day, air pollution) as well as internal factors (skin color, age, clothing, use of sunscreen) influence the cutaneous synthesis of vitamin D, and consequently 25-hydroxyvitamin D levels (Webb 2006). According to the recent report of the Institute of Medicine (IOM 2011) a serum 25-hydroxyvitamin D level of 20 ng/ml (50 nmol/L) meets the requirements of at least 97.5% of the population. Our results support earlier claims that participants with insufficient vitamin D status benefit from vitamin D supplementation (Bischoff-Ferrar 2009c; Holick 2008; Zittermann 2009).

Our review identified a possible difference between the two forms of supplemental vitamin D, that is, vitamin D_3 and vitamin D_2. Vitamin D_3 significantly decreased mortality while the effect of vitamin D_2 may be neutral or even detrimental. The World Health Organization has officially regarded these two forms as equivalent, based on the results of quite old studies on rickets prevention (World Health Organization 1950). Biological differences between vitamins D_3 and D_2 are found in some species such as birds and monkeys (Hoy 1988; Marx 1989). The evidence in humans has been sparse and contradictory. Currently, there is no routine clinical assay for measuring the serum concentrations of vitamin D_3 or vitamin D_2 (Norman 2008). Vitamin D status can be assessed only indirectly by measuring the circulating levels of 25-hydroxyvitamin D. The circulating 25-hydroxyvitamin D level is the sum of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 levels and, until recently, reference measurement procedures for determination of their levels did not exist (Tai 2010). A number of recently published clinical trials found evidence that vitamin D_3 increases serum 25-hydroxyvitamin D more efficiently than vitamin D_2 (Armas 2004; Leventis 2009; Romagnoli 2008; Trang 1998). An emerging body of evidence suggests several plausible explanations for this observation. The plasma half-life of vitamin D_3 is longer; and it has higher affinity to the vitamin D binding protein, hepatic vitamin D hydroxylase, and the vitamin D receptor (Holmberg 1986; Houghton 2006; Mistretta 2008). Vitamin D_3 is the only naturally occurring form of vitamin D produced endogenously in our body while vitamin D_2 can only be obtained from the diet (Norman 2008). Vitamin D_2 seems to upregulate several enzymes that degrade administered vitamin D_2 and endogenous D_3 (Heaney 2008). However, recent randomised clinical trial found that vitamin D_3 and vitamin D_2 were comparable in maintaining serum 25-hydroxyvitamin D levels (Holick 2008b). Our result could be of interest to the health policy makers in different countries. The predominant supplemental form of vitamin D in the United States is vitamin D_2 (Houghton 2006). In Europe, Japan, and Canada vitamin D supplements principally contain vitamin D_3 (Holick 2008), although in some of the European countries, like France and Great Britain, vitamin D_2 is also present on the market.

Another important finding of our review is that vitamin D_3 was beneficial in combination with calcium. The trial sequential analysis revealed that we need more randomised trials assessing the influence of vitamin D_3 combined with calcium on mortality to attain firm evidence of a 5% relative risk reduction, or to discard such an intervention effect, with the required information size. Vitamin D_3 administered singly had no statistically significant effect on mortality. Due to the small number of included trials these findings could be due to a type II error. Vitamin D_3 was tested singly in nine trials and combined with calcium in 25 trials. Our finding is in contrast to the result obtained by Autier et al (Autier 2007), who found that calcium supplements do not affect mortality, but in accordance with a recent meta-analysis (DIPART 2010) examining the influence of vitamin D on bone health. That meta-analysis concluded that vitamin D is effective in preventing hip fractures only if combined with calcium. The complex interactions between vitamin D and calcium make it difficult to separate their effects. The current recommendation for adequate intake of calcium for adults is in the range of 1000 mg to 1200 mg. The tolerable upper limit is 2000 mg (IOM 2011). The dosages used in the trials included in our meta-analysis are in accordance with the recommended intakes. In a majority of the included trials the primary outcome measure was bone health. Vitamin D and calcium are well recognised nutritional factors related to bone health. Fractures, especially in elderly people, are associated with increased mortality risk (Haentjens 2010). We speculate that by preventing fractures, especially in elderly people, vitamin D combined with calcium can indirectly decrease mortality. Our result fully concurs with the results of a recently published Cochrane review, which found that vitamin D singly could not prevent hip fracture but combined with calcium had a significant beneficial effect (Avenell 2009). However, Avenell et al (Avenell 2009) found no significant effect of vitamin D on mortality. A number of meta-analyses of randomised trials found that vitamin D combined with calcium could prevent falls and fractures (Bischoff-Ferrar 2005; Bischoff-Ferrar 2009a; Bischoff-Ferrar 2009b; Tang 2007). A recent meta-analysis (Bolland 2010) observed that calcium supplementation (without co-administration of vitamin D) is associated with an increased risk of myocardial infarction.

A further important finding of our review is that vitamin D_3 had a beneficial effect on mortality in dosages less than 800 IU a day. The cut-off value for dividing trials was the median daily dose of vitamin D_3 in the included trials (800 IU). The trial sequential analysis revealed that we may need more randomised trials assessing the influence of low doses of vitamin D_3 (less than 800 IU) on mortality in order to attain the required information size. A controversy persists about the optimal dosage of vitamin D. The

recommended daily intakes of vitamin D proposed by the Institute of Medicine are 600 IU per day for adults up to 70 years of age, and 800 IU per day for those aged 70 years and over (IOM 2011). Recent randomised trials and meta-analyses of randomised trials that have falls and fractures as a primary outcome measure have concluded that the reduction of risk for falls and hip and non-vertebral fractures is dose dependant (Bischoff-Ferrar 2009a; Bischoff-Ferrar 2009b; Bischoff-Ferrar 2009c). The Uppsala Longitudinal Study of Adult Men aimed to examine how vitamin D status relates to mortality (Michaëlsson 2010). The authors found a U-shaped association between vitamin D status and all-cause mortality as well as cancer mortality. Both high and low concentrations of plasma 25-hydroxyvitamin D were associated with elevated risks of mortality (Michaëlsson 2010). Those results warn us to be very cautious about the changes of dietary reference intake for vitamin D as suggested by some (Bischoff-Ferrar 2010).

It is still not known which route of administration and dosing schedules are optimal for vitamin D supplementation. We found that vitamin D_3 applied orally and daily had a beneficial effect on mortality. Other dosing schedules and routes of application (intermittently and parenterally) were without a statistically significant effect on mortality. This could be due to type II errors. Our results are in accordance with the result of the Chel et al (Chel 2008) randomised trial comparing daily, weekly, and monthly dosing of vitamin D_3. They found that daily dosing is more effective than weekly and monthly dosing.

We observed that vitamin D_2 may increase mortality in trials with a high risk of bias, as well as in the vitamin D insufficient participants. Those subgroup findings may be due to a random error and our trial sequential analysis supports this. Until more data become available, regulatory authorities need to consider how to handle this information.

We lack evidence for drawing conclusions about the influence of the active forms of vitamin D (alfacalcidol and calcitriol) on mortality. The available evidence suggests that alfacalcidol and calcitriol have no statistically significant effect on mortality risk. However, only few trials were conducted and type II errors are possible. We were not able to identify other meta-analyses or systematic reviews assessing the influence of alfacalcidol and calcitriol on mortality. A recent systematic review that examined the influence of alfacalcidol and calcitriol on falls and fractures found no significant effect on vertebral fractures, a beneficial effect on non-vertebral fractures and falls, as well as increased risk of hypercalcaemia (O'Donnell 2008). Active forms of vitamin D significantly increased hypercalcaemia in our review too.

We were not able to identify a specific cause of death responsible for the differences in overall mortality. Vitamin D had no significant effect on cardiovascular mortality but there was a trend toward decreased cancer mortality. There has been much debate in the literature about the possible beneficial effect of vitamin D on cardiovascular diseases (Holick 2004; Scragg 2010; Zittermann 2006; Zittermann 2010). Two recently published systematic reviews summarised the role of vitamin D in cardiovascular diseases (Pittas 2010; Wang 2010). Although the available evidence was promising, the effect of vitamin D on cardiovascular diseases remains uncertain (Pittas 2010; Wang 2010).

Pilz and coworkers recently reviewed the evidence on vitamin D status and cancer mortality (Pilz 2009b). They concluded that epidemiological data are inconsistently in favour of the hypothesis that optimal vitamin D status is related to decreased cancer mortality. However, they lacked randomised evidence to strengthen their conclusion (Pilz 2009b). Several mechanisms have been proposed to explain how vitamin D may modify cancer risk. Experimental studies revealed that vitamin D inhibits cellular proliferation and stimulates apoptosis (Artaza 2010; Pan 2010). A large number of observational studies have provided evidence suggesting that vitamin D may have a role in cancer prevention (Garland 2007; Gorham 2007; Schwartz 2007). The first evidence came from ecologic studies, which found an inverse relationship between exposure to sunlight and cancer risk (Apperly 1941; Garland 1980). However, some observational studies found that high vitamin D status was connected with increased oesophageal (Chen 2007), pancreatic (Stolzenberg 2006), breast (Goodwin 2009), and prostate cancer risks (Ahn 2008). One should consider the possibility of a U-shaped relation between vitamin D status and cancer risk (Toner 2010). Our results are in accordance with the conclusions of the recently published International Agency for Research on Cancer and Institute of Medicine reports that vitamin D status is not correlated with cancer incidence (IARC 2008; IOM 2011). We still lack evidence and we need more randomised trials to better understand the effect of vitamin D on cancer.

Vitamin D_3 combined with calcium significantly increased nephrolithiasis. Active forms of vitamin D significantly increased hypercalcaemia. Other adverse events, like elevated urinary calcium excretion; renal insufficiency; cardiovascular, gastrointestinal, psychiatric, or skin disorders, were not statistically significant influenced by vitamin D supplementation.

We lack sufficient evidence on the effect of vitamin D supplementation on health-related quality of life or the cost-effectiveness of vitamin D supplementation. However, vitamin D_3 products and calcium are cheap, with multiple producers across the world, so these interventions are likely to be cost-effective.

AUTHORS' CONCLUSIONS

Implications for practice

We found evidence that vitamin D_3 decreases mortality in predominantly elderly women, living independently or in institutional care. Vitamin D_3 combined with calcium seems to increase nephrolithiasis. Vitamin D_2, alfacalcidol, and calcitriol had no statistically significant beneficial effect on mortality. Alfacalcidol and

calcitriol seem to increase hypercalcaemia. Elevated urinary calcium excretion; renal insufficiency; cardiovascular, gastrointestinal, psychiatric, or skin disorders were not significantly influenced by vitamin D supplementation.

Implications for research

More randomised trials are needed on the effects of vitamin D_3 on mortality in younger, healthy persons and in males. We need more evidence before drawing final conclusions on the effect of vitamin D on cancer, especially when we consider the different forms of vitamin D used for supplementation. More randomised trials are needed testing the efficacy of vitamin D applied singly or in combination with calcium and comparing different doses of vitamin D_3. The effect of vitamin D on health-related quality of life and cost-effectiveness deserve further investigation.

ACKNOWLEDGEMENTS

We extend our gratitude to all participants and investigators in the randomised clinical trials. We are grateful to the many authors who kindly responded to our requests for further information on the trials they were involved in.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aloia 2005

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United States. Number of participants randomised: 208 healthy calcium-replete, black postmenopausal African American women, 50 to 75 (mean 60) years of age. African American ancestry of the participants was assessed by self-declaration that both parents and at least three of four grandparents were African American. Inclusion criteria: ambulatory postmenopausal African American women not receiving hormone therapy. Exclusion criteria: previous treatment with bone active agents and any medication or illness that affects skeletal metabolism.
Interventions	Participants were randomly assigned to receive: Intervention group: vitamin D_3 (800 IU) plus calcium (1200 to 1500 mg) daily, (n = 104); Control group: matched placebo plus calcium (1200 to 1500 mg) daily, (n = 104); for a two-year period. After two years, the vitamin D_3 dose was increased to 2000 IU daily in the intervention group, and the trial continued for an additional year. The calcium supplements were provided as calcium carbonate.
Outcomes	The primary outcome measure was the bone mineral density of the total hip.
Notes	"81 participants from the intervention group and 78 participants form the control group completed two years in the trial. 81 participants from the intervention group switched to vitamin D_3 2000 IU daily plus 1200 to 1500 mg of calcium daily after two years. 78 participants from the control group switched to matched placebo plus 1200 to 1500 mg of calcium daily after two years. 74 participants from the intervention group completed 36 months of trial. 74 participants from the control group completed 36 months of the trial. A total of 222 adverse events were reported in the trial over three years. There were 15 serious adverse events, eight in the intervention group and seven in the control group. Mean pill count compliance was 87% ± 8% of vitamin D_3 pills consumed after the randomisation visit." Vitamin D_3 capsules and matched placebo capsules were custom manufactured for the trial (Tishcon Corp, Westbury, NY). Vitamin D_3 content was also analysed in an independent laboratory (Vitamin D, Skin, and Bone Research Laboratory, Department of Medicine, Boston University School of Medicine, Boston, Mass). The calcium supplements were provided as calcium carbonate." Additional information on the risk of bias domains was received through personal communication with Dr John F Aloia (30.01.2009; 03.02.2009).

Aloia 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Avenell 2004

Methods	Randomised clinical trial using 2 x 2 factorial design.
Participants	Country: United Kingdom. Number of participants randomised: 134, aged 70 years or over (mean age 77), 83% women. Inclusion criteria: people aged 70 years or over with an osteoporotic fracture within the last 10 years. Exclusion criteria: daily oral treatment with more than 200 IU (5 μg) vitamin D or more than 500 mg calcium or other bone active medications.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) daily (n = 35); Intervention group 2: calcium (1000 mg) daily (n = 29); Intervention group 3: vitamin D_3 (800 IU) plus calcium (1000 mg) daily (n = 35); Intervention group 4 (Control group): no tablets daily (n = 35); for a one-year period.

Avenell 2004 (*Continued*)

	The calcium supplements were provided as calcium carbonate.
Outcomes	Primary outcomes were recruitment, compliance, and retention within a randomised trial.
Notes	"All participants were asked to return unconsumed tablets for a tablet count compliance. Compliance amongst those who returned their tablet containers was similar (overall 85% versus 84.5% of tablet takers took their tablets on more than 80% of days). The same pattern was observed for self-reported tablet consumption at four, eight or 12 months during the trial." "Shire Pharmaceuticals funded the capsules, which were co-funded and manufactured by Nycomed." Additional information on mortality was received through personal communication with Dr Alison Avenell (28.01.2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	High risk	Participants were told to which compound they had been allocated.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Participants were told to which compound they had been allocated. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	High risk	There are other factors in the trial that could put it at risk of bias.

Baeksgaard 1998

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (three intervention groups).
Participants	Country: Denmark. Number of participants randomised: 240 healthy postmenopausal women, 58 to 67

Baeksgaard 1998 (*Continued*)

	(mean 62.5) years of age. Inclusion criteria: Caucasian background, age 58 to 67 years, good general health and postmenopausal status defined as cessation of menstrual bleeding for at least six months. Exclusion criteria: treatment with estrogen or calcitonin during the previous 12 months or with bisphosphonates in the previous 24 months, presence of diseases known to affect bone metabolism, renal disease with serum creatinine above 120 mmol/L, and hepatic disease with increased alanine aminotransferase and/or decreased extrinsic coagulation factors II, VII and X.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (560 IU) plus calcium 1000 mg daily, (n = 80); Intervention group 2: vitamin D_3 (560 IU) plus calcium (1000 mg) plus multivitamin containing retinol 800 μg; thiamine 1.4 mg; riboflavine 1.6 mg; pyridoxine 2 mg; cyanocobalamine 1 μg; folic acid 100 μg; niacine 18 mg; pantothenic acid 6 mg; biotin 150 μg; ascorbic acid 60 mg; D-alpha tocopherol 10 mg; and phylloquinone 70 μg; daily, (n = 80); Intervention group 3 (Control group): matched placebo in a similar combination daily (n = 80); for a two-year period. Participants were asked to take no calcium or vitamin D supplement other than the supplement supplied for the trial. Calcium was in the form of calcium carbonate.
Outcomes	The primary outcome was changes from baseline in the bone mineral density (BMD) in the lumbar spine (L2-4). Secondary outcome measures were hip BMD, forearm BMD, serum calcium, serum phosphate and serum intact parathyroid hormone.
Notes	"For all variables measured, authors observed no significant differences between the two experimental intervention groups. In presenting the results, authors, therefore, considered the two groups as one group. During the trial, 41 of the 240 women dropped out. No significant difference in drop-out rate was found between the groups. One hundred and ninety-nine women completed all visits. In the analysis, an additional two women were excluded due to development of radiologically verified vertebral fractures in the lumbar spine. No formal assessment of compliance, such as tablet counting, was made. At each visit, the participants were questioned about their compliance with the trial medication and encouraged to comply." All placebo and active treatment tablets were provided by Lube Ltd.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.

Baeksgaard 1998 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described
Selective reporting (reporting bias)	High risk	Not all pre-defined or clinically relevant and reasonably expected outcomes are reported on, or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Bischoff 2003

Methods	Randomised, double-blind, controlled trial using parallel group design (two intervention groups).
Participants	Country: Switzerland. Number of participants randomised: 122 elderly women in long-stay geriatric care, aged 60 years or older (mean age 85.3 years). Inclusion criteria: age 60 or older and the ability to walk three meters with or without a walking aid. Exclusion criteria: primary hyperparathyroidism, hypocalcaemia, hypercalciuria, renal insufficiency, and fracture or stroke within the last three months, any treatment with hormone replacement therapy, calcitonin, fluoride, or bisphosphonates during the previous 24 months.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) plus calcium 1200 mg daily (n = 62); Intervention group 2 (Control group): calcium 1200 mg daily (n = 60); for a three-month period.
Outcomes	The primary outcome measure was number of falls per person. Secondary outcome measures were musculoskeletal function and bone remodeling.

Notes	"Tablets containing vitamin D and calcium or calcium alone were taken in the presence of the trial nurse to ensure compliance." The trial was supported by Strathmann AG, Germany. Authors reported deaths but not according to intervention group of the trial. All-cause mortality data was taken from a Cochrane systematic review prepared by Avenell et al (Avenell 2009) who obtained mortality data by personal communication with Bischoff trial authors.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by sealed envelopes so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. "Tablets in both groups had an identical appearance. Participants, nurses, and all investigators were blinded to the intervention assignment throughout the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	High risk	There are other factors in the trial that could put it at risk of bias. The trial was supported by Strathmann AG, Germany.

Bjorkman 2007

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (three intervention groups).
Participants	Country: Finland. Number of participants randomised: 218 chronically bedridden patients (81.7 % women), 65 to 104 (mean 84.5) years of age. Inclusion criteria: age over 65 years, chronically impaired mobility, stable general condition, and no known present disease (except osteoporosis) or medication (vitamin D supplements, glucocorticoids, antiepileptics, etc.) affecting calcium or bone metabolism. Exclusion criteria: markedly elevated creatinine levels (> 125 µmol/L) hypercalcaemia (ionised calcium > 1.32 mmol/L), hypothyroidism (thyrotropin > 5.3 mU/L) or hyperthyroidism (thyrotropin < 0.2 mU/L).
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (1200 IU) daily, (n = 73); 17 participants from this group received calcium 500 mg daily; Intervention group 2: vitamin D_3 (400 IU) daily, (n = 77); 11 participants from this group received calcium 500 mg daily; Intervention group 3 (Control group): matched placebo vitamin D_3 (0 IU) daily (n = 68), 15 participants from this group received calcium 500 mg daily; for a six-month period. "Participants received vitamin D_3 (Vigantol, Merck KGaA, Darmstadt, Germany 20,000 IU/ml in Migliol oil) in doses of 0 µg, 140 µg, or 420 µg (groups 1, 2, 3) every 2 weeks, equivalent with average daily intakes of 0 IU, 400 IU, or 1200 IU. To ensure that all three groups received identical volumes (26 drops = 0.84 ml), medication oil was diluted three-fold with Migliol oil in group 2, and group 1 received plain Migliol oil. Furthermore, the oil was swallowed entirely in the presence of the nurse and given with a small amount of food or drink, if necessary." "Before the start of the intervention, the use of dairy products was roughly evaluated to be insufficient among 40 patients, who received a daily calcium carbonate substitution of 500 mg during the intervention. Three other patients also received a previous daily medication of 500 mg calcium carbonate at entry, which they continued to receive through the intervention."
Outcomes	The primary outcome measures were parathyroid function and bone turnover.
Notes	"Vitamin D supplementation was well tolerated. One patient, however, developed a mild hypercalcaemia (ionised calcium from 1.24 to 1.40 mmol/L) in group 3." Treatment agents were produced by Vigantol, Merck KGaA, Darmstadt, Germany. Authors did not provide data about compliance. Additional information on the risk of bias domains was received through personal communication with Dr Mikko Björkman (31.01.2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.

Bjorkman 2007 (*Continued*)

Allocation concealment (selection bias)	Low risk	"Allocation was controlled by coded bottles. Each bottle was individually coded to blind the participants and the ward nurses of not only the content of the bottles but also of the group labels (1, 2, 3)."
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Bolton-Smith 2007

Methods	Randomised, double-blind, placebo controlled trial using 2 x 2 factorial design.
Participants	Country: United Kingdom. Number of participants randomised: 244 healthy, nonosteoporotic women, aged 60 years or over (mean 68). Inclusion criteria: healthy, non-osteoporotic women, aged 60 years or over. Exclusion criteria: clinical osteoporosis or chronic disease (e.g., diabetes mellitus, cardiovascular disease, cancer, fat malabsorption syndromes), routine medication that interferes with vitamin K, vitamin D, or bone metabolism (notably warfarin and steroids) , and consumption of nutrient supplements that provided in excess of 30 µg vitamin K, 400 IU vitamin D, or 500 mg calcium daily.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (400 IU) plus calcium 1000 mg daily, (n = 62); Intervention group 2: vitamin D_3 (400 IU) plus calcium 1000 mg plus vitamin K_1 200 μg daily, (n = 61); Intervention group 3: vitamin K_1 200 μg daily (n = 60); Intervention group 4 (Control group): matched placebo daily (n = 61); for a two-year period.
Outcomes	The primary outcome measure was bone mineral density. Secondary outcome measure was possible interaction with vitamin K, of vitamin D and calcium.

Bolton-Smith 2007 (*Continued*)

Notes	"Of the 244 eligible women randomised in the trial, 209 (85.6%) completed the two-year trial. Compliance with the trial intervention was good based on pill count (median, 99; interquartile range, 97.3 to 99.8%)." Hoffmann-La Roche (Basel, Switzerland) provided the supplementation tablets. Additional information on mortality, adverse events, and risk of bias domains was received through personal communication with Dr Martin J Shearer (03.02.2009; 05.02.2010).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. "An independent statistician at Hoffmann-La Roche, who had no other connection to the trial, provided a randomisation list to the researchers."
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Brazier 2005

Methods	Multicentre, randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: France. Number of participants randomised: 192 women with a 25-hydroxyvitamin D level $\leq$ 12 ng/mL, mean age 74.6 years.

	Inclusion criteria: community-dwelling ambulatory women aged > 65 years who spontaneously consulted a practitioner and presented with vitamin D insufficiency (i.e., serum 25-hydroxy vitamin D $\leq$ 12 ng/mL). Exclusion criteria: hypercalcaemia (serum calcium > 2.62 mmol/L), primary hyperparathyroidism, renal insufficiency (serum creatinine >130 pmol/L), hepatic insufficiency, treatment with a bisphosphonate, calcitonin, vitamin D or its metabolites, estrogen, raloxifene, fluoride, anticonvulsives, or any other drug acting on bone metabolism (e.g., glucocorticoids) in the past six months.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) plus calcium (1000 mg) daily (n = 95); Intervention group 2 (Control group): matched placebo tablets (n = 97); for a one-year period.
Outcomes	The primary outcome was to assess the effects of vitamin D_3 plus calcium on bone mineral density and biochemical markers of bone formation and resorption. Secondary outcome was to evaluate the clinical and laboratory safety of treatment.
Notes	Fifty women (21/95 vitamin D plus calcium, 29/97 placebo) were prematurely withdrawn from the trial for various reasons. Treatment-related adverse events were reported in 21 and 23 women in the respective intervention groups. These events consisted mainly of metabolic disorders (9 and 10), particularly hypercalcaemia (6 and 8) and gastrointestinal disorders (9 and 8). "Treatment compliance was assessed at each visit based on counts of the number of tablets taken compared with the number that was to be taken. Compliance at each visit ranged from a median of 93% to 94% in the vitamin D plus calcium group and from 93% to 96.5% in the placebo group. Global compliance was 92% in the vitamin D plus calcium group and 92.5% in the placebo group. No significant difference in compliance was observed between the two groups at any visit." This trial was supported by Innothera Laboratories, Arcueil, France.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.

Brazier 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	High risk	There are other factors in the trial that could put it at risk of bias. This trial was supported by Innothera Laboratories, Arcueil, France.

Broe 2007

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (five intervention groups).
Participants	Country: United States. Number of participants randomised: 124 nursing home residents (73% women), mean 89 years of age. Inclusion criteria: a life expectancy of at least six months, the ability to swallow medication, and three months residency at Hebrew Rehabilitation Center for the Aged. Exclusion criteria: use of glucocorticoids, anti-seizure medication, or pharmacological doses of vitamin D; calcium metabolism disorders; severe mobility limitations; or fracture within the previous six months.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 (800 IU) daily (n = 23); Intervention group 2: vitamin D_2 (600 IU) daily (n = 25); Intervention group 3: vitamin D_2 (400 IU) daily (n = 25); Intervention group 4: vitamin D_2 (200 IU) daily (n = 26); Intervention group 5 (Control group): matched placebo tablets daily (n = 25); for a five-month period.
Outcomes	The primary outcome measure was effect of the vitamin D doses on falls over the trial period.
Notes	"Over the 5-month trial period, 114 completed the trial. Of the 10 participants who did not complete the trial, seven died and three withdrew. There were no significant differences between the intervention groups in the number who did not complete the 5-month trial period with a loss of one to three participants from each intervention group." "Compliance was calculated as the number of pills taken, as determined according to blister pack counts after the completion of the trial divided by the total days a participant was actively participating (alive, living at Hebrew Rehabilitation Center for Aged, not withdrawn from the trial)." "Average compliance was 97.6%, with only two participants having a compliance level of less than 50%. Compliance did not differ between the intervention groups."

	The vitamin D_2 tablets were purchased from Tishcon Corporation (Westbury, NY). Vitamin D content of the supplements was verified at the BU Vitamin D Laboratory.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. "The pharmacy of The Hebrew Rehabilitation Center for the Aged randomised participants in blocks of 15 to one of the five intervention groups."
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. "The pharmacy labelled pill blister packs with names and patient identification numbers only. Blister packs and tablets from all five groups were identical in appearance and taste, so nursing staff, participants, and the trial team were unaware of the group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Burleigh 2007

Methods	Randomised, double-blind, controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 205 (59 % women), aged 65 years or over (mean age 83), acute admissions to a geriatric medical unit. Inclusion criteria: patients newly transferred or admitted into the general assessment and rehabilitation wards in an acute geriatric unit aged 65 years or over. Exclusion criteria: known hypercalcaemia, urolithiasis or renal dialysis therapy, terminal or bed-bound patients with a reduced Glasgow Coma Scale, those already prescribed vitamin D supplements and calcium, and those who were deemed 'nil by mouth'.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) plus calcium (1200 mg) daily (n = 101); Intervention group 2 (Control group): calcium (1200 mg) daily (n = 104); for a 30-day period.
Outcomes	The primary outcomes were numbers of fallers and falls.
Notes	"Vitamin D and calcium were well tolerated in the total trial cohort with a median compliance level of 88%." Strakan Pharmaceuticals supplied all trial drugs free of charge.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using a random number table.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. Randomisation was known only to the statistician and pharmacist.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. "Statistician and pharmacist subsequently issued an appropriate uniquely numbered drug blister pack to each patient's ward. Thereafter, trained staff nurses administered trial drugs as part of routine drug rounds. The researchers, therapists, and patients remained blinded to trial drug allocation."

Burleigh 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Campbell 2005

Methods	Randomised controlled trial using 2 x 2 factorial design. The VIP (visual impairment) trial.
Participants	Country: New Zealand. Number of participants randomised: 391 elderly people (68 % women) aged 75 to 96 (mean 83.6) years, with visual acuity of 6/24 or worse, who were living in the community. Inclusion criteria: elderly people aged 75 years or over with visual acuity of 6/24 or worse who were living in the community. Exclusion criteria: those who could not walk around their own residence, who were receiving physiotherapy at the time of recruitment, or could not understand the trial requirements.
Interventions	Participants were randomly assigned to receive: Intervention group 1: home safety assessment and modification programme delivered by an occupational therapist (n = 100); Intervention group 2: an exercise programme prescribed at home by a physiotherapist plus vitamin D_3 100,000 IU initially and then 50,000 IU monthly (n = 97); Intervention group 3: both interventions (intervention 1 plus intervention 2) (n = 98); Intervention group 4 (Control group): social visits (n = 96); for a one-year period. The one-year exercise intervention consisted of the specific muscle strengthening and balance retraining exercises that progress in difficulty and a walking plan, modified for those with severe visual acuity loss, with vitamin D supplementation. The home safety assessment and modification programme was specifically designed for people with severe visual impairments. The occupational therapist visited the person at home and used a home safety assessment checklist to identify hazards and to initiate discussion with the participant about any items, behaviour, or lack of equipment that could lead to falls. Research staff made two home visits lasting an hour each during the first six months of the trial to participants in intervention group four.
Outcomes	The primary outcome measures were number of falls and number of injuries resulting from falls. Secondary outcome measure was costs of implementing the home safety programme.

Campbell 2005 (*Continued*)

Notes	Additional information received through personal communication with Professor John Campbell (19.02.2010).	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using a random number table.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. "The schedule was held by an independent person at a separate site and was accessed by a research administrator for the trial, who telephoned after each baseline assessment was completed. The administrator then informed the occupational therapist, physiotherapist, or social visitor, who delivered the assigned intervention to that participant where possible within the next two weeks."
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Chapuy 1992

Methods	Vitamin D, Calcium, Lyon Study I (DECALYOS I). Randomised, double-blind, placebo controlled trial using parallel group design (two intervention groups).

Chapuy 1992 (*Continued*)

Participants	Country: France. Number of participants randomised: 3270, 69 to 106 (mean 84) years of age, healthy ambulatory women. Inclusion criteria: ambulatory woman (with activity levels ranging from going outdoors easily to walk indoors with a cane or a walker), with no serious medical conditions, and with a life expectancy of at least 18 months. Exclusion criteria: receiving drugs known to alter bone metabolism, such as corticosteroids, thyroxine, or anticonvulsant drugs within the past year, women who had been treated with fluoride salts for more than three months, or with vitamin D or calcium during the previous six months or for more than one year within the past five years.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) plus calcium (1200 mg) daily (n = 1634); Intervention group 2 (Control group): double placebo daily (n = 1636); for a 18 month period. Participants were followed for four years. Calcium was in a form of tricalcium phosphate powder in an aqueous suspension. Placebo pills contained lactose and suspension of lactose, kaolin, and starch. The supplements were taken in the presence of a nurse to ensure compliance.
Outcomes	The primary outcome was frequency of hip fractures and other nonvertebral fractures, identified radiologically.
Notes	Duphar and Company Laboratories provided the vitamin D_3 (Devaron), and Merck-Clevenot Laboratories provided the tricalcium phosphate (Ostram). Additional information on mortality was received through personal communication with Professor Pierre Meunier (27.02.2010).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.

Chapuy 1992 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Chapuy 2002

Methods	Vitamin D, Calcium, Lyon Study II (DECALYOS II). Multicenter, randomised, double-blind, placebo controlled trial using parallel group design (three intervention groups).
Participants	Country: France. Number of participants randomised: 610, 64 to 99 (mean 85) years of age, healthy ambulatory women. Inclusion criteria: ambulatory woman (able to walk indoors with a cane or a walker) and life expectancy of at least 24 months. Exclusion criteria: intestinal malabsorption, hypercalcaemia (serum calcium 42.63 mmol/L) or chronic renal failure (serum creatinine 4150 mmol/L), receiving drugs known to alter bone metabolism, such as corticosteroids, anticonvulsants, or a high dose of thyroxine within the past year, treatments with fluoride salts (43 months), bisphosphonates, calcitonin (41 month), calcium (4500 mg/day), and vitamin D (4100 IU/day) during the last 12 months.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) plus calcium (1200 mg) daily (fixed combination) (n = 199); Intervention group 2: vitamin D_3 (800 IU) plus calcium (1200 mg) daily (separate combination) (n = 194); Intervention group 3 (Control group): double placebo daily (n = 190); for a two-year period. "The sachet of the calcium-vitamin D_3 fixed combination (Ostram-vitamin D_3, Merck KGaA) contains a fixed combination of 1200 mg elemental calcium in the form of tricalcium phosphate and 800 IU of vitamin D_3. The calcium (Ostram, Merck KGaA) contains 1200 mg of elemental calcium in the form of tricalcium phosphate. Vitamin D_3 (Devaron, i.e., cholecalciferol, Duphar Solvay) was given in two pills of 400 IU each. Each day women in intervention groups one and two received 1200 mg of elemental calcium and 800 IU of vitamin D_3 given either by a sachet of calcium-vitamin D_3 fixed combination (Ca-D_3 group) or as a sachet of calcium and two tablets of vitamin D_3 (Ca+D_3 group). The other women received a placebo of vitamin D_3 and calcium (one sachet containing lactose, microcrystalline cellulose and the same excipient as the active treatment and two tablets of vitamin D_3 placebo)."

Chapuy 2002 (*Continued*)

Outcomes	The primary outcomes were biochemical variables of calcium homeostasis, femoral neck bone mineral density, and hip fracture risk.
Notes	"The supplements were taken in the presence of a nurse to ensure compliance. The mean compliance was more than 95% for both sachets and tablets in each treatment group." The trial was sponsored by MERCK KGaA, Darmstadt, Germany. Additional information on mortality was received through personal communication with Professor Pierre Meunier (27.02.2010).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	High risk	There are other factors in the trial that could put it at risk of bias. The trial was sponsored by MERCK KGaA, Darmstadt, Germany.

Chel 2008

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (six intervention groups).
Participants	Country: the Netherlands. Number of participants randomised: 338 (77 % women), aged 70 years or over (mean age 84), nursing home residents. Inclusion criteria: nursing home residents aged 70 years or over. Exclusion criteria: going outside in the sunshine more than once a week, the use of vitamin D or calcium supplementation, the use of more than one vitamin D fortified food or drink per day, complete immobilisation and a very poor life expectancy.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (600 IU) daily (n = 55); Intervention group 2 (control group): matched placebo tablet daily (n = 57); Intervention group 3: vitamin D_3 (4200 IU) weekly (n = 54); Intervention group 4 (Control group): matched placebo tablets weekly (n = 58); Intervention group 5: vitamin D_3 (18,000 IU) powder monthly (n = 57); Intervention group 6 (Control group): matched placebo powder monthly (n = 57); for a four and a half month period. The treatment period of four and a half months was completed by 276 out of 338 participants. The 276 participants who completed the vitamin D intervention trial were randomly assigned to receive: Intervention group: calcium 800 mg or 1600 mg daily (n = 138); Control group: matched placebo tablet daily (n = 138); for the period of 14 days. The treatment was completed by 269 participants. The first 156 randomised participants received 800 mg calcium carbonate or placebo; the subsequent 120 participants received 1600 mg calcium carbonate or placebo.
Outcomes	The primary outcome was to assess efficacy of different doses and intervals of oral vitamin D_3 supplementation with the same total dose. Secondary outcome measure was to assess the additional effect of calcium supplementation following vitamin D supplementation on serum parathyroid hormone and markers of bone turnover.
Notes	"The trial medication was centrally distributed to ensure compliance. Random samples of the returned medication were counted in order to verify compliance." "The compliance assessed within 96 random samples of the returned medication was good. In the daily administration group, all 33 participants were compliant, used at least 80% of the tablets. For weekly administration, 80% of the 35 participants were compliant, used at least 80% of the tablets. For monthly administration, 93% of the 28 participants were compliant, used at least four out of five powders." Solvay Pharmaceuticals supplied the research medication.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Chel 2008 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was described as double blind, but the method of blinding was not described so that knowledge of allocation was possible during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Cooper 2003

Methods	Randomised, double-blind, placebo controlled trial using parallel group design (two intervention groups).
Participants	Country: Australia. Number of participants randomised: 187 healthy, white, postmenopausal women, mean age 56 years. Inclusion criteria: healthy, white women who were postmenopausal for one to ten years, and who were not receiving hormone replacement therapy. Exclusion criteria: malignant disease, renal, hepatic, endocrine, or gastrointestinal disorder associated with abnormal calcium metabolism, use of oestrogen, progesterone, glucocorticoids, anticonvulsants, thiazide diuretics, vitamin D supplements, or other medications known to affect calcium or bone metabolism in the previous 12 months. Participants with laboratory evidence of renal, hepatic, or endocrine disorder; a serum follicle-stimulating hormone concentration < 40 mIU/mL, or bone mineral density at any site ± 2 standard deviation from the mean for potential participant matched for age were also excluded.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 (10,000 IU) weekly plus calcium (1000 mg) daily (n = 93);

	Intervention group 2 (Control group): calcium (1000 mg) daily (n = 94); for a two-year period. Calcium was in a form of tricalcium phosphate powder in an aqueous suspension.
Outcomes	The primary outcome was bone mineral density.
Notes	"Compliance was assessed by tablet counts and diary review. Compliance with treatment was 98.2 ± 6.1% for the calcium plus vitamin D group and 97.7 ± 5.4% for the calcium group." Vitamin D_2 was provided by Ostelin; Boots Healthcare Pharmaceuticals, Sydney, Australia. Calcium carbonate was provided by Cal-Sup; 3M Pharmaceutical, Sydney, Australia. Additional information on mortality and risk of bias domains was received through personal communication with Professor Philip Clifton-Bligh (12.11.2007; 08.02.2010) .

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Corless 1985

Methods	Randomised double-blind placebo controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 65, elderly hospital patients (78% women), mean age 82.4 years. Inclusion criteria: elderly hospital patients. Exclusion criteria: overt clinical osteomalacia, either plasma calcium less than 1.95 mmol/L or Looser's zones, or on calciferol therapy; a judgement that he or she was unlikely to be able to co-operate in the trial; plasma creatinine more than 150/mmol/L, potassium less than 3.3 mmol/L; plasma 25(OH)D more than 40nmol/L (16ng/ml); refused consent or unable to give informed consent.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 (9000 IU) daily (n = 32); Intervention group 2 (Control group): matching placebo tablets daily (n = 33); for a nine-month period. Placebo tablets were identical in appearance to the vitamin D_2 tablets containing lactose.
Outcomes	The primary outcome measure was abilities of elderly hospital patients to carry out basic activities of daily life.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.

Free of other bias?	Unclear risk	The trial may or may not be free of other components that could put it at risk of bias.

Daly 2008

Methods	Randomised controlled trial using parallel group design (two intervention groups).
Participants	Country: Australia. Number of participants randomised: 167 ambulatory community living men 50 to 87 (mean 61.9) years of age. Inclusion criteria: ambulatory community living men aged 50 years or over. Exclusion criteria: taking calcium and/or vitamin D supplements in the preceding 12 months, participating in regular high-intensity resistance training in the previous six months or more, then 150 minutes a week of moderate- to high-impact weight-bearing exercise, had a body mass index > 35 kg/m^2, lactose intolerance, consuming more than four alcoholic beverages per day, a history of osteoporotic fracture or medical disease, or medication use that is known to affect metabolism of bones.
Interventions	Participants were randomly assigned to receive: Intervention group 1: calcium-vitamin D_3-fortified milk containing vitamin D_3 (800 IU) plus calcium (1000 mg) daily (n = 85); Intervention group 2 (Control group): usual diet (n = 82); for a two-year period. Participants were followed for additional a year and a half.
Outcomes	The primary outcome measure was bone mineral density.
Notes	"To monitor milk compliance, participants were asked to record the number of tetra packs consumed per day on a compliance calendar, which was collected and checked every three months. Compliance proportion (expressed as a percentage) was calculated as the actual number of tetra packs consumed, divided by the expected consumption each month. The overall mean reported milk compliance, calculated as the percentage of the tetra packs consumed and based on daily diaries was 85.1%. Milk was specifically formulated by Murray Goulburn Cooperative Co. (Brunswick, Australia). The added milk calcium salt (Natra-Cal) was prepared by Murray Goulburn Cooperative Co. The vitamin D (Vitamin D_3) used to fortify the milk was obtained from DSM Nutritional Products Pty (NSW, Australia)." Additional information on mortality was received through personal communication with Professor Robin Daly (04.02.2009).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using a random number table.

Daly 2008 (*Continued*)

Allocation concealment (selection bias)	High risk	The allocation sequence was known to the investigators who assigned participants.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Dawson-Hughes 1997

Methods	Boston STOP IT (Sites Testing Osteoporosis Prevention Intervention Treatment). Randomised, double-blind, placebo controlled trial using parallel group design (two intervention groups).
Participants	Country: United States. Number of participants randomised: 389, healthy, ambulatory participants (55% women), aged 65 years or older (mean 71). Inclusion criteria: healthy, ambulatory men and women 65 years of age or older. Exclusion criteria: current cancer or hyperparathyroidism; a kidney stone in the past five years; renal disease; bilateral hip surgery; therapy with a bisphosphonate, calcitonin, estrogen, tamoxifen, or testosterone in the past six months or fluoride in the past two years; femoral-neck bone mineral density more than 2 SD below the mean for participants of the same age and sex; dietary calcium intake exceeding 1500 mg per day; and laboratory evidence of kidney or liver disease.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (700 IU) plus calcium (500 mg) daily (n = 187); Intervention group 2 (Control group): matched placebo tablets daily (n = 202); for a three-year period. Calcium was in the form of calcium citrate malate. Placebo pills contained microcrystalline cellulose.
Outcomes	The primary outcome measures were bone mineral density, biochemical measures of bone metabolism, and the incidence of nonvertebral fractures.
Notes	Procter & Gamble, Cincinnati manufactured calcium tablets. Additional information on mortality was received through personal communication with Professor Bess Dawson-Hughes (04.02.2009).

Dawson-Hughes 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Dukas 2004

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: Switzerland. Number of participants randomised: 378 (51% women), mean age 71 years, community-dwelling elderly people. Inclusion criteria: community-dwelling elderly people who are mobile and have an independent life style. Exclusion criteria: primary hyperparathyroidism, polyarthritis or inability to walk, calcium intake by supplement of more than 500 mg daily, vitamin D intake of more than 200 IU daily, active kidney stone disease, history of hypercalcuria or cancer or other incurable diseases, dementia, elective surgery within the next three months, severe renal insufficiency (creatinine clearance < 20 mL/min, and fracture or stroke within the last 3 months. Calcium supplementation of 500 mg/d or less was accepted.

Dukas 2004 (*Continued*)

Interventions	Participants were randomly assigned to receive: Intervention group 1: 1 α(OH)D3 (alfacalcidol), (1 μg) daily (n = 192); Intervention group 2 (Control group): placebo (n = 186); for a nine-month period.
Outcomes	The primary outcome measure was number of fallers. Secondary outcome measures were muscle strength, balance, blood pressure, and bone quality.
Notes	Trial medication was provided by TEVA Pharmaceuticals Industries Ltd, Israel. Additional information on the risk of bias domains was received through personal communication with Dr Laurent C Dukas (28.01.2010).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. "An independent statistical group performed the blinding and randomisation. All investigators and staff conducting the trial remained blinded throughout the intervention period."
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Flicker 2005

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: Australia. Number of participants randomised: 625, older residents (mean age 83.4), 95% females, with serum 25-hydroxyvitamin D levels between 25 and 90 nmol/L. Inclusion criteria: older people resident in hostels and nursing homes with serum 25-hydroxyvitamin D levels between 25 and 90 nmol/L. Exclusion criteria: use of agents that could affect bone and mineral metabolism, such as warfarin, chronic heparin therapy, vitamin D therapy within the previous three months, glucocorticoids at an average daily dose of greater than 5 mg prednisolone (or equivalent) for more than one month within the preceding year, current use of bisphosphonates, and hormone replacement therapy, thyrotoxicosis within the previous three years, primary hyperparathyroidism treated within the previous three years, multiple myeloma, Paget's disease of bone, history of malabsorption, intercurrent active malignancy, and other disorders affecting bone and mineral metabolism.
Interventions	Participants were randomly assigned to receive: Intervention group: vitamin D_3 (10000 IU) weekly until November 1998 and thereafter vitamin $D_3$1000 IU daily plus calcium (600 mg) daily (n = 313); Control group: calcium (600 mg) (n = 312); for a two-year period.
Outcomes	The primary outcomes were falls and fractures.
Notes	"Supplements and placebos were purchased commercially, and the suppliers played no role in the trial design or in the collection, analysis, or interpretation of data."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. An individual who was not involved in contact with the participants or the residential care institutions performed randomisation.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. "Participants were randomised

Flicker 2005 (*Continued*)

		to receive sequentially numbered bottles containing vitamin D or placebo. Both interventions had matching placebo preparations given in identical fashion, and residents, institutional staff, and trial staff were blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Gallagher 2001

Methods	Sites Testing Osteoporosis Prevention / Intervention Treatment (STOP IT). Randomised, double-blind, placebo-controlled trial using 2 x 2 factorial design.
Participants	Country: United States. Number of participants randomised: 489 healthy elderly women 65 to 77 (mean 71.5) years of age. Inclusion criteria: healthy elderly women 65 to 77 years of age and femoral neck density within the normal range for their age. Exclusion criteria: severe chronic illness, primary hyperparathyroidism or active renal stone disease, and were on certain medications, such as bisphosphonates, anticonvulsants, oestrogen, fluoride, or thiazide diuretics in the previous 6 months.
Interventions	Participants were randomly assigned to receive: Intervention group 1: calcitriol (0.5 μg) daily (n = 123); Intervention group 2: conjugated oestrogens (Premarin) 0.625 mg/daily plus medroxyprogesterone acetate (Provera) 2.5 mg daily (n = 121); Intervention group 3: calcitriol (0.5 μg) plus conjugated oestrogens daily; (Premarin) 0.625 mg/daily plus medroxyprogesterone acetate (Provera) 2.5 mg daily (n = 122); Intervention group 4 (Control group): matched placebo daily (n = 123); for a three-year period.
Outcomes	The primary outcome measure was the change in bone mineral density of the femoral neck and spine. Secondary outcome measure was incidence of nonvertebral fractures.
Notes	"Compliance to trial medication was evaluated by pill counts. At 36 months, treatment group differences in adherence to assigned therapy were evident, with 78% of those assigned to placebo, 70% of those assigned to calcitriol, 65% of those assigned to HRT/ERT and 62% of those assigned to HRT/ERT calcitriol still adherent to their assigned

Gallagher 2001 (*Continued*)

	medication. Among those still on medication the compliance for the groups calculated at six months and compared with 36 months, respectively, was: conjugated estrogens, 86% and 92%; medroxyprogesterone acetate, 91% and 94%; calcitriol, 87% and 93%; placebos, 94% and 92%." The active trial drug and placebo were supplied by Wyeth-Ayerst Laboratories, Inc Pharm, Hoffman-LaRoche Inc and Pharmacia & Upjohn, Inc. Additional information on mortality and risk of bias domains was received through personal communication with Dr John Gallagher (09.02.2009; 11.03.2010).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. An independent statistical group performed the blinding and randomisation.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Grady 1991

Methods	Randomised, double-blind, controlled trial using parallel group design (two intervention groups).
Participants	Country: United States. Number of participants randomised: 98 elderly ambulatory men and women (54%)

Grady 1991 (*Continued*)

	women, aged 70 to 97 (mean 79.1) years of age. Inclusion criteria: elderly ambulatory men and women. Exclusion criteria: serum calcium levels of 2.57 mmol/L or more, urinary calcium levels of 7.28 mmol/day or more, creatinine clearance less than 0.42 mmol/s, history of hypercalcaemia, nephrolithiasis, seizure disorder, hyperparathyroidism, treatment with calcium, vitamin D or thiazide diuretics, and average calcium intake greater than 1000 mg/day.
Interventions	Participants were randomly assigned to receive: Intervention group 1: calcitriol (0.5 μg) daily (n = 50); Intervention group 2 (Control group): placebo vitamin D (n = 48); for a six-month period.
Outcomes	The primary outcome measure was muscle strength.
Notes	"Participants were evaluated at 1, 2, 4, 8, 12, 18, and 24 weeks of intervention regimen to maintain compliance. Participants in both groups took more than 95% of the assigned medication." Calcitriol and placebo capsules were provided by Hoffman-LaRoche (Nutley, NJ).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.

Grady 1991 (*Continued*)

Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Grant 2005

Methods	Randomised Evaluation of Calcium Or vitamin D (RECORD). Multicentre, randomised, double-blind, placebo-controlled trial using 2 x 2 factorial design.
Participants	Country: United Kingdom. Number of participants randomised: 5292 people (85% women) aged 70 and over (mean 77 years) with low-trauma, osteoporotic fracture in the previous 10 years. Inclusion criteria: elderly people aged 70 years or older, who were mobile before developing a low-trauma fracture. Exclusion criteria: bed or chair bound before fracture; cognitive impairment indicated by an abbreviated mental test score of less than seven; cancer in the past 10 years that was likely to metastasise to bone; fracture associated with pre-existing local bone abnormality; those known to have hypercalcaemia; renal stone in the past 10 years; life expectancy of less than 6 months; individuals known to be leaving the United Kingdom; daily intake of more than 200 IU vitamin D or more than 500 mg calcium supplements; intake in the past 5 years of fluoride, bisphosphonates, calcitonin, tibolone, hormone-replacement therapy, selective oestrogen-receptor modulators, or any vitamin D metabolite (e.g., calcitriol); and vitamin D by injection in the past year.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) daily (n = 1343); Intervention group 2: calcium (500 mg) daily (n = 1311); Intervention group 3: vitamin D_3 (800 IU) plus calcium (500 mg) daily (n = 1306); Intervention group 4 (Control group): matched placebo tablets (n = 1332); for a 45 month period. Participants were followed for a period of five years. Tablets varied in size and taste, and thus each had matching placebos.
Outcomes	The primary outcome measure was all-new low-energy fractures including clinical, radiologically confirmed vertebral fractures, but not those of the face or skull.
Notes	"Compliance was measured by a postal questionnaire sent every four months, in which participants were asked how many days of the past seven days they had taken tablets. A randomly selected 10% sample was asked to return unused tablets for pill counting. Based on questionnaire responses at 24 months, 2886 (54,5%) of 5292 were still taking tablets. Throughout the trial about 80% of those taking tablets did so on more than 80% of days, which is consistent with pill counts in the subsample (data not shown). However, the number who were taking any tablets fell over time. At 24 months, 2268 of 4841 (46,8%), who returned questionnaires, had taken pills on more than 80% of days." Shire Pharmaceuticals co-funded the drugs, with Nycomed, who also manufactured the drugs. Additional information received through personal communication with Dr Alison

Grant 2005 (*Continued*)

	Avenell (02.02.2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. "Allocation was controlled by a central and independent randomisation unit. The allocation programme was written by the trial programmer and the allocation remained concealed until the final analyses (other than for confidential reports to the data monitoring committee)."
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Harwood 2004

Methods	The Nottingham Neck of Femur Study (NONOF). Randomised controlled trial, using parallel group design (four intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 150 previously independent elderly women, 67 to 92 (mean 81.2) years of age, recruited following surgery for hip fracture. Inclusion criteria: elderly women post-hip fracture, previous community residence, independence in activities of daily living.

Harwood 2004 (*Continued*)

	Exclusion criteria: institutionalised patients, diseases or medication known to affect bone metabolism, and those with a 10-point abbreviated mental test score less than seven at the time of recruitment.
Interventions	Participants were randomly assigned to receive: Intervention group 1: single injection of 300,000 IU of vitamin D_2 (n = 38); Intervention group 2: single injection of 300,000 IU of vitamin D_2 plus oral calcium (1000 mg) daily (n = 36); Intervention group 3: oral vitamin D_3 (800 IU) plus calcium (1000 mg) daily (n = 39); Intervention group 4 (Control group): no treatment (n = 37); for a one-year period.
Outcomes	The primary outcomes were bone biochemical markers, bone mineral density, and rate of falls and new fractures.
Notes	"There were no cases of hypercalcaemia, and no participants were withdrawn because of adverse effects of trial medication." The trial was supported by Provalis Healthcare Ltd.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a opaque and sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	High risk	There are other factors in the trial that could put it at risk of bias. The trial was supported by Provalis Healthcare Ltd.

Jackson 2006

Methods	Women's Health Initiative (WHI). Multicentre, randomised, double-blind, placebo controlled trial using parallel group design (two intervention groups).
Participants	Country: United States. Number of participants randomised: 36,282 50 to 79 (mean 62) years of age, healthy postmenopausal women. Inclusion criteria: postmenopausal women 50 to 79 years of age at the initial screening without evidence of a medical condition associated with a predicted survival of less than three years and no safety, adherence, or retention risks. Exclusion criteria: hypercalcaemia, renal calculi, corticosteroid use, and calcitriol use. Personal supplemental calcium (up to 1000 mg per day) and vitamin D (up to 600 IU per day) were allowed. In 1999, the upper limit of personal vitamin D intake was raised to 1000 IU. The calcium with vitamin D trial permitted the use of bisphosphonates and calcitonin. Use of estrogen (with or without a progestin) was according to randomisation among women in the Hormone Therapy trial. Independent use of hormone therapy or selective estrogen-receptor modulators was permitted for women in the Dietary Modification trial.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (400 IU) plus calcium (1000 mg) daily (n = 18176); Intervention group 2 (Control group): matched placebo daily (n = 18106); for a seven-year period.
Outcomes	The primary outcome measure was hip fracture. The secondary outcomes were other fractures and colorectal cancer.
Notes	"The Women's Health Initiative was clinical investigation of strategies for the prevention of some of the most common causes of morbidity and mortality among postmenopausal women. It consisted of two components, the randomised controlled clinical trial and observational study. Randomised controlled trial tested two interventions (hormone therapy and dietary modification. Women who were ineligible or unwilling to enrol in randomised trial were invited to participate in the observational study. One year later participants enrolled in the dietary modification trial, hormone therapy trials, or both were invited to join the Women Health Initiative calcium-vitamin D trial." "Adherence to the trial medication was established by weighing returned pill bottles during clinic visits. The rate of adherence (defined as use of 80% or more of the assigned trial medication) ranged from 60% to 63% during the first three years of follow-up, with an additional 13% to 21% of the participants taking at least half of their trial pills. At the end of the trial, 76% were still taking the trial medication, and 59% were taking 80% or more of it." The active trial drug and placebo were supplied by GlaxoSmithKline Consumer Healthcare (Pittsburgh).

Risk of bias

Bias	Authors' judgement	Support for judgement

Jackson 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Komulainen 1999

Methods	Randomised, double-blind, placebo-controlled trial using 2 x 2 factorial design.
Participants	Country: Finland. Number of participants randomised: 464, recently postmenopausal women without contraindications to hormone replacement therapy 47 to 56 (mean 52.7) years of age. Inclusion criteria: nonosteoporotic, early postmenopausal women (6 to 24 months had elapsed since their last menstruation). Exclusion criteria: history of breast or endometrial cancer, thromboembolic diseases, and medication-resistant hypertension.
Interventions	Participants were randomly assigned to receive: Intervention group 1: sequential combination of 2 mg estradiol valerate (E_2Val; days 1 to 21) and 1 mg cyproterone acetate (days 12 to 21) and a treatment-free interval (days 22 to 28) (n = 116); Intervention group 2: vitamin D_3 (300 IU) plus calcium (500 mg) daily, intervention-free interval June-August, the Vit D_3 dosage was lowered to 100 IU/day after 4 years of treatment because of adverse lipid changes noticed during the first years of the trial (N = 116); Intervention group 3: sequential combination of 2 mg estradiol valerate (E_2Val; days 1 to 21) and 1 mg cyproterone acetate (days 12 to 21) and a intervention-free interval

	(days 22 to 28) plus vitamin D_3 (300 IU) and calcium (500 mg) daily (n = 116); Intervention group 4 (Control group): placebo daily (n = 116); for a five-year period.
Outcomes	The primary outcome was bone mineral density.
Notes	"Of the 464 women enrolled in the trial, 435 (94%) eligible women completed it. Among the 29 drop-outs were 20 women who could not be contacted in the end of the trial and 3 who died from unrelated causes during the trial period. In addition, 6 osteoporotic women were withdrawn from the trial after enrolment when participant eligibility data were available (baseline lumbar or femoral BMD above -2 SD of the mean of the whole trial population)." The trial was supported by Leiras Oy, Finland and Schering AG, Germany. Hormone replacement therapy provided by Climen, Schering AG, Germany; Vitamin D_3 by D-Calsor, Orion Ltd, Finland, and calcium by Rohto Ltd, Tampere, Finland.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Krieg 1999

Methods	Randomised clinical trial using parallel group design (two intervention groups).
Participants	Country: Switzerland. Number of participants randomised: 248 elderly institutionalised women 62 to 98 (mean 84.5) years of age. Inclusion criteria: elderly institutionalised women. Exclusion criteria: not reported.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (880 IU) plus calcium (1000 mg) daily (n = 124); Intervention group 2 (Control group): no treatment (n = 124); for a two-year period.
Outcomes	The primary outcomes were quantitative ultrasound parameters of bones and metabolic disturbances.
Notes	"The drugs were given by the nursing staff to avoid lack of compliance." Trial agents were provided by Novartis Pharma, Basle, Switzerland.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	High risk	The allocation sequence was known to the investigators who assigned participants.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Kärkkäinen 2010

Methods	Osteoporosis Risk Factor and Prevention Study-Fracture Prevention Study (OSTPRE-FPS). Randomised controlled trial using parallel group design (two intervention groups).
Participants	Country: Finland. Number of participants randomised: 3139 ambulatory postmenopausal women, aged 65 to 71 (mean 67) years. Inclusion criteria: ambulatory women aged 65 years or more at the end of November 2002, living in Kuopio province area at the onset of the trial, and not belonging to the former OSTPRE bone densitometry sample. Exclusion criteria: none stated.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 800 IU plus calcium (calcium carbonate) 1000 mg daily (n = 1718); Intervention group 2 (Control group): no intervention (n = 1714); for a three-year period.
Outcomes	The primary outcome measure was the occurrence of falls.
Notes	This trial was based on the OSTPRE-FPS (Osteoporosis Risk Factor and Prevention Study-Fracture Prevention Study) which began in 2003 in Kuopio, Finland. "The compliance was calculated as the dispensed tablets on prescriptions and not on exact number of tablets consumed. The mean compliance in the entire trial population was 78%. The values for 70%, 80% and 90% compliance were 77.4%, 74.2% and 69.1% of the intervention group (entire trial population), respectively." Supported by Leiras-Nycomed Ltd with calcium and vitamin D supplementation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded, so that the allocation was known during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.

Kärkkäinen 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Lappe 2007

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (three intervention groups).
Participants	Country: United States. Number of participants randomised: 1179 healthy postmenopausal white women, 55 years of age and older (mean 66.7). Inclusion criteria: age > 55 years, at least four years past last menses; in generally good health, living independently in the community, and weighing less than 300 pounds. Exclusion criteria: a medical diagnosis of any chronic kidney disease, Paget's or other metabolic bone disease, and history of cancer except for superficial basal or squamous cell carcinoma of the skin and other malignancies treated curatively more than 10 years prior to entry into the trial.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (1000 IU) plus calcium (1400 to 1500 mg) daily (n = 446); Intervention group 2: vitamin D_3 placebo plus calcium (1400 to 1500 mg) daily (n = 445); Intervention group 3 (Control group): placebo, consisting of both vitamin D_3 placebo and a brand-specific calcium placebo daily (n = 288); for a four-year period.
Outcomes	The primary outcome was fracture incidence, and the principal secondary outcome was cancer incidence.
Notes	"Compliance with trial medication was assessed at six months intervals by bottle weight. Mean adherence (defined as taking 80% of assigned doses) was 85.7% for the vitamin D component of the combined regimen and 74.4% for the calcium component." The calcium supplements were provided by Mission Pharmacal (San Antonio, TX) and GlaxoSmithKline (Parsippany, NJ). The vitamin D_3 was obtained from Tishcon Corporation (Westbury, NY). Additional information on mortality was received through personal communication with Professor Joan M Lappe (21.11.2007).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Lappe 2007 (*Continued*)

Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were not described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Larsen 2004

Methods	Cluster-randomised clinical trial using 2 x 2 factorial design.
Participants	Country: Denmark. Number of participants randomised: 9605, (60 % women), 66 to 103 (mean 75) years or over community-dwelling residents. Inclusion criteria: community-dwelling residents, aged 66 years or over. Exclusion criteria: elderly, who were living in nursing homes, severely impaired persons living in sheltered homes for the elderly, as well as elderly with mental retardation who were unable to give informed consent.
Interventions	Municipality of Randers, Denmark was divided into four comparable blocks. The four blocks were allocated at random to three different fracture prevention programs or no intervention. Intervention group 1: home safety inspection by a community nurse to identify and remedy possible hazards and identify and correct potential health or dietary problems. The nurse evaluated the resident's prescribed medication to identify possible errors or necessary dose adjustments. Those who accepted a home visit in this area were given leaflets with information of different ways to avoid falling (n = 2532); Intervention group 2: vitamin D_3 (400 IU) plus calcium (1000 mg) daily. Furthermore, these participants were offered an evaluation of their prescribed medication. This revision

	also ensured that the elderly took no other types of vitamin D products and calcium. If the participants used cardiovascular medicine (digoxin or calcium antagonists) that may interact with calcium, they were referred to their general practitioner. Those who accepted a home visit were given leaflets with information of different ways to avoid osteoporosis (n = 2426); Intervention group 3: a combination of the intervention 1 and intervention 2 (n = 2531) ; Intervention group 4 (Control group): no intervention (n = 2116); for a three and a half year period.
Outcomes	The primary outcome was osteoporotic fractures leading to acute hospital admission.
Notes	The trial was supported by Nycomed DAK. Nycomed DAK supplied the free vitamin D tablets and calcium (Calcichew). Additional information on mortality was received through personal communication with Dr Leif Mosekilde and Dr Lars Rejnmark (06.02.2009).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised, but the method of sequence generation was not specified.
Allocation concealment (selection bias)	High risk	The allocation sequence was known to the investigators who assigned participants.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	High risk	The number or reasons for dropouts and withdrawals were not described.
Selective reporting (reporting bias)	Unclear risk	Not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
Free of other bias?	High risk	There are other factors in the trial that could put it at risk of bias. The trial was supported by Nycomed DAK. Nycomed DAK supplied the free vitamin D tablets and calcium (Calcichew). Recruitment bias was judged as probably adequate.

Latham 2003

Methods	The Frailty Interventions Trial in Elderly Subjects (FITNESS). Multicentre, randomised, placebo controlled trial using 2 x 2 factorial design.
Participants	Country: New Zealand. Number of participants randomised: 243, 64 to 99 (mean 85) years of age, healthy ambulatory women. Inclusion criteria: aged 65 and older, considered frail according to simple clinical measures of frailty and no clear indication or contraindication to either of the trial interventions (i.e., the clinician had substantial uncertainty about the benefits or harms of either interventions for a specific patient). Exclusion criteria: if patients were considered not frail (i.e., fit and independent or fully dependent in activity of daily living) or if, in the opinion of the responsible clinician, that treatment was considered to be potentially hazardous or definitely indicated for a patient; had a poor prognosis and were unlikely to survive six months; severe cognitive impairment that would compromise adherence to the exercise programme (generally people with scores < 20 on a 30-point Mini-Mental State Examination); physical limitations that could limit adherence to the exercise programme (e.g., poor upper limb function that limited application of the weights); unstable cardiac status, or large ulcers about the ankles that would preclude safe application of the ankle weights. In addition, because of difficulties that would arise with their follow-up assessments, people who lived outside the hospitals' normal geographical zones and patients who were not fluent in English were excluded.
Interventions	Participants were randomly assigned to receive: Intervention group 1: resistance exercise to the quadriceps muscles with frequency-matched social home visits (ten week programme) (n = 120); Intervention group 2: vitamin D_3 (300,000 IU) (n = 121); Intervention group 3: attention control (n = 123); Intervention group 4 (Control group): placebo vitamin D_3 (n = 122); for a six-month period. The vitamin D intervention was given in a single oral dose. Patients received either six vitamin D_3 (300,000 IU) or matching placebo tablets. A trial nurse administered the tablets. Overall, vitamin D received 121 participant and placebo 122 participants.
Outcomes	The primary outcomes were self-rated physical health at three months and falls over the sixth-month period. Secondary outcomes were physical performance and self-rated function.
Notes	"Compliance was monitored using a participants diary. Compliance with the single high dose of calciferol or placebo was 100%. No participants were lost to follow-up." Additional information on mortality and form of vitamin D used in the trial was received through personal communication with Professor Nancy K Latham (01.02.2009) and Professor Ian Cameron (24.02.2010).

Risk of bias

Bias	Authors' judgement	Support for judgement

Latham 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	The trial biostatistician generated the randomisation sequence using a computerised central randomisation scheme.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	It was specified that there were no dropouts or withdrawals.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Law 2006

Methods	Cluster-randomised clinical trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 3717 participating residents (76% women), average age 85 years. Inclusion criteria: elderly people aged 60 years or over. Exclusion criteria: temporary residents admitted for respite care, residents who were already taking calcium/vitamin D or drugs that increase bone density (such as bisphosphonates), and residents who had sarcoidosis or malignancy, or other life-threatening illness.
Interventions	Participants (30-bedded units) were randomly assigned to receive: Intervention group 1: vitamin D_2 (1100 IU) daily (n = 1762); Intervention group 2 (Control group): no intervention (n = 1955); for a ten-month period. Vitamin D was given as tablets containing vitamin D_2 (ergocalciferol) 100,000 IU (Norton Healthcare (now Ivax Pharmaceuticals)) every three months; Residents in the control group took no vitamin D (there was no placebo).
Outcomes	The primary outcomes were non-vertebral fractures and falls.

Law 2006 (*Continued*)

Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using cluster randomisation by computer.
Allocation concealment (selection bias)	High risk	The allocation sequence was known to the investigators who assigned participants.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Unclear risk	The trial may or may not be free of other components that could put it at risk of bias. There was potential selection bias as no data given on non-participants. Recruitment bias judged as unknown.

Lips 1996

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: the Netherlands. Number of participants randomised: 2578 independently living elderly persons (74% women), 70 to 97 (mean 80) years of age. Inclusion criteria: elderly people, aged 70 years or over, reasonable healthy and able to give informed consent. Exclusion criteria: history of hip fracture or total hip arthroplasty, known hypercalcaemia, sarcoidosis, or recent urolithiasis (< 5 years earlier), diseases or medications that influence bone metabolism (such as thyroid disease or glucocorticoid medication).
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 400 IU daily (n = 1291); Intervention group 2 (Control group): matched placebo daily (n = 1287); for a three and a half year period.

Lips 1996 (*Continued*)

Outcomes	The primary outcomes were hip fractures and other peripheral bone fractures.
Notes	"Compliance was checked when the tablet containers were replaced (every 6 months) , by questionnaire (every year), and by measurement of the serum 25(OH)D concentration. Compliance was considered to be adequate if the participants reported on the questionnaire that they took the tablets five or more days per week. This occurred in 85% of the participants and was similar in both groups." Vitamin D and placebo tablets were provided by Solvay-Duphar, Inc, Weesp, the Netherlands.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation or a random number table.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Lips 2010

Methods	Randomised, double-blind, placebo-controlled multicentre trial using parallel group design (two intervention groups).

Lips 2010 (*Continued*)

Participants	Country: the Netherlands. Number of participants randomised: 226 men and women aged ≥ 70 (mean 78) years who were vitamin D insufficient (serum 25-hydroxyvitamin D concentrations ≤ 20 but ≥ 6 ng/mL). Inclusion criteria: ambulatory elderly people who were vitamin D insufficient, aged 70 years or over, able to walk 10 feet without a walking aid) and mentally competent. If patients had serum 25-hydroxyvitamin D concentrations ≥ 6 but ≤ 9 ng/mL, they needed to have 24-h urine calcium concentrations ≥ 50 mg/d and bone-specific alkaline phosphatase concentrations not higher than the upper limit of normal. Exclusion criteria: primary hyperparathyroidism, active thyroid disease, impaired renal function, osteomalacia, neurologic impairment, peripheral neuropathy, myocardial infarction within 6 months of screening, uncontrolled hypertension, postural hypotension, malabsorption syndrome, alcohol abuse (i.e., > 2 drinks/day), cancer, treatment with oral glucocorticoids, anabolic steroids, or a growth hormone within 12 months of screening; treatment with > 800 IU vitamin D a day or with active metabolites of vitamin D within 6 months of screening; or treatment with any drug that might affect vitamin D metabolism or interfere with postural stability at screening.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 8400 IU weekly (n = 114); Intervention group 2 (Control group): matched placebo weekly (n = 112); for a 16 weeks period. "For participants with a daily dietary calcium intake <1000 mg (as assessed by a questionnaire at screening), daily calcium carbonate containing 500 mg elemental calcium was also prescribed."
Outcomes	The primary outcome measure was mediolateral sway with eyes open. Secondary outcome measures were change in functional status assessed with the short physical performance battery, mean serum 25-hydroxyvitamin D, calcium, and phosphate concentrations, and adverse events.
Notes	"All patients who completed the trial were adherent to treatment, which was defined as taking ≥ 13 of the 16 total doses prescribed."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit. Participants were stratified (2:1) at randomisation according to baseline serum 25-hydroxyvitamin D concentration. Patients were assigned a unique allocation number according to their appropriate stratification block.

Lips 2010 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. Investigators were blinded to serum 25-hydroxyvitamin D concentrations and to stratum definitions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Lyons 2007

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 3440 older people living in institutional care (76% women), 62 to 107 (mean 84) years of age. Inclusion criteria: elderly people, including those with mobility, cognitive, visual, hearing or communication impairments living in nursing homes, residential homes, and sheltered housing. Exclusion criteria: people already receiving $\geq$ 400 IU of vitamin D/day and those already known to have contraindications to vitamin D supplementation.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 100,000 IU three times a year (four-monthly) (n = 1725); Intervention group 2 (Control group): matched placebo tablet three times a year (four-monthly) (n = 1715); for a three-year period.
Outcomes	The primary outcome measure was the incidence of first fracture. Secondary outcome measures were the incidence of hip fractures, fractures at common osteoporotic sites (hip/wrist/forearm/vertebrae), and mortality rates.
Notes	"Dosing was supervised by the research nurse to ensure adherence, but nurse, participant, and analysts were blinded to the allocation. Adherence among participants in the trial was 80% overall (percentage of occasions observed to take tablets whilst in the trial)."

Lyons 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Meier 2004

Methods	Randomised controlled trial using parallel group design (two intervention groups).
Participants	Country: Germany. Number of participants randomised: 55 healthy volunteers (65% postmenopausal women), 33 to 78 (mean 55,8) years of age. Inclusion criteria: healthy volunteers. Exclusion criteria: history or clinical evidence of significant skeletal or nonskeletal disease, taking any medication known to affect bone metabolism, including vitamin D and mineral supplements.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 500 IU daily plus calcium 500 mg daily (n = 30); Intervention group 2 (Control group): no intervention (n = 25); for a six-month period. Participants were followed an additional year. The first year of the trial after randomisation was designed as an observation period only, during which the participants followed their usual daily routine with no intervention per

Meier 2004 (*Continued*)

	protocol. During the winter of the second year, from October to March, the participants assigned to the intervention group received a daily supplement of oral vitamin D_3 (500 IU) and calcium (500 mg), whereas the participants in the control group received no supplements and were asked to remain off such agents. The trial medication was open label.
Outcomes	The primary outcomes were circannual changes in bone turnover, and bone mineral density and rates of bone turnover and bone loss during the winter months.
Notes	"Adherence to intervention was checked in monthly intervals through personal interviews."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Unclear risk	The trial may or may not be free of other components that could put it at risk of bias.

Moschonis 2006

Methods	Postmenopausal Health Study (PMHS). Randomised controlled trial using parallel group design (two intervention groups).
Participants	Country: Greece. Number of participants randomised: 112 postmenopausal women, aged 55 to 65 (mean 60.3) years.

	Inclusion criteria: postmenopausal non-osteoporotic women. Exclusion criteria: a T-score lower than 22.5, taking medications (i.e., thiazide diuretics, glucocorticoids) and/or dietary supplements (calcium, magnesium, phosphate or vitamin D) that affect bone metabolism, having any kind of degenerative chronic disease (i.e., diabetes, nephrolithiasis, heart disease, cancer, hyper- and hypothyroidism, hyperparathyroidism, impaired renal and liver function), smoking and being postmenopausal for less than 1 year
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 300 IU plus calcium 1200 mg daily (n = 42); Intervention group 2: calcium 1200 mg (n = 30); Intervention group 3 (Control group): no intervention (n = 40); for a one-year period.
Outcomes	The primary outcome measure was bone mineral density.
Notes	"To ensure compliance with the intervention scheme, 'Health and Nutrition Education' sessions were held biweekly within the settings of the university and the required quantities of fortified dairy products for the next two weeks were provided at the end of the sessions. Adherence of the participants in the calcium group was assessed by checking for remaining calcium tablets in the returned packages but also via weekly phone calls. Compliance to the intervention scheme was reaching a rate of 93% (range 89 to 100 %) . Compliance rate in calcium group was approximately 95% (range 91 to 100 %)." The trial was supported by a research grant from Friesland Foods Hellas. Additional information on mortality was received through personal communication with Dr George Moschonis (23.02.2010).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using a random number table.
Allocation concealment (selection bias)	High risk	The allocation sequence was known to the investigators who assigned participants.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.

Free of other bias?	High risk	There are other factors in the trial that could put it at risk of bias. The trial was supported by a research grant from Friesland Foods Hellas.

Ooms 1995

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: The Netherlands. Number of participants randomised: 348 women, aged 70 years or older, who were reasonably mobile. Inclusion criteria: elderly mobile women aged 70 years or older. Exclusion criteria: hip fracture in the past, total hip prosthesis, and recent history of urolithiasis, hypercalcaemia, or sarcoidosis.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 400 IU daily (n = 177); Intervention group 2 (Control group): matched placebo daily (n = 171); for a two-year period.
Outcomes	The primary outcome measures were bone mineral density of both hips (femoral neck and trochanter) and the distal radius, as well as biochemical markers of bone turnover.
Notes	"Compliance was established by questionnaire, by pill counting, and by measuring serum 250HD levels in blood. If participants were suspected of poor compliance resulting from memory problems, the nursing staff were asked to supervise the taking of the trial intervention or to administer it." "The compliance was good in both groups. According to the yearly questionnaire, 85% used one tablet daily, and 14% used between three and six tablets weekly. The analysis of the remaining tablets showed a slightly better compliance in the second trial year. In the first year, 63% had used between six and seven tablets weekly, and 4% had used less than three weekly; in the second year, these compliance rates were 78% and 1%, respectively. Of the women receiving the vitamin D supplement, only 5 participants (3%) did not achieve a serum 25 hydroxyvitamin D level higher than 30 nmol/L, whereas 68.4% of the participants in the placebo group had serum levels below 30 nmol/L." The trial medication was provided by Duphar Nederland BV, Amsterdam, the Netherlands.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.

Ooms 1995 (*Continued*)

Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. Randomisation was performed by the hospital pharmacy, and double-blinding was assured.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Ott 1989

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United States. Number of participants randomised: 86 postmenopausal women, 50 to 80 (mean 67.5) years of age. Inclusion criteria: postmenopausal women with at least two compression fractures (> 15% reduction in anterior height) without history of serious trauma. Exclusion criteria: history of corticosteroid use, malnutrition, sarcoidosis, liver disease, rheumatoid arthritis, nephrolithiasis, renal disease, or recent malignancy.
Interventions	Participants were randomly assigned to receive: Intervention group 1: calcitriol 0.25 to 2 μg plus calcium 1000 mg (n = 43); Intervention group 2 (Control group): placebo vitamin D plus calcium 1000 mg daily (n = 43); for a two-year period.
Outcomes	The primary outcome measure was bone mass. Secondary outcome measure was adverse effects of calcitriol.
Notes	Hoffman-La Roche (Nutley, New Jersey) supplied the vitamin D supplements.

Ott 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Porthouse 2005

Methods	Randomised controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 3314 women, aged 70 and over (mean 76.8) years, with one or more risk factors for hip fracture. Inclusion criteria: elderly women, aged 70 years or older, who had at least one self reported risk factor for hip fracture: low bodyweight (< 58 kg), any previous fracture, maternal history of hip fracture, smoker, and poor or fair health. Exclusion criteria: unable to give written consent, receiving of any calcium supplementation of more than 500 mg a day, a history of kidney or bladder stones, renal failure, or hypercalcaemia.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 800 IU plus calcium 1000 mg daily (n = 1321); Intervention group 2 (Control group): information leaflet on dietary calcium intake and prevention of falls, or leaflet only (n = 1993);

Porthouse 2005 (*Continued*)

	for a 25-month period.
Outcomes	The primary outcome measure was fracture, excluding those of the digits, rib, face, and skull. Secondary outcomes included hip fracture; quality of life as measured by the 12 item short-form health survey questionnaire, and the European quality of life instrument, death, visits to the doctor and hospital admissions, falls and fear of falling.
Notes	"Adherence was measured through self report every six months. Rates for adherence at 12 months were about 63%." The trial was supported by Shire and Nycomed. Shire supplied the vitamin D supplements and calcium.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	High risk	Trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Unclear risk	Not all clinically relevant and reasonably expected outcomes are reported on. Adverse events were not reported.
Free of other bias?	High risk	There are other factors in the trial that could put it at risk of bias. The trial was supported by Shire and Nycomed. Shire supplied the vitamin D supplements and calcium.

Prince 2008

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: Australia. Number of participants randomised: 302 community-dwelling ambulant older women aged 70 to 90 (mean 77.2) years with a history of falling and vitamin D insufficiency. Inclusion criteria: community-dwelling ambulant older women with a history of falling in the past 12 months and a plasma 25 hydroxyvitamin D concentration of less than 24.0 ng/mL. Exclusion criteria: current vitamin D consumption; current consumption of bone or mineral active agents apart from calcium; a bone mineral density *z* score at the total hip site of less than -2.0; medical conditions or disorders that influence bone mineral metabolism, including laboratory evidence of renal insufficiency (a creatinine level more than two-fold above the reference range); a fracture in the past 6 months; a Mini-Mental State Examination score of less than 24; or the presence of marked neurological conditions likely to substantially impair balance or physical activity, such as stroke and Parkinson's disease.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 1000 IU plus calcium 1000 mg daily (n = 151); Interventio group 2 (Control group): matched placebo tablet of vitamin D plus calcium 1000 mg daily (n = 151); for a one-year period.
Outcomes	The primary outcome measure was risk of falls in older women at high risk of falling.
Notes	"Adherence to the trial medications was established by counting tablets returned at the clinic visits at 6 and 12 months. The rate of compliance with trial medication in participants who continued to receive the medication, as determined from tablet counting, was 86% in both groups." Vitamin D_2 (ergocalciferol) or identical placebo was provided by Ostelin; Boots Healthcare, North Ryde, Australia. Calcium as calcium citrate was provided by Citracal; Mission Pharmacal, Key Pharmaceutical Pty Ltd, Rhodes, Australia.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias)	Low risk	The trial was described as blinded, the parties that were blinded, and the method of

Prince 2008 (*Continued*)

All outcomes		blinding was described, so that knowledge of allocation was adequately prevented during the trial. Randomisation schedule was kept in the pharmacy department, where the bottles were labelled and dispensed to the participants.The trial participants and the trial staff remained blinded to the treatment code until all the data had been entered, evaluated for accuracy, and the a priori hypotheses reviewed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Sanders 2010

Methods	Single centre, randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups). The Vital D study.
Participants	Country: Australia. Number of participants randomised: 2258 community-dwelling women, 70 years or older (mean age 76 years) considered to be at high risk of fracture. Inclusion criteria: community-dwelling women at higher risk of hip fracture, defined by criteria such as maternal hip fracture, past fracture, or self-reported faller. Exclusion criteria: unable to provide informed consent or information about falls or fractures; permanently resided at a high-level care facility; had an albumin-corrected calcium level higher than 2.65 mmol/L; or had a creatinine level higher than 150 μmol/L, or currently took vitamin D doses of 400 IU or more, calcitriol, or antifracture therapy.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 500,000 IU yearly (n = 1131); Interventio group 2 (Control group): matched placebo tablet of vitamin D yearly (n = 1127); for a three to five years (in autumn or winter), median 2.96 years. "Ten tablets were mailed to participants annually (March-August, determined by recruitment date) with instructions to take all tablets on a single day. Study staff confirmed by telephone the ingestion of study medication within 2 weeks. Subsequent dosing occurred within 2 weeks of the anniversary of the first dose."

Sanders 2010 (*Continued*)

Outcomes	The primary outcome measures were falls and fractures. Secondary outcome measures were serum 25-hydroxycholecalciferol and intact parathyroid hormone levels.
Notes	"Study staff confirmed by telephone the ingestion of study medication." Study medication was supplied by PSM Healthcare, Auckland, New Zealand.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	"Allocation was performed by an independent statistician. Treatment allocation status was e-mailed directly to the hospital clinical trials pharmacist responsible for dispensing study medication."
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. The participants and study staff were blinded to intervention group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Sato 1997

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: Japan. Number of participants randomised: 64 (45% women) mean age 68.5 years) outpatients with hemiplegia after stroke. Inclusion criteria: patients with hemiplegia after stroke. Exclusion criteria: shoulder-hand syndrome, multiple strokes, history of hip fracture, a stroke duration of less than 1 month, or the use of medication known to affect bone

	metabolism, including estrogen, calcium, vitamin D, corticosteroids, thyroxine, or anticonvulsants.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D in the form of $1(OH)D_3$ (alfacalcidol) 1 μg plus calcium 300 mg daily (n = 45); Intervention group 2 (Control group): matched placebo tablet of vitamin D plus calcium 300 mg daily (n = 39); for a six-month period.
Outcomes	The primary outcome measures were bone mineral density and hip fractures.
Notes	Additional information on mortality was received through personal communication with Dr Yoshiro Sato (05.02.2009).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The method of blinding was not described, so that knowledge of allocation was possible during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Unclear risk	Not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on. Adverse events were not reported.
Free of other bias?	Unclear risk	The trial may or may not be free of other components that could put it at risk of bias.

Sato 1999a

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: Japan. Number of participants randomised: 86 elderly patients (78% women) aged 65 to 88 (mean 70.6) with Parkinson's disease. Inclusion criteria: elderly patients with Parkinson's disease and low serum 1,25-dihydroxyvitamin D concentrations. Exclusion criteria: other known causes of osteoporosis, such as hyperparathyroidism or renal osteodystrophy; impairment of renal, cardiac, or thyroid function; a history of therapy with corticosteroids, estrogens, calcitonin, etidronate, calcium, or vitamin D for three months or longer during the 18 months preceding the trial; or even brief treatment of this nature during the two months immediately preceding the trial. Patients at Hoehn and Yahr stage 5 were excluded because their poor ambulation status largely precluded any chance of fracture. Patients with a history of non-vertebral fracture were also excluded.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D in a form of 1-α hydroxyvitamin D_3 (alfacalcidol) (1 μg) daily (n = 43); Intervention group 2 (Control group): matched placebo tablet daily (n = 43); for a 18-month period.
Outcomes	The primary outcome measure was non-vertebral fractures. Secondary outcome was progression of osteopenia in the second metacarpal bone.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was described as double blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described

Sato 1999a (*Continued*)

Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Unclear risk	The trial may or may not be free of other components that could put it at risk of bias.

Sato 1999b

Methods	Randomised controlled trial using parallel group design (three intervention groups).
Participants	Country: Japan. Number of participants randomised: 103 patients (56% women), mean age 70.7 with hemiplegia after stroke. Inclusion criteria: outpatients with post-stroke hemiplegia of more than one year duration. Exclusion criteria: congestive heart failure or obstructive pulmonary disease, other known causes of osteoporosis, such as hyperparathyroidism or renal osteodystrophy; impairment of renal, cardiac, or thyroid function; a history of therapy with corticosteroids, estrogens, calcitonin, etidronate, calcium, or vitamin D for 3 months or longer during the 12 months preceding the trial; or even brief treatment of this nature during the 2 months immediately preceding the trial.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D in a form of 1-α hydroxyvitamin D_3 (alfacalcidol) (1 μg) daily (n = 34); Intervention group 2: ipriflavone 600 mg daily (n = 34); Intervention group 2 (Control group): no treatment (n = 35); for a one-year period.
Outcomes	The primary outcome measures was bone mineral density.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	High risk	The allocation sequence was known to the investigators who assigned participants.
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded, so that the allocation was known during the trial.

Sato 1999b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Unclear risk	The trial may or may not be free of other components that could put it at risk of bias.

Sato 2005a

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: Japan. Number of participants randomised: 96 hospitalised elderly women with post stroke hemiplegia mean age 74.1 years. Inclusion criteria: hospitalised elderly women with post stroke hemiplegia who had first-ever cerebral infarction or haemorrhage more than two years before and were in a convalescent stage with post-stroke hemiplegia. Exclusion criteria: dementia, total disability, or hospitalisation of less than two years' duration, receiving any drugs known to alter vitamin D metabolism, such as anticonvulsants, calcium, or vitamin D, during the 12 months preceding the trial.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 (1000 IU) daily (n = 48); Intervention group 2 (Control group): matched placebo tablet daily (n = 48); for a two-year period.
Outcomes	The primary outcome measure was number of falls. Secondary outcome measures were muscular strength and morphological changes of muscle.
Notes	Additional information on mortality was received through personal communication with Dr Yoshiro Sato (05.02.2009).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation or a random number table.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been

Sato 2005a (*Continued*)

		foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Schleithoff 2006

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: Germany. Number of participants randomised: 123 patients (17% women) aged 50 to 63 (mean 51) years with congestive heart failure. Inclusion criteria: patients with congestive heart failure and New York Heart Association functional class II. Exclusion criteria: hypercalcaemia, serum creatinine concentration > 2 mg/dL, nephrolithiasis, sarcoidosis, use of a biventricular pacemaker, acute heart insufficiency, and an actual intake of supplements containing vitamin D and calcium.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (2000 IU) plus calcium (500 mg) daily (n = 61); Intervention group 2 (Control group): matched placebo tablet of vitamin D plus calcium 500 mg daily (n = 62); for a nine-month period. Participants were followed-up for a 15-month period.
Outcomes	The primary outcome measures were survival rates, and biochemical variables such as natriuretic peptides and cytokines. Secondary outcomes were those haemodynamic variables, which were assessed routinely during the ambulatory visits, such as left ventricular ejection fraction, left ventricular end-diastolic diameter, the cardiothoracic ratio, maximal oxygen intake (spiroergometry; O_2max), and blood pressure.
Notes	"Compliance was measured by controlling the trial medication at each visit (bottle counts) and by the analysis of serum 25 hydroxyvitamin D concentrations." Vitamin D_3 was provided by Vigantol Oel; Merck, Darmstadt, Germany, and placebo

Schleithoff 2006 (*Continued*)

	by Migliol-Oel; Merck, Darmstadt, Germany. Additional information received thorough personal communication with Professor Armin Zittermann (10.02.2010).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Smith 2007

Methods	Wessex Fracture Prevention Trial (WFPT). Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 9440 elderly people (54% women) aged 75 years and over. Inclusion criteria: elderly people aged 75 years and over. Exclusion criteria: current cancer or any history of treated osteoporosis, taking 400 IU or more vitamin D daily, bilateral total hip replacement, renal failure, renal stones, hypercalcaemia or sarcoidosis.

Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 (300,000 IU) intramuscular injection yearly (n = 4727); Intervention group 2 (Control group): matched placebo intramuscular injection of vitamin D yearly (n = 4713); for a three-year period. Active or placebo injections were administered every autumn at annual intervals and concealed in the same way as the first injection.
Outcomes	The primary outcome measure was all non-vertebral fracture. Secondary outcome measures were hip and wrist fractures, and all falls.
Notes	The trial was supported by Celltech UK plc. Additional information on mortality was received through personal communication with Professor Cyrus Cooper and Dr Sarah Crozier (16.11.2007).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. Packing and labelling were carried out by an external contractor; allocation was concealed from investigators, practice nurses, and participants.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. Each participating practice was sent mixed boxes containing previously randomised, numbered ampoules of either vitamin D or placebo, which were identical in visual appearance and consistency. As each participant consented to participate in the trial, they were allocated consecutive ampoules. The number of the ampoule was then linked to the participant's name and phoned to a central location. This trial number remained with the participant for the duration of the trial.

Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Trivedi 2003

Methods	Randomised double-blind placebo-controlled trial with parallel group design (two intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 2686 elderly people (24% women) aged 65 to 85 (mean 74) years. Inclusion criteria: elderly people living in the general community. Exclusion criteria: already taking vitamin D supplements and conditions that were contraindications to vitamin D supplementation (a history of renal stones, sarcoidosis, or malignancy).
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (100,000 IU) every four months orally (n = 1345); Intervention group 2 (Control group): matched placebo every four months orally (n = 1341); for a five-year period.
Outcomes	The primary outcome measures were fracture incidence and total mortality by cause.
Notes	"Seventy six percent of participants had at least 80% compliance (12/15 doses). Compliance for the final dose was 66%; excluding participants who had died, compliance was estimated to be 80%. The 100,000 IU vitamin D supplement or placebo used in this trial was specially prepared by the Ipswich Hospital Pharmacy."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that in-

Trivedi 2003 (*Continued*)

		tervention allocations could not have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. Participants and investigators were blinded to the treatment until the trial ended, when Ipswich Pharmacy revealed the coding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Witham 2010

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Number of participants randomised: 105 patients with systolic heart failure aged 70 or over (mean 79.7) years, 34% females with 25-hydroxyvitamin D levels < 50nmol/L (20 ng/ml). Inclusion criteria: aged 70 years or over with a previously recorded clinical diagnosis of chronic heart failure, previously documented left ventricular systolic dysfunction by echocardiography, radionuclide ventriculography or angiography as part of their usual clinical care, a New York Heart Association class II or III symptoms, and a 25-hydroxyvitamin D level of < 50nmol/L (20 ng/ml). Exclusion criteria: a clinical diagnosis of osteomalacia, under investigation for recurrent falls, already taking vitamin D supplements, moderate to severe cognitive impairment, defined as a Folstein mini-mental state examination < 15/30), serum creatinine > 200umol/L, liver function tests (bilirubin, alanine aminotransferase, alkaline phosphatase) > 3 times the upper limit of the local reference range, systolic blood pressure < 90mmHg, albumin adjusted calcium > 2.55 mmol/L or < 2.20 mmol/L), metastatic malignancy, and wheelchair bound patients unable to perform the primary outcome, and excluded patients unwilling or unable to give informed consent.

Witham 2010 (*Continued*)

Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 (10,000 IU) tablet at baseline and 10 weeks (n = 53); Intervention group 2 (Control group): matched placebo tablet at baseline and 10 weeks (n = 52). Participants were followed for 20 weeks.
Outcomes	The primary outcome measure was the six-minute walk test, a measure of submaximal exercise capacity. Secondary outcomes were muscle function, daily physical activity levels, health status/health-related quality of life, cardiovascular and inflammatory markers.
Notes	"Administration of vitamin D_2 was supervised in the participant's own home by the research nurse to ensure 100% adherence."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed using computer generated random number tables by DHP Pharmaceuticals (Gwent, UK).
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit. Code allocation was concealed from the research nurse and investigators until after data analysis was complete.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial. DHP Pharmaceuticals (Gwent, UK) encapsulated the trial medication to render it identical to placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Zhu 2008

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (three intervention groups).
Participants	Country: Australia. Number of participants randomised: 120 community-dwelling women aged 70 to 80 (mean 75) years. Inclusion criteria: aged over 70 year old, likely to survive a five year trial, and not receiving bone active agent. Exclusion criteria: none stated.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_2 (1000 IU) plus calcium (1200 mg) daily (n = 39); Intervention group 2: calcium 1200 mg plus placebo vitamin D daily (n = 40); Intervention group 3 (Control group): matched placebo vitamin D and placebo calcium daily (n = 41); for a five year period.
Outcomes	The primary outcome measures were bone mineral density, plasma 25-hydroxyvitamin D, biomarkers of bone turnover, parathyroid hormone, and intestinal calcium absorption.
Notes	"This trial was nested within the larger Calcium Intake Fracture Outcome Study, a five year double-blinded, randomised, controlled calcium supplementation trial, in which 1500 community-living ambulant women over the age of 70 years old were randomised to received either 1200 mg calcium per day or identical placebo. The first 120 sequential participants presenting in September 1998 (end of winter in Western Australia) enrolled in this substudy and were randomised." "Adherence to the trial interventions was established by counting tablets returned every 12 months. There were no significant differences among the three groups in the compliance rates determined by tablet counting for calcium or placebo in the intervention groups 1, 2, and 3 (80.7, 80.9, and 86.9%, respectively) or for vitamin D or placebo (84.2, 86.9, and 89.8%, respectively)." Vitamin D_2 (ergocalciferol) or identical placebo was provided by Ostelin; Boots Healthcare, North Ryde, New South Wales, Australia. Calcium as calcium citrate was provided by Caltrate; Wyeth Consumer Healthcare, Baulkham Hills, New South Wales, Australia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit so that intervention allocations could not have been foreseen in advance of, or during, enrolment. "Randomisation was undertaken by an independent research fellow and was

		kept in the Pharmacy Department of the Sir Charles Gairdner Hospital, in which the bottles were labelled and dispensed to participants. The trial participants and trial staff remained blinded to the treatment code until all the data had been entered, evaluated for accuracy, and the *a priori* hypotheses reviewed."
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Free of other bias?	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Abbreviations:
BMD: bone mineral density; HRT: hormone replacement therapy; ERT: estrogen replacement therapy;

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

Study	Reason for exclusion
Adachi 1996	Randomised controlled trial. This trial included patients receiving corticosteroids (diagnosed with polymyalgia rheumatica, temporal arteritis, asthma, vasculitis, or systemic lupus erythematosus).
Andersen 2008	Randomised controlled trial. This trial included participants younger than 18 years (adolescent girls median age 12.2 years).
Arthur 1990	Randomised controlled trial. All participants received vitamin D.
Bacon 2008	Randomised controlled trial. All participants received vitamin D.

(*Continued*)

Bernstein 1996	Randomised controlled trial. This trial included patients receiving corticosteroids (diagnosed with inflammatory bowel disease).
Berry 2010	This is not a randomised controlled trial.
Bischoff-Ferrari 2010	Randomised controlled trial. All participants received vitamin D.
Bizzarri 2010	Randomised controlled trial. This trial included participants younger than 18 years.
Buckley 1996	Randomised controlled trial. This trial included patients receiving corticosteroids (diagnosed with rheumatoid arthritis).
Caniggia 1992	This is not a randomised controlled trial.
Chapuy 1996	This is not a randomised controlled trial.
Chen 2001	Randomised controlled trial. All women received hormone replacement therapy.
Dawson-Hughes 1995	Randomised controlled trial. All participants received vitamin D.
den Uyl 2010	Randomised controlled trial. All participants received vitamin D.
Diamond 2005	This is not a randomised controlled trial.
Dykman 1984	Randomised controlled trial in patients with glucocorticoid-induced osteopenia.
Falch 1987	Randomised controlled trial. All participants received vitamin D.
Francis 1996	Randomised controlled trial. All participants received vitamin D.
Gallagher 1990	Randomised controlled trial. All participants received 400 IU of vitamin D_2.
Gannage-Yared 2003	This is not a randomised controlled trial.
Geusens 1986	Randomised controlled trial comparing the effect of nandrolone decanoate, 1-alphahydroxyvitamin D_3 and intermittent calcium infusions. Vitamin D group was not supplemented with calcium.
Glendenning 2009	Randomised controlled trial. All participants received vitamin D.
Goswami 2008a	This is not a randomised controlled trial.
Goussous 2005	Randomised controlled trial. All participants received vitamin D.
Gupta 2010	This is not a randomised controlled trial.
Hedström 2002	Randomised controlled trial. Vitamin D group also received anabolic steroids.

(*Continued*)

Heikinheimo 1992	This is not a randomised controlled trial. Participants were divided into treatment groups according to month of birth.
Hill 2010	Randomised controlled trial. All participants received vitamin D.
Holecki 2008	This is not a randomised controlled trial.
Holick 2008b	Randomised controlled trial. This trial did not fulfil our inclusion criteria.
Holvik 2007	Randomised controlled trial. All participants received vitamin D.
Inkovaara 1983	Quasi-randomised trial. Participants randomised by date of birth.
Inomata 1986	This is not a randomised controlled trial.
Ish-Shalom 2008	Randomised controlled trial. All participants received vitamin D.
Iwamoto 2000	Randomised controlled trial. Participants in the control group supplemented with calcium. Participants in the vitamin D group were not supplemented with calcium.
Kamel 1996	This is not a randomised controlled trial.
Keane 1992	Randomised controlled trial. Participants in a control group supplemented with small dose of vitamin D.
Kenny 2004	Randomised controlled trial. All participants received vitamin D.
Kilpinen-Loisa 2009	This is not a randomised controlled trial.
Lakatos 2000	Randomised controlled trial. This trial included patients receiving corticosteroids (diagnosed with systemic lupus erythematodes, multiple sclerosis, rheumatoid arthritis or asthma bronchiale).
Leventis 2009	This is not a randomised controlled trial.
Lind 1988	Randomised controlled trial. This trial included participants with primary hyperparathyroidism.
Lind 1989c	This is not a randomised controlled trial.
Matsumoto 2010	Randomised controlled trial. All participants received vitamin D or vitamin D analogs.
Meyer 2002	Quasi-randomised trial. Before the trial started, the days of the month (1-31 days) were divided randomly into group A and group B, and based on the day of birth, a participant was placed automatically in group A or group B when registered in the trial database.
Nugent 2009	This is not a randomised controlled trial.
Nuti 2006	Randomised controlled trial. All participants received vitamin D.
Orwoll 1989	Randomised controlled trial. Participants received 25-hydroxyvitamin D_3.

(*Continued*)

Prestwood 1996	This is not a randomised controlled trial.
Reginster 1999	Randomised controlled trial. This trial included patients receiving high doses of corticosteroids (cardiac transplant, severe inflammatory syndrome, etc).
Reginster 2001	Randomised controlled trial. All participants received vitamin D.
Romagnoli 2008	Randomised controlled trial. All participants received vitamin D.
Sambrook 1993	Randomised controlled trial. This trial included patients on a long-term corticosteroid therapy.
Sambrook 2000	Randomised controlled trial in patients after cardiac or lung transplantation.
Sambrook 2003	Randomised controlled trial. All participants received vitamin D_2 plus calcium, vitamin D_3 or alendronate plus calcium. There is no control group of the trial.
Sato 2005b	Randomised controlled trial. All participants received vitamin D.
Sato 2005c	Randomised controlled trial. Participants received a combination of menatetrenone, vitamin D_2, and calcium.
Sato 2006	Randomised controlled trial. Participants were randomised to a combination of alendronate and vitamin D_2.
Sebert 1995	Randomised controlled trial. All participants received vitamin D.
Serhan 2005	Randomised controlled trial. All participants received vitamin D.
Shipowick 2009	This is not a randomised controlled trial.
Shiraki 1991	This is not a randomised controlled trial.
Sidbury 2008	Randomised controlled trial in children.
Smith 2009	Randomised controlled trial. All randomised participants received vitamin D.
Stephens 1981	Randomised controlled trial. All participants received vitamin D. Participants younger than 18 years were included.
Tfelt-Hansen 2004	Randomised controlled trial. All participants received vitamin D.
Tilyard 1992	Randomised controlled trial. Participants in active treatment group treated with vitamin D and participants in the control group treated with calcium.
Trang 1998	Randomised controlled trial. All participants received vitamin D.
Verschueren 2010	Randomised controlled trial. All participants received vitamin D.

(*Continued*)

Vieth 2004	Randomised controlled trial. All participants received vitamin D.
Viljakainen 2006b	Randomised controlled trial in adolescent girls.
von Restorff 2009	This is not a randomised controlled trial.
Wejse 2009	Randomised controlled trial in patients with tuberculosis starting antituberculosis treatment.

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

Aloia 2008b

Trial name or title	The interaction between calcium and vitamin D Intake
Methods	Randomised, double-blind, placebo-controlled trial using 2 x 2 factorial design.
Participants	Country: United States. Estimated number of participants: 120. Inclusion criteria: healthy women aged 45 and above who have been menopausal for at least one year (absence of menstrual period for a period of 12 months or more). Exclusion criteria: any chronic medical illness including uncontrolled diabetes mellitus, recent history of myocardial infarction, or heart failure, malignancy, uncontrolled hypertension, obesity (BMI > 35 kg/m2) , history of anaemia, leukaemia, or other hematologic abnormalities, lupus, rheumatoid arthritis, or other rheumatologic disease, or kidney disease of any kind as determined by history and physical examination, participants with osteoporosis of the hip (total hip T-score equal or less than -2.5) or taking medications for osteoporosis such as bisphosphonate, pregnancy, use of medication that influences bone metabolism (i.e. anticonvulsant medications, chronic use of steroids and high dose diuretics), significant deviation from normal in medical history, physical examination, or laboratory tests as evaluated by the primary investigator, history of hypercalciuria, hypercalcaemia, nephrolithiasis, and active sarcoidosis, participation in another investigational trial in the past 30 days prior to the screening evaluation, unexplained weight loss of >15% during the previous year or history of anorexia nervosa, medications that interfere with vitamin D metabolism; patients with a habitual dietary calcium intake that exceeds 800 mg/day; smokers greater than one pack per day, patients reporting alcohol intake greater than two drinks daily, and serum 25-hydroxyvitamin D level > 75 nmol/L.
Interventions	Participants will be randomly assigned to receive: Intervention 1: vitamin D_3 (4000 IU) daily; Intervention 2: calcium (1200 mg) daily; Intervention 3: vitamin D_3(4000 IU) plus calcium (1200 mg) daily; Intervention group 4 (Control group): placebo daily; for a period of six months.
Outcomes	The primary outcome measures will be: the influence of calcium supplementation alone on serum parathyroid hormone levels and bone markers in healthy adult women. Secondary outcome measures will be: the interaction between calcium and vitamin D supplementation and their combined effect on serum parathyroid hormone levels and bone markers in healthy adult women.
Starting date	November 2008. Expected completion: 2009.

Aloia 2008b (*Continued*)

Contact information	John F Aloia, MD jaloia@winthrop.org
Notes	

Baron 2004

Trial name or title	Vitamin D/Calcium Polyp Prevention Study
Methods	Randomised, double-blind, placebo-controlled trial using 2 x 2 factorial design.
Participants	Country: United States. Estimated number of participants: 2200. Inclusion criteria: aged 45 to 75 years; one or more histologically verified neoplastic polyp (adenoma) that is at least 2 mm in size removed from the large bowel with the entire large bowel examined by colonoscopy and documented to be free of further polyps or areas suspicious for neoplasia within 120 days of trial entry; anticipated colonoscopic follow-up three years or five years after the qualifying colonoscopy; agreement to avoid pregnancy (i.e., use of standard contraception); willingness to forego calcium supplementation (including multivitamins containing calcium) or, for women only, option of taking calcium supplementation of 1200 mg/daily (contained in the trial pills; willingness to forego vitamin D supplementation (including multivitamins containing vitamin D; agreement to daily dietary intake of the equivalent of not more than 1200 mg calcium; agreement to daily dietary intake of the equivalent of not more than 400 IU vitamin D; blood calcium level within normal range; blood creatinine level not to exceed 20% above upper limit of normal; serum 25-hydroxyvitamin D within lower limit of normal to 70 ng/ml; ability and willingness to follow the trial protocol, as indicated by provision of informed consent to participate; good general health, with no severely debilitating diseases or active malignancy that might compromise the patient's ability to complete the trial. Exclusion criteria: participation in another colorectal (bowel) trial in the past five years; current participation in any other clinical trial (intervention trial); pregnancy or lactation; a diagnosis of narcotic or alcohol dependence in the past five years; a diagnosis of dementia (e.g., Alzheimer's) in the past five years; a diagnosis of a significant psychiatric disability (e.g., schizophrenia, refractory bipolar disorder, current severe depression) in the past five years; any diagnosis of kidney stones; a diagnosis of granulomatous diseases, e.g., sarcoidosis, active chronic fungal or mycobacterial infections (tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis), berylliosis, Wegener's granulomatosis in the past five years; hyperparathyroidism or other serious disturbance of calcium metabolism in the past five years; a diagnosis of severe kidney disease, e.g., chronic renal failure in the past five years; unexplained hypercalcaemia in the past five years; osteoporosis with physician recommendation for treatment of low bone mass; two or more low trauma fractures in the past five years; medical condition requiring treatment with vitamin D (e.g., osteomalacia) in the past five years; invasive carcinoma of the large bowel (even if confined to a polyp); familial colorectal cancer syndromes, e.g., Familial Adenomatous Polyposis (FAP) (including Gardner syndrome, Turcot's syndrome), Hereditary Nonpolyposis Colorectal Cancer (HNPCC), Hamartomatous Polyposis syndromes (including Peutz-Jeghers or Familial Juvenile Polyposis); inflammatory bowel disease, e.g., Crohn's Disease, Ulcerative Colitis; a diagnosis of chronic intestinal malabsorption syndromes, e.g., celiac sprue, bacterial overgrowth, chronic pancreatitis, pancreatic insufficiency in the past 5 years; large bowel resection; a diagnosis of malignancy, other than non-melanoma skin cancer in the past five years; severe lung disease - class three or four (e.g., COPD or emphysema requiring; oxygen) in the past five years; severe heart disease: cardiovascular disease functional class 3 or 4 in the past 5 years; severe liver disease, e.g., cirrhosis; any HIV positive diagnosis; active hepatitis B, defined as : Hep B surface antigen positive; active hepatitis C, defined as: measurable HCV RNA; use of chronic oral cortico-

Baron 2004 (*Continued*)

	steroid therapy in the past five years; use of lithium in the past five years; use of phenytoin's in the past five years; use of quinidine in the past five years; use of therapeutic vitamin D in the past five years.
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (1000 IU) daily; Intervention group 2: calcium (1200 mg) daily; Intervention group 3: vitamin D_3 (1000 IU) plus calcium (1200 mg) daily; Intervention group 4 (Control group): placebo daily; for a period of five years. Women who decline to forego calcium supplementation will be randomised only to calcium alone or to calcium plus vitamin D intervention group.
Outcomes	The primary outcome measure will be new adenomas detected on follow-up colonoscopy.
Starting date	July 2004 Expected completion: December 2017.
Contact information	John A Baron, MD, Principal Investigator, Dartmouth-Hitchcock Medical Center.
Notes	

Binkley 2007

Trial name or title	Clinical approaches to correcting vitamin D inadequacy and maintaining adequacy
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (four intervention groups).
Participants	Country: United States. Estimated number of participants: 64. Inclusion criteria: community dwelling men and women aged 65 years or over able and willing to sign informed consent; serum 25OHD concentration $\geq$ 10 and less than 60 ng/ml by HPLC; willing to avoid use of cod-liver oil and non-trial vitamin D supplementation; standard multiple vitamins containing $\leq$ 400 IU used no more than once daily will be allowed. Exclusion criteria: current hypercalcaemia (serum calcium > 10.5 mg/dl) or untreated primary hyperparathyroidism; history of nephrolithiasis; screening 25-hydroxyvitamin D concentration $\geq$ 60 ng/ml; baseline 24-hour urine calcium > 250 mg if female, > 300 mg if male; known risk factors for hypercalcaemia, e.g., malignancy, tuberculosis, sarcoidosis, Paget's disease; history of any form of cancer within the past five years with the exception of adequately treated squamous cell or basal cell skin cancer; renal failure defined as a calculated creatinine clearance $\leq$ 25 ml/minute; severe end-organ disease, e.g., cardiovascular, hepatic, hematologic, pulmonary, etc, which may limit ability to complete the trial; known malabsorption syndromes, e.g., celiac disease, radiation enteritis, active inflammatory bowel disease, etc.; use of medications known to alter bone turnover including bisphosphonates, oestrogen, selective oestrogen receptor modulators, parathyroid hormone, testosterone or calcitonin vitamin D intake greater than 5000 IU daily; treatment with any active metabolites of vitamin D within six months of screening; treatment with any drug which may interfere with vitamin D metabolism, e.g., phenobarbital, phenytoin.
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_2 (50,000 IU) monthly; Intervention group 2: vitamin D_2 (1600 IU) daily;

Binkley 2007 (*Continued*)

	Intervention group 3: vitamin D_3 (50,000 IU) monthly; Intervention group 4: vitamin D_3 (1600 IU) daily; Intervention group (Control group): placebo daily; for a period of one year.
Outcomes	The primary outcome measure will be change in 25-hydroxyvitamin D with various D_2 and D_3 dosing regimens. Secondary outcome measures will be to determine whether once monthly vitamin D_2 or D_3 dosing is as effective as daily dosing in attainment, and subsequent maintenance, of 25-hydroxyvitamin D status and to delineate the effect of these vitamin D regimens on other parameters of skeletal relevance.
Starting date	February 2007; Expected completion: November 2008.
Contact information	Neil Binkley, MD UW Osteoporosis Clinical and Research Program Madison, Wisconsin 53705.
Notes	

Gallagher 2006

Trial name or title	Vitamin D supplementation in older women
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (seven intervention groups).
Participants	Country: United States. Estimated number of participants: 320. Inclusion criteria: women aged 57 years or older; at least seven years post-menopause; serum 25-hydroxyvitamin D level 5 ng/ml to 20 ng/ml; body mass index less than or equal to 40 kg/m^2; willing to discontinue multivitamins that contain vitamin D during the trial. Exclusion criteria: cancer (except basal cell carcinoma) or terminal illness; previous hip fracture; hemiplegia (paralysis of one side of the body); uncontrolled type I diabetes or fasting blood sugar greater than 140 mg in type II; kidney stones more than twice in a lifetime; chronic renal failure; evidence of chronic liver disease, including alcoholism; physical conditions such as severe osteoarthritis, rheumatoid arthritis, heart failure severe enough to prevent reasonable physical activity; previous treatment with bisphosphonates (more that 3 months), parathyroid hormone or parathyroid hormone derivatives, (e.g., teriparatide or fluoride) in the last 6 months; previous treatment within the last six months with calcitonin or estrogen chronic high dose corticosteroid therapy (more than 10 mg per day) for over six months and not within the last 6 months; anticonvulsant therapy; high dose thiazide therapy (more than 37.5 mg); 24 hour urine calcium greater than 290 mg on two baseline tests; serum calcium exceeding upper normal limit on 2 baseline tests; bone mineral density score less than -3.0 for spine or hip.
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) daily; Intervention group 2: vitamin D_3 (1600 IU) daily; Intervention group 3: vitamin D_3 (2400 IU) daily; Intervention group 4: vitamin D_3 (3200 IU) daily; Intervention group 5: vitamin D_3 (4000 IU) daily; Intervention group 6: vitamin D_3 (4800 IU) daily; Intervention group 7 (Control group): placebo daily; for a period of one year.

Gallagher 2006 (*Continued*)

Outcomes	The primary outcome measures will be: changes in serum 25-hydroxyvitamin D and parathyroid hormone levels. Secondary outcome measures will be: calcium absorption; serum/urine calcium; bone markers; bone density; muscle strength; falls.
Starting date	October 2006; Expected completion: October 2010.
Contact information	JC Gallagher, MD, MD tel: 402-280-4518 bones@creighton.edu
Notes	

Gallagher 2007

Trial name or title	Vitamin D supplementation in younger women
Methods	Randomised, double-blind, placebo controlled trial using parallel group design (five intervention groups).
Participants	Country: United States. Estimated number of participants: 200. Inclusion criteria: premenopausal Caucasian or African American women, aged 25 to 45 years; (women with hysterectomy and/or oophorectomy must have a premenopausal Follicle-stimulating hormone level); serum 25-hydroxyvitamin D level: 5 to 20 ng/ml; BMI < 45 kg/m2; willing to discontinue vitamin D supplements after entering the trial; negative pregnancy test before BMD and calcium absorption tests; willing to give signed informed consent form. Exclusion criteria: cancer (exceptions: basal cell carcinoma or if cancer occurred more than 10 years ago) or terminal illness; previous hip fracture; hemiplegia; uncontrolled type I diabetes ± significant proteinuria or fasting blood sugar >140 mg in type II diabetes; kidney stones more than two in a lifetime; chronic renal failure (serum creatinine > 1.4 mg/dl); evidence of chronic liver disease, including alcoholism; physical conditions such as severe osteoarthritis, rheumatoid arthritis, heart failure severe enough to prevent reasonable physical activity; previous treatment with bisphosphonates (more that three months), parathyroid hormone (PTH) or PTH derivatives, (e.g., teriparatide or fluoride in the last six months; previous treatment within the last six months with calcitonin or estrogen (except birth control pills); chronic high dose corticosteroid therapy (> 10 mg/day) for over six months and not within the last six months; anticonvulsant therapy. (Dilantin, Phenobarbital); high dose thiazide therapy (> 37.5 mg); 24 hour urine calcium > 290 mg on two baseline tests; serum calcium exceeding upper normal limit on two baseline tests; bone mineral density. T-score less than -3.0 for spine or hip.
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (400 IU) daily; Intervention group 2: vitamin D_3 (800 IU) daily; Intervention group 3: vitamin D_3 (1600 IU) daily; Intervention group 4: vitamin D_3 (2400 IU) daily; Intervention group 5 (Control group): placebo daily; for a period of one year.
Outcomes	The primary outcome measures will be serum 25-hydroxyvitamin D, and parathyroid hormone. Secondary outcome measures will be serum and urine calcium levels.

Gallagher 2007 (*Continued*)

Starting date	October 2007; Expected completion January 2012.
Contact information	JC Gallagher, MD tel: 402-280-4518 bones@creighton.edu
Notes	

Giovannucci 2007

Trial name or title	Vitamin D for chemoprevention
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (four intervention groups).
Participants	Country: United States. Estimated number of participants: 320. Inclusion criteria: healthy black participants 30 to 80 years of age; comfortable communicating in English; currently has a primary care physician; willing to discontinue vitamin D or calcium supplements; willing to have all protocol specific tests run. Exclusion criteria: plans on taking a vacation or travel to a sunny region within three months of vitamin supplementation period except for a short period (i.e., one weekend); pregnant or breast feeding or planning on becoming pregnant in the following year; pre-existing calcium (including hypercalcaemia), parathyroid conditions (including hyperparathyroidism), sarcoidosis; no concurrent active malignancies (other than non-melanoma skin cancer) or previous diagnosis of prostate cancer; cognitively impaired; active thyroid disease (e.g., Graves, Hashimoto's or thyroiditis); history of nephrolithiasis, chronic liver disease, chronic renal disease, or renal dialysis.
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (1000 IU) daily; Intervention group 2: vitamin D_3 (2000 IU) daily; Intervention group 3: vitamin D_3 (4000 IU) daily; Intervention group 4 (Control group): placebo daily; for a period of three months. Participants will be followed six months.
Outcomes	The primary outcome measures will be: among Blacks, identify a dose of oral vitamin D supplementation that will result in levels of plasma 25-hydroxyvitamin D that would be predicted to reduce colorectal cancer incidence. Secondary outcome measures will be: the influence of oral vitamin D supplementation on inflammatory markers and compare germline polymorphic variation in Vitamin D pathway genes between Blacks and a cohort of Whites.
Starting date	October 2007; Expected completion October 2009.
Contact information	Charles Fuchs, MD tel: (617) 632-5840 Charles_Fuchs@dfci.harvard.edu
Notes	

Goswami 2008b

Trial name or title	Cholecalciferol supplementation, muscle strength
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: India. Estimated number of participants: 96. Inclusion criteria: age 20 years or older; residents of Delhi; commitment for follow-up at eight weeks, 6 months and 1 year; consent for eight weeks of supplementation. Exclusion criteria: participants taking drugs, which can affect bone mineral metabolism such as glucocorticoids, antitubercular, antiepileptics, levothyroxine, bisphosphonates; chronic renal or liver disorder; chronic diarrhoea.
Interventions	Participants will be randomly assigned to receive: Intervention group: vitamin D_3 (60,000 IU) weekly plus calcium (1000 mg) daily for first two months; followed by vitamin D_3 (60,000 IU) monthly plus calcium (1000 mg) daily for the next four months. Control group: placebo (lactose placebo granules in identical sachet given weekly and two lactose tablets for first two months followed one sachet of placebo granules every month and two tablets of lactose containing placebo tablets taken daily for next four months).
Outcomes	The primary outcome measure will be improvement in peripheral muscle strength as revealed by muscle power and magnetic resonance spectroscopic trial.
Starting date	May 2008; Expected completion: June 2009.
Contact information	Ravinder Goswami, MD Department of Endocrinology and Metabolism, All India Institute of Medical sciences, New Delhi 110029 India
Notes	

Harris 2008

Trial name or title	Vitamin D, glucose control and insulin sensitivity in African-Americans
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United States. Estimated number of participants: 96. Inclusion criteria: African-American by self designation aged 40 and older; glucose intolerance; body mass index 25.0 to 39.9. Exclusion criteria: diabetes potentially requiring pharmacotherapy, defined as A1c > 7%; uncontrolled thyroid disease; current parathyroid, liver or kidney disease; renal stone within five years; sarcoidosis, current pancreatitis, active tuberculosis, hemiplegia, gout; inflammatory bowel disease, colostomy, malabsorption; cancer other than basal cell skin cancer within five years; uncontrolled arrhythmia in past year; albinism or other condition associated with reduced skin pigmentation; pregnancy over the last 1 year; intent to become pregnant; menopause onset within 1 year; any other unstable medical condition laboratory tests; fasting plasma glucose < 100; haemoglobin A1c > 7%; laboratory evidence of liver disease (e.g., AST > 70 U/L or ALT > 72 IU/L); laboratory evidence of kidney disease (e.g., estimated glomerular filtration rate < 60 ml/min/1.73 m^2; elevated spot urine calcium to creatinine ratio > 0.38 mg/dl; abnormal serum calcium (serum calcium > 10.5 mg/dl); anaemia (hematocrit < 36% in men, < 33% in women); medications (use in past

Harris 2008 (*Continued*)

	three months; oestrogen or testosterone); prescription vitamin D, lithium; oral corticosteroids; anti-seizure medications; unstable doses of psychotropics or phenothiazines; cholestyramine supplements (current use - may discontinue after screening); vitamin D supplements, cod liver oil, calcium supplements; body mass index less < 25 or > 39.9; consumption of more than 14 alcoholic drinks per week; inability to attend all three trial visits as scheduled; inability to provide written informed consent; age < 40 years; not African-American (by self-designation); participation in another research intervention trial; corresponds to a 24-hour urinary calcium excretion > 400 mg.
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (4000 IU) daily; Intervention group 2 (Control group): placebo daily; for a period of 12 weeks.
Outcomes	The primary outcome measure will be insulin secretion, insulin sensitivity and glucose control.
Starting date	July 2008; Expected completion: February 2011.
Contact information	Nancy Palermo, B.S. tel: 617-556-3073 nancy.palermo@tufts.edu
Notes	

Khan 2009

Trial name or title	The effects of oral vitamin D supplementation on cardiovascular disease risk in UK South Asian women
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Estimated number of participants: 60. Inclusion criteria: South Asian healthy women aged 18 years or over; serum 25 hydroxyvitamin D less than 75 nmol/L. Exclusion criteria: symptomatic; cardiovascular disease (including previous stroke, transient ischaemic attack, angina, myocardial infarction, angioplasty, coronary bypass grafting, symptomatic peripheral vascular disease, chronic heart failure, atrial fibrillation); already taking vitamin D supplements; estimated glomerular filtration rate less than 40 ml/min (by four-variable Modification of Diet in Renal Disease equation); liver function tests (alanine aminotransferase, bilirubin, alkaline phosphatase) greater than three times normal; unable to give written informed consent; corrected calcium level of greater than 2.60 or less than 2.15 mmol/L; clinical diagnosis of osteomalacia; history of renal calculi, sarcoidosis or metastatic malignancy; pregnant or of child bearing age and not taking reliable contraception.
Interventions	Patients will be randomly assigned to receive: Intervention group 1: vitamin D_3 (100,000 IU) in a single dose orally; Intervention group 2 (Control group): placebo; Participants will be followed eight weeks.

Khan 2009 (*Continued*)

Outcomes	The primary outcome measures will be: change in macrovascular endothelial function, which will be assessed by flow mediated dilation according to standard guidelines. All measurements will be taken at the start of the trial (i.e., before the intervention) and at 4 and 8 weeks post-intervention. Secondary outcome measures will be: microvascular endothelial function tested using Iontophoresis according to standard guidelines; arterial stiffness as measured by pulse wave velocity using the validated SphygmoCor pulse waveform analysis system; office blood pressure measured by oscillometric automatic blood pressure device; metabolic and inflammatory markers; fasting serum lipid profiles; fasting glucose, glycosylated haemoglobin (HbA1c) and insulin levels; adiponectin and leptin; plasminogen activator inhibitor-1 and tissue plasminogen activator antigen; C-reactive protein; tumour necrosis factor alpha and interleukin-6; E-selectin - an adhesion molecule expressed only on activated endothelial cells; change in serum 25-hydroxyvitamin D and parathyroid hormone levels.
Starting date	12.01.2009; Expected completion 11.07.2010.
Contact information	The Institute of Cardiovascular Research (TICR) Vascular & Inflammatory Diseases Research Unit University of Dundee Ninewells Hospital & Medical School Dundee United Kingdom DD1 9SY f.khan@dundee.ac.uk
Notes	

McAlindon 2006

Trial name or title	Vitamin D to Slow Progression of Knee Osteoarthritis
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United States. Estimated number of participants: 146. Inclusion criteria: patients with symptomatic knee osteoarthritis (OA) aged 45 years and older (chronic knee discomfort based on affirmative response to the question "During the past 12 months, have you had pain, aching, or stiffness in or around your knee(s) on most days for at least one month)"; WOMAC pain subscale score of at least 1; tibiofemoral OA on posterior anterior weight-bearing semi-flexed knee radiographs with severity equivalent to Kellgren and Lawrence grade of at least 2; clinical examination confirming knee pain or discomfort referable to the knee joint; prepared to refrain from use of glucosamine, chondroitin, MSM, DMSO, and doxycycline; pass faintness of heart trial period. Exclusion criteria: serum 25-hydroxyvitamin D level greater than 80 ng/ml; use of glucosamine, chondroitin, or doxycycline within three months of random assignment; use of MSM, DMSO within three months of random assignment; use of vitamin D supplements such that the total daily dose is greater than 1000 IU or a single source is greater than 800 IU; intra-articular joint injections (e.g., glucocorticoid or hyaluronic acid formulations, within three months of random assignment); chronic glucocorticoid use; hypercalcaemia (total serum calcium greater than 10.5 mg/dL); hypercalcuria (spot urine calcium: creatinine ratio of 0.275 for women and 0.325 for men, corresponding to 24-hour calcium excretion of 0.30 and 0.35 g, respectively) ; estimated glomerular filtration rate less than 30; hyperparathyroidism (parathyroid hormone greater than 65 pg/mL; history of lymphoma or sarcoidosis; Reiter's syndrome; psoriatic arthritis; rheumatoid arthritis;

McAlindon 2006 (*Continued*)

	ankylosing spondylitis; currently on treatment for tuberculosis; malabsorption disorders (e.g., advance liver disease, chronic renal disease-stage four or five, Crohn's disease, Whipple's disease, celiac sprue); serious medical conditions or impairments that, in the view of the investigator, would obstruct trial participation; pregnancy; plan to permanently relocate from the region during the trial period; planned knee or hip arthroplasty during the trial period; any contra-indication to having an MRI scan.
Interventions	Patients will be randomly assigned to receive: Intervention group 1: vitamin D_3 (2000) IU daily; Intervention group 2 (Control group): placebo daily; for a period of two years.
Outcomes	The primary outcome measures will be cartilage volume loss and knee symptoms. Secondary outcome measures will be physical function, quality of life, and pathological severity global score.
Starting date	March 2006; Expected completion May 2009.
Contact information	Timothy E McAlindon, MD, MPH, Principal Investigator, Tufts Medical Center
Notes	

Pande 2006

Trial name or title	A trial to study the effect of vitamin D supplementation on glucose and insulin metabolism in centrally obese men
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: India. Estimated number of participants: 100. Inclusion criteria: male, aged 35 years or older, waist circumference $\geq$ 78 cm. Exclusion criteria: diabetic (fasting blood sugar >126 mg/dl or on anti-diabetic medication; blood pressure > 140/90 mmHg or on anti-hypertensive medication; receiving Vitamin D or calcium supplementation; chronic disease - renal/hepatic/malignancy/gastrointestinal; on any medication within the last one month which could potentially influence insulin secretion, insulin sensitivity, vitamin D or calcium metabolism; febrile illness or infective morbidity in the past 10 days; past history of nephrolithiasis.
Interventions	Paraticipants will be randomly assigned to receive: Intervention group 1: vitamin D weekly; Intervention group 2 (Control group): placebo weekly; for a period of six weeks.
Outcomes	The primary outcome measure will be: oral glucose insulin sensitivity (OGIS). Secondary outcome measures will be: lipid profile, CRP, ApoA1, ApoB, and blood pressure.
Starting date	July 2006; Expected completion: September 2006.
Contact information	Jitendra N Pande, MD Sitaram Bhartia Institute of Science and Research New Delhi 110016 India

Pande 2006 (*Continued*)

Notes	

Papaioannou 2007

Trial name or title	A randomised, controlled comparison of vitamin D strategies in acute hip fracture patients.
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (three intervention groups).
Participants	Country: India. Estimated number of participants: 66. Inclusion criteria: fragility hip fracture patient with or without previous vitamin D supplementation. Exclusion criteria: patients with pathological fracture secondary to malignancy or intrinsic bone disease (e.g.. Paget's disease); cancer in the past 10 years likely to metastasize to bone; renal insufficiency (creatinine <30 ml/min); hypercalcaemia (primary hyperparathyroidism; granulomatous diseases; drug-induced such as lithium, thiazides), hypocalcaemia, hypercalciuria, fracture or stroke within the last three months; hormone replacement therapy, calcitonin, fluoride, or bisphosphonates during the previous 24 months; pre-existing bone abnormality; renal stones in past 10 years.
Interventions	Paraticipants will be randomly assigned to receive: Intervention group 1: vitamin D_2 (50,000 IU) one time bolus followed by vitamin D_3 (800 IU) daily; Intervention group 2: vitamin D_2 (100,000 IU) one time bolus followed by vitamin D_3 (800 IU) daily; Intervention group 3 (Control group): placebo one time bolus; for a period of three months.
Outcomes	The primary outcome measures will be: baseline blood work for 25 hydroxyvitamin D, parathyroid hormone, calcium, phosphate, alkaline phosphatase, creatine. Secondary outcome measures will be: functional assessment using the two minute walk test and timed up and go at discharge and three month follow-up.
Starting date	October 2007; Expected completion: July 2009.
Contact information	Alexandra Papaioannou MD, McMaster University, United States.
Notes	

Pittas 2007b

Trial name or title	Vitamin D and calcium homeostasis for prevention of type 2 diabetes
Methods	Randomised, double-blind, placebo-controlled trial using 2 x 2 factorial design.
Participants	Country: United States. Estimated number of participants: 112 Inclusion criteria: healthy participants aged 40 years or older; lower body mass index limit: 25 inclusive; upper body mass index limit: 40 inclusive; glucose intolerance/mild diabetes defined as fasting glucose $\geq$ 100 mg/dl or 2. 2-hour glucose after oral glucose tolerance test $\geq$ 140 mg/dl or 5.8 $\leq$ haemoglobin A1c $\leq$ 7. Exclusion criteria: diabetes requiring pharmacotherapy; smoking; hyperparathyroidism; hypercalcaemia (calcium > 10.5 mg/dl); kidney stone; pregnancy.

Pittas 2007b (*Continued*)

Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (2000 IU) daily plus calcium (800 mg) daily; Intervention group 2: vitamin D_3 (2000 IU) daily; Intervention group 3: calcium (800 mg) daily; Intervention group 4 (Control group): vitamin D_3 placebo plus calcium placebo daily; for a period of four months.
Outcomes	The primary outcome measures will be insulin sensitivity, insulin secretion and disposition Index. Secondary outcome measures will be glucose tolerance (fasting, after oral glucose tolerance test), systemic inflammation, lipoprotein profile, blood pressure, body weight and body composition; genetic studies on Vitamin D related genes and risk of type 2 diabetes and cardiometabolic outcomes; to collect and archive biological specimens (serum, plasma, DNA) so that they can be used for testing of new hypotheses either within the parent trial or through future ancillary studies.
Starting date	September 2007; Expected completion July 2010.
Contact information	Anastassios Pittas, MD tel: 617-636-2834 caddm@tufts-nemc.org
Notes	

Schwartz 2008

Trial name or title	Effects of vitamin D on lipids
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (three intervention groups).
Participants	Country: United States. Estimated number of participants: 90. Inclusion criteria: any medically stable person with hypercholesterolaemia able to swallow pills. Exclusion criteria: clinical instability of underlying disease process (e.g., recent hospitalisation, change of dosages of medications within the prior two weeks, or new medications within one month); recent transfusion; severe renal failure or dialysis; hypercalcaemia; malignancy under active treatment; feeding tube; intestinal bypass surgery; inability to swallow tablets.
Interventions	Paraticipants will be randomly assigned to receive: Intervention group 1: vitamin D_2 (1000 IU) daily; Intervention group 2: vitamin D_3 (1000 IU) daily; Intervention group 3 (Control group): placebo daily; for a period of 12 weeks.
Outcomes	The primary outcome measure will be low-density lipoprotein-cholesterol. Secondary outcome measures will be: vitamin D and metabolite concentrations with supplementation and time course of repletion in deficient or insufficient participants, measures of inflammatory markers.
Starting date	July 2008; Expected completion April 2010.
Contact information	Janice B Schwartz, MD Jewish Home, University of California, San Francisco

Schwartz 2008 (*Continued*)

Notes	

Shapses 2007

Trial name or title	The effect of vitamin D supplementation during caloric restriction on intestinal calcium absorption
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Estimated number of participants: 60. Inclusion criteria: postmenopausal women aged 50 to 70 years who are more than 2 years since last menses; obese or overweight; live in the geographic vicinity of Rutgers University. Exclusion criteria: currently on any medication known to influence calcium or bone metabolism, including hormone replacement therapy, or with evidence of diseases known to influence calcium metabolism (i.e., metabolic bone disease, hyperparathyroidism, untreated thyroid disease, significant immune, hepatic, or renal disease, significant cardiac disease (i.e., heart attack or stroke in the past 6 months, abnormal electrocardiogram) , active malignancy or cancer therapy within the past year); history of kidney stones; weight gain or weight loss (5% of body weight) within three months prior to recruitment; participation in other investigational studies during the 12-month trial period; travel for longer than two consecutive weeks during the trial period; usually have a very high or low intake of calcium (more than 1500 mg or less than 500 mg per day).
Interventions	Paraticipants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (1200 IU) daily plus weight loss; Intervention group 2 (Control group): placebo daily plus weight loss; Intervention group 3: vitamin D_3 (1200 IU) daily plus weight maintenance; Intervention group 4 (Control group): vitamin D_3 (1200 IU) daily plus weight maintenance; for a period of five weeks.
Outcomes	The primary outcome measure will be changes in calcium absorption. Secondary outcome measures will be changes in serum and urine bone markers, hormones, proteins and genes.
Starting date	March 2007; Expected completion May 2011.
Contact information	Sue Shapses, PhD, RD shapses@aesop.rutgers.edu
Notes	

Struthers 2008

Trial name or title	Does vitamin D reduce blood pressure and left ventricular (LV) mass in resistant hypertensive patients with vitamin D insufficiency?
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Estimated number of participants: 74. Inclusion criteria: aged 18 years or over; serum 25 hydroxyvitamin D less than 75 nmol/L; office blood

Struthers 2008 (*Continued*)

	pressure greater than 140/90 mmHg despite three or more antihypertensives. Exclusion criteria: hypertension known to be due to a correctable underlying medical or surgical cause; estimated glomerular filtration rate less than 40 ml/min (by four variable Modification of Diet in Renal Disease equations); liver function tests (alanine aminotransferase, bilirubin, alkaline phosphatase) greater than 3 x normal; corrected calcium greater than 2.60 mmol/L or less than 2.15 mmol/L; known metastatic malignancy or sarcoidosis; clinical diagnosis of osteomalacia; history of renal calculi; diagnosis of heart failure with left ventricular systolic dysfunction; atrial fibrillation; already taking vitamin D supplements (consumption of fish oils will not be a contra-indication to enrolment); unable to give written informed consent; pregnant or of childbearing age and not taking reliable contraception.
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (100,000 IU) orally daily every two months; Intervention group 2 (Control group): placebo every two months; for a period of four months. Participants will be followed six months.
Outcomes	The primary outcome measure will be change in office blood pressure, measured at zero, two, four and six months.
Starting date	01.08.2008; Expected completion 31.07.2010.
Contact information	Prof Allan Struthers Department of Clinical Pharmacology Ninewells Hospital Dundee United Kingdom DD1 9SY a.d.struthers@dundee.ac.uk
Notes	

VIDEO 2004

Trial name or title	A randomised, double-blind, placebo-controlled trial of Vitamin D supplementation in the management of symptomatic knee osteoarthritis (the VIDEO study).
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Estimated number of participants: 800. Inclusion criteria: participants aged 50 years or over; ambulatory (not wheel chair bound); able and willing to attend or comply with treatment and follow-up; radiological evidence of early disease at medial tibio-femoral knee compartment (modified Kellgren & Lawrence score 2/3, joint space width >1 mm); pain in knee for most days of previous month; written informed consent. Exclusion criteria: secondary osteoarthritis, septic arthritis, gout, Wilson's disease, Paget's disease, pseudo gout; history of inflammatory arthritis; knee stiffness > 30 minutes duration; current user of cod liver oil or vitamin D supplementation; current use of glucosamine or chondroitin for less than 3 months; history of hyperparathyroidism or osteomalacia; current use of anti-epileptic medication; current use of bisphosphonates or use within two years; history of hypercalcaemia or hypercalciuria; history of hyperthyroidism, sarcoidosis; history of renal stones; previous intra-articular injection: steroid within three months, hyalgan within six months; previous knee surgery or arthroscopy within six months; history of osteoporotic fracture; history of cancer within last five years, excluding skin cancer; serious psychiatric disorders including dementia; inability to understand the procedures; inability to attend or comply with treatment or follow-up scheduling; pregnancy.

VIDEO 2004 (*Continued*)

Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (800 IU) daily; Intervention group 2 (Control group): placebo daily; for a period of three years.
Outcomes	The primary outcome measure will be radiological progression of knee osteoarthritis in medial joint compartment at 36 months. Secondary outcome measures will be radiological progression of knee osteoarthritis in other joint compartments. Reduction in pain and functional disability. Improvement in quality of life.
Starting date	1.02.2004 Expected completion: 31.01.2009.
Contact information	Dr Richard Keen Metabolic Unit Royal National Orthopaedic Hospital Stanmore Brockley Hill Stanmore HA7 4LP United Kingdom.
Notes	

Vital D 2009

Trial name or title	The Vital D Study
Methods	A randomised, double-blind, placebo-controlled trial of Vitamin D supplementation.
Participants	Country: Australia. Number of participants randomised: 1500 community dwelling women at high risk of fracture. Inclusion criteria: women aged 70 years and older who were not taking medication that affected bone and calcium metabolism at baseline, did not have renal disease, hypercalcaemia, sarcoidosis, tuberculosis or lymphoma. Exclusion criteria: serum corrected calcium was greater than 2.65 mmol/L, serum creatinine greater than 150 μmol/L or if their current medications included any of the following:- vitamin D greater than 400 IU/day; bisphosphonates, selective oestrogen receptor modulators, hormone replacement therapy, or calcitriol.
Interventions	Participants were randomised to orally receive either 500,000 IU of vitamin D_3 (cholecalciferol) or placebo every autumn for five consecutive years.
Outcomes	The primary outcome measures were fractures. Secondary outcome measures were falls, mental well-being, duration of independent residency, reduction in total healthcare utilisation.
Starting date	01.04.2003
Contact information	Prof Geoffrey Nicholson, Department of Clinical and Biomedical Sciences P.O. Box 281, 3220 Geelong, Australia geoffn@barwonhealth.org.au
Notes	

Witham 2009

Trial name or title	Can high-dose vitamin D supplementation reduce blood pressure and markers of cardiovascular risk in older people with isolated systolic hypertension?
Methods	Randomised, double-blind, placebo controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Estimated number of participants: 74. Inclusion criteria: aged 70 years or over, office systolic blood pressure greater than 140 mmHg; serum 25 hydroxyvitamin D less than 75 nmol/L. Exclusion criteria: hypertension known to be due to a correctable underlying medical or surgical cause; diastolic blood pressure greater than 90 mmHg; systolic blood pressure greater than 180 mmHg; estimated glomerular filtration rate less than 40 ml/min (by four-variable modification of diet in renal disease rate equation); liver function tests (alanine aminotransferase, bilirubin, alkaline phosphatase) greater than three times normal; corrected calcium greater than 2.60 mmol/L or less than 2.15 mmol/L; known metastatic malignancy or sarcoidosis; clinical diagnosis of osteomalacia; history of renal calculi; diagnosis of heart failure with left ventricular systolic dysfunction; atrial fibrillation; already taking vitamin D supplements (consumption of fish oils will not be a contraindication to enrolment); unable to give written informed consent.
Interventions	Patients will be randomly assigned to receive: Intervention group 1: vitamin D_3 (4000 IU) daily; Intervention group 2 (Control group): placebo daily; for a period of one year.
Outcomes	The primary outcome measure will be change in office blood pressure at three months. Secondary outcome measures will be: office blood pressure (at 0, 6, 9, 12 months); 24 hour mean blood pressure (at 0, 3, 6, 9, 12 months); B-type natriuretic peptide, high sensitivity C-reactive protein (hsCRP) and homeostatic model assessment index at 0, 3 and 12 months; endothelial function measured by flow-mediated dilatation of the brachial artery at 0, 3 and 12 months; pulse wave velocity at 0, 3 and 12 months; change in 25-hydroxyvitamin D and parathyroid hormone levels, cholesterol and triglycerides.
Starting date	1.02.2009; Expected completion: 31.01.2012.
Contact information	Dr Miles Witham Section of Ageing and Health Ninewells Hospital Dundee DD1 9SY United Kingdom m.witham@dundee.ac.uk
Notes	

Witte 2009

Trial name or title	The impact of vitamin D supplementation in chronic heart failure
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups).
Participants	Country: United Kingdom. Estimated number of participants: 100. Inclusion criteria: patients aged 18 years or over with class II and III heart failure due to left ventricular systolic dysfunction (left ventricular ejection fraction less than or equal to 40%); stable symptoms for 3 months on maximally tolerated medical therapy with no recent change in medication; able to give informed written consent.

Witte 2009 (*Continued*)

	Exclusion criteria: currently taking (or have taken in the previous 3 months) calcium or other vitamin supplements; currently prescribed amlodipine or other calcium channel antagonists (intake of spironolactone will be recorded); chronic heart failure due to untreated valvular heart disease; history of primary hyperparathyroidism, sarcoidosis, tuberculosis or lymphoma; vitamin D levels greater than 50 nmol/L.
Interventions	Patients will be randomly assigned to receive: Intervention group 1: vitamin D_3 (4000 IU) daily; Intervention group 2 (Control group): placebo daily; for a period of one year.
Outcomes	The primary outcome measure will be: left ventricular function assessed at baseline and twelve months, measured by cardiac magnetic resonance. Secondary outcome measures will be: symptom status (New York Heart Association status), measured at baseline, one month, four months, eight months, twelve months; exercise tolerance, measured at baseline and twelve months; quality of life (Minnesota living with heart failure questionnaire, European Quality of Life instrument and a 19-item Likert scale index), measured at baseline, one month, four months, eight months, twelve months; flow mediated dilatation, measured at baseline and twelve months; immune status, measured at baseline and twelve months; insulin resistance, measured at baseline and twelve months; autonomic activation (measured by heart rate variability), measured at baseline and 12 months; renal function, measured at baseline, 1, 4, 8, and 12 months; B-type natriuretic peptide, measured at baseline, 1, 4, 8, and 12 months.
Starting date	01.01.2009; Expected completion 31.12.2012.
Contact information	Klaus Witte Division of Cardiovascular and Diabetes Research LIGHT building University of Leeds, Leeds, United Kingdom, LS2 9JT klauswitte@hotmail.com
Notes	

Abbreviations
BMI: body mass index; PTH: parathyroid hormone; DMSO: dimethyl sulphoxide; MSM: methylsulfonylmethane; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; DNA: deoxyribonucleic acid

DATA AND ANALYSES

Comparison 1. Vitamin D versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality in trials with a low or high risk of bias	50	94148	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.93, 0.99]
1.1 Trials with low risk of bias	26	66474	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 0.99]
1.2 Trials with high risk of bias	24	27674	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.94, 1.03]
2 All-cause mortality in individually and cluster randomised trials	50	94148	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 1.00]
2.1 Individually randomised trials	48	80826	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 0.99]
2.2 Cluster randomised trials	2	13322	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.82, 1.34]
3 All-cause mortality in placebo controlled and no intervention trials	50	94148	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 1.00]
3.1 Placebo in the control group	38	72754	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 0.99]
3.2 No intervention in the control group	12	21394	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.91, 1.21]
4 All-cause mortality in primary and secondary prevention trials	50	94148	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 1.00]
4.1 Primary prevention trials	44	93585	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 1.00]
4.2 Secondary prevention trials	6	563	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.55, 2.43]
5 All-cause mortality and vitamin D status	50	94148	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 1.00]
5.1 Vitamin D insufficiency	22	56295	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.99]
5.2 Vitamin D adequacy	18	15597	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.04]
5.3 Unknown vitamin D status	10	22256	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.14]
6 All-cause mortality in trials using vitamin D_3 (cholecalciferol))	32	74789	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.91, 0.98]
6.1 Vitamin D_3 trials with low risk of bias	16	51603	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.87, 0.99]
6.2 Vitamin D_3 trials with high risk of bias	16	23186	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 1.00]
7 All-cause mortality in trials using vitamin D_3 singly or combined with calcium	32		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Vitamin D_3 singly	9	11587	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.02]
7.2 Vitamin D_3 combined with calcium	25	62914	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.99]

8 All-cause mortality in trials using low- or high dose of vitamin D_3	32		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Low-dose of vitamin D_3 (< 800 IU a day)	12	50367	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.87, 0.97]
8.2 High-dose of vitamin D_3 (≥ 800 IU a day)	21	24490	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.01]
9 All-cause mortality in trials applying vitamin D_3 daily or intermittently	32		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Vitamin D_3 daily	28	69002	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.99]
9.2 Vitamin D_3 intermittently	5	5899	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
10 All-cause mortality in trials using vitamin D_3 and vitamin D status	32	74789	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.91, 0.98]
10.1 Vitamin D insufficiency	16	55481	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.90, 0.99]
10.2 Vitamin D adequacy	9	4293	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.79, 1.07]
10.3 Unknown vitamin D status	7	15015	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.19]
11 All-cause mortality in trials using vitamin D_2 (ergocalciferol)	12	18349	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.97, 1.09]
11.1 Vitamin D_2 trials with low risk of bias	9	14439	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.05]
11.2 Vitamin D_2 trials with high risk of bias	3	3910	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.05, 1.37]
12 All-cause mortality in trials using vitamin D_2 singly or combined with calcium	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Vitamin D_2 singly	8	17079	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.97, 1.11]
12.2 Vitamin D_2 combined with calcium	5	1307	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.64, 1.57]
13 All-cause mortality in trials using low- or high dose of vitamin D_2	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Low-dose of vitamin D_2	1	101	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.17, 3.98]
13.2 High-dose of vitamin D_2	12	18273	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.10]
14 All-cause mortality in trials applying vitamin D_2 daily or intermittently	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Vitamin D_2 daily	6	1349	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.68, 1.12]
14.2 Vitamin D_2 intermittently	6	17000	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.95, 1.18]
15 All-cause mortality in trials using vitamin D_2 and vitamin D status	12	18349	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.97, 1.09]
15.1 Vitamin D insufficiency	6	4413	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.05, 1.37]
15.2 Vitamin D adequacy	5	10496	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.10]
15.3 Unknown vitamin D status	1	3440	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.07]

16 All-cause mortality in trials using alfacalcidol (1-α hydroxyvitamin D)	4	617	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.22, 4.15]
17 All-cause mortality in trials using alfacalcidol and vitamin D status	4	617	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.22, 4.15]
17.1 Vitamin D insufficiency	2	155	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.11, 9.52]
17.2 Vitamin D adequacy	1	378	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.37]
17.3 Unknown vitamin D status	1	84	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.06, 13.40]
18 All-cause mortality in trials using calcitriol (1,25-dihydroxyvitamin D)	3	430	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.27, 7.03]
19 All-cause mortality in trials using calcitriol and vitamin D status	3	430	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.27, 7.03]
19.1 Vitamin D insufficiency	1	86	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.96]
19.2 Vitamin D adequacy	2	344	Risk Ratio (M-H, Random, 95% CI)	2.28 [0.34, 15.39]
20 Cardiovascular mortality	7	41879	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.13]
21 Cancer mortality	3	39200	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.02]
22 Adverse events	30		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 Hypercalcemia in trials using supplemental forms of vitamin D	13	11091	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.78, 2.05]
22.2 Hypercalcemia in trials using active forms of vitamin D	3	710	Risk Ratio (M-H, Random, 95% CI)	3.18 [1.17, 8.68]
22.3 Nephrolithiasis in trials using vitamin D_3 combined with calcium	4	42876	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.02, 1.34]
22.4 Nephrolithiasis in trials using calcitriol	1	246	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.10]
22.5 Hypercalciuria	3	695	Risk Ratio (M-H, Random, 95% CI)	4.64 [0.99, 21.76]
22.6 Renal insufficiency	3	5495	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.27, 10.70]
22.7 Cardiovascular disorders	6	3763	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.05]
22.8 Gastrointestinal disorders	15	9656	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.85, 2.14]
22.9 Psychiatric disorders	3	580	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.56, 3.73]
22.10 Skin disorders	2	3810	Risk Ratio (M-H, Random, 95% CI)	3.27 [0.17, 62.47]
22.11 Cancer	10	7377	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.89, 1.27]
23 All-cause mortality ('best-worst-case' and 'worst-best-case' scenario)	47		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 Best-worst-case scenario	47	83280	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.32, 0.53]
23.2 Worst-best-case scenario	47	83280	Risk Ratio (M-H, Random, 95% CI)	2.73 [2.04, 3.65]

Analysis 1.1. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 1 All-cause mortality in trials with a low or high risk of bias.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 1 All-cause mortality in trials with a low or high risk of bias

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Trials with low risk of bias					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Bjorkman 2007	27/150	9/68		0.2 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Broe 2007	5/99	2/25		0.1 %	0.63 [0.13, 3.07]
Burleigh 2007	16/101	13/104		0.2 %	1.27 [0.64, 2.50]
Cooper 2003	0/93	1/94		0.0 %	0.34 [0.01, 8.16]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Dukas 2004	1/192	1/186		0.0 %	0.97 [0.06, 15.37]
Flicker 2005	76/313	85/312		1.6 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Grant 2005	438/2649	460/2643		8.5 %	0.95 [0.84, 1.07]
Jackson 2006	744/18176	807/18106		14.9 %	0.92 [0.83, 1.01]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		5.6 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Lyons 2007	713/1725	715/1715		13.2 %	0.99 [0.92, 1.07]
Ooms 1995	11/177	21/171		0.4 %	0.51 [0.25, 1.02]
Prince 2008	0/151	1/151		0.0 %	0.33 [0.01, 8.12]
Sanders 2010	40/1131	47/1127		0.9 %	0.85 [0.56, 1.28]
Sato 2005a	1/48	2/48		0.0 %	0.50 [0.05, 5.33]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Smith 2007	355/4727	354/4713		6.5 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		4.6 %	0.90 [0.77, 1.07]

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Witham 2010	4/53	2/52		0.0 %	1.96 [0.38, 10.26]
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**33348**	**33126**		**57.1 %**	**0.95 [0.91, 0.99]**
Total events: 2961 (Vitamin D), 3091 (Control)					
Heterogeneity: Chi^2 = 17.09, df = 25 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 2.25 (P = 0.024)					
2 Trials with high risk of bias					
Avenell 2004	4/70	3/64		0.1 %	1.22 [0.28, 5.24]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bischoff 2003	1/62	4/60		0.1 %	0.24 [0.03, 2.10]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Campbell 2005	6/195	10/196		0.2 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		16.9 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		1.1 %	0.76 [0.55, 1.06]
Chel 2008	25/166	33/172		0.6 %	0.78 [0.49, 1.26]
Corless 1985	8/41	8/41		0.1 %	1.00 [0.42, 2.41]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Krieg 1999	21/124	26/124		0.5 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.2 %	1.15 [0.55, 2.41]
Lappe 2007	4/446	18/733		0.3 %	0.37 [0.12, 1.07]
Larsen 2004	832/4957	839/4648		15.9 %	0.93 [0.85, 1.01]
Law 2006	347/1762	322/1955		5.6 %	1.20 [1.04, 1.37]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Ott 1989	0/43	1/43		0.0 %	0.33 [0.01, 7.96]
Porthouse 2005	57/1321	68/1993		1.0 %	1.26 [0.90, 1.79]
Sato 1997	1/45	1/39		0.0 %	0.87 [0.06, 13.40]
Sato 1999a	1/43	0/43		0.0 %	3.00 [0.13, 71.65]
Sato 1999b	0/34	1/35		0.0 %	0.34 [0.01, 8.13]
Subtotal (95% CI)	**13545**	**14129**		**42.9 %**	**0.98 [0.94, 1.03]**
Total events: 2314 (Vitamin D), 2319 (Control)					
Heterogeneity: Chi^2 = 26.78, df = 23 (P = 0.27); I^2 =14%					

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.80 (P = 0.42)					
Total (95% CI)	**46893**	**47255**		**100.0 %**	**0.96 [0.93, 0.99]**
Total events: 5275 (Vitamin D), 5410 (Control)					
Heterogeneity: Chi^2 = 44.60, df = 49 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.26 (P = 0.024)					
Test for subgroup differences: Chi^2 = 0.95, df = 1 (P = 0.33), I^2 =0.0%					

Analysis 1.2. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 2 All-cause mortality in individually and cluster randomised trials.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 2 All-cause mortality in individually and cluster randomised trials

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Individually randomised trials					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Avenell 2004	4/70	3/64		0.0 %	1.22 [0.28, 5.24]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Bjorkman 2007	27/150	9/68		0.2 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Broe 2007	5/99	2/25		0.0 %	0.63 [0.13, 3.07]
Burleigh 2007	16/101	13/104		0.2 %	1.27 [0.64, 2.50]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		26.8 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.9 %	0.76 [0.55, 1.06]

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chel 2008	25/166	33/172		0.5 %	0.78 [0.49, 1.26]
Cooper 2003	0/93	1/94		0.0 %	0.34 [0.01, 8.16]
Corless 1985	8/41	8/41		0.1 %	1.00 [0.42, 2.41]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Dukas 2004	1/192	1/186		0.0 %	0.97 [0.06, 15.37]
Flicker 2005	76/313	85/312		1.4 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Grant 2005	438/2649	460/2643		7.2 %	0.95 [0.84, 1.07]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	807/18106		10.7 %	0.92 [0.83, 1.01]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Krieg 1999	21/124	26/124		0.4 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.2 %	1.15 [0.55, 2.41]
Lappe 2007	4/446	18/733		0.1 %	0.37 [0.12, 1.07]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		5.0 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Lyons 2007	713/1725	715/1715		16.2 %	0.99 [0.92, 1.07]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Ooms 1995	11/177	21/171		0.2 %	0.51 [0.25, 1.02]
Ott 1989	0/43	1/43		0.0 %	0.33 [0.01, 7.96]
Porthouse 2005	57/1321	68/1993		0.9 %	1.26 [0.90, 1.79]
Prince 2008	0/151	1/151		0.0 %	0.33 [0.01, 8.12]
Sanders 2010	40/1131	47/1127		0.6 %	0.85 [0.56, 1.28]
Sato 1997	1/45	1/39		0.0 %	0.87 [0.06, 13.40]
Sato 1999a	1/43	0/43		0.0 %	3.00 [0.13, 71.65]
Sato 1999b	0/34	1/35		0.0 %	0.34 [0.01, 8.13]
Sato 2005a	1/48	2/48		0.0 %	0.50 [0.05, 5.33]

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Smith 2007	355/4727	354/4713		5.1 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.8 %	0.90 [0.77, 1.07]
Witham 2010	4/53	2/52		0.0 %	1.96 [0.38, 10.26]
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**40174**	**40652**		**81.2 %**	**0.96 [0.92, 0.99]**
Total events: 4096 (Vitamin D), 4249 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 34.45, df = 47 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 2.36 (P = 0.018)					
2 Cluster randomised trials					
Larsen 2004	832/4957	839/4648		13.4 %	0.93 [0.85, 1.01]
Law 2006	347/1762	322/1955		5.4 %	1.20 [1.04, 1.37]
Subtotal (95% CI)	**6719**	**6603**		**18.8 %**	**1.05 [0.82, 1.34]**
Total events: 1179 (Vitamin D), 1161 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 9.18, df = 1 (P = 0.002); I^2 =89%					
Test for overall effect: Z = 0.38 (P = 0.71)					
Total (95% CI)	**46893**	**47255**		**100.0 %**	**0.97 [0.94, 1.00]**
Total events: 5275 (Vitamin D), 5410 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 44.60, df = 49 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.13 (P = 0.033)					
Test for subgroup differences: Chi^2 = 0.50, df = 1 (P = 0.48), I^2 =0.0%					

Analysis 1.3. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 3 All-cause mortality in placebo controlled and no intervention trials.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 3 All-cause mortality in placebo controlled and no intervention trials

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Placebo in the control group					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Bjorkman 2007	27/150	9/68		0.2 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Broe 2007	5/99	2/25		0.0 %	0.63 [0.13, 3.07]
Burleigh 2007	16/101	13/104		0.2 %	1.27 [0.64, 2.50]
Chapuy 1992	893/1634	917/1636		26.8 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.9 %	0.76 [0.55, 1.06]
Chel 2008	25/166	33/172		0.5 %	0.78 [0.49, 1.26]
Cooper 2003	0/93	1/94		0.0 %	0.34 [0.01, 8.16]
Corless 1985	8/41	8/41		0.1 %	1.00 [0.42, 2.41]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Dukas 2004	1/192	1/186		0.0 %	0.97 [0.06, 15.37]
Flicker 2005	76/313	85/312		1.4 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Grant 2005	438/2649	460/2643		7.2 %	0.95 [0.84, 1.07]
Jackson 2006	744/18176	807/18106		10.7 %	0.92 [0.83, 1.01]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Lappe 2007	4/446	18/733		0.1 %	0.37 [0.12, 1.07]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		5.0 %	0.92 [0.80, 1.06]

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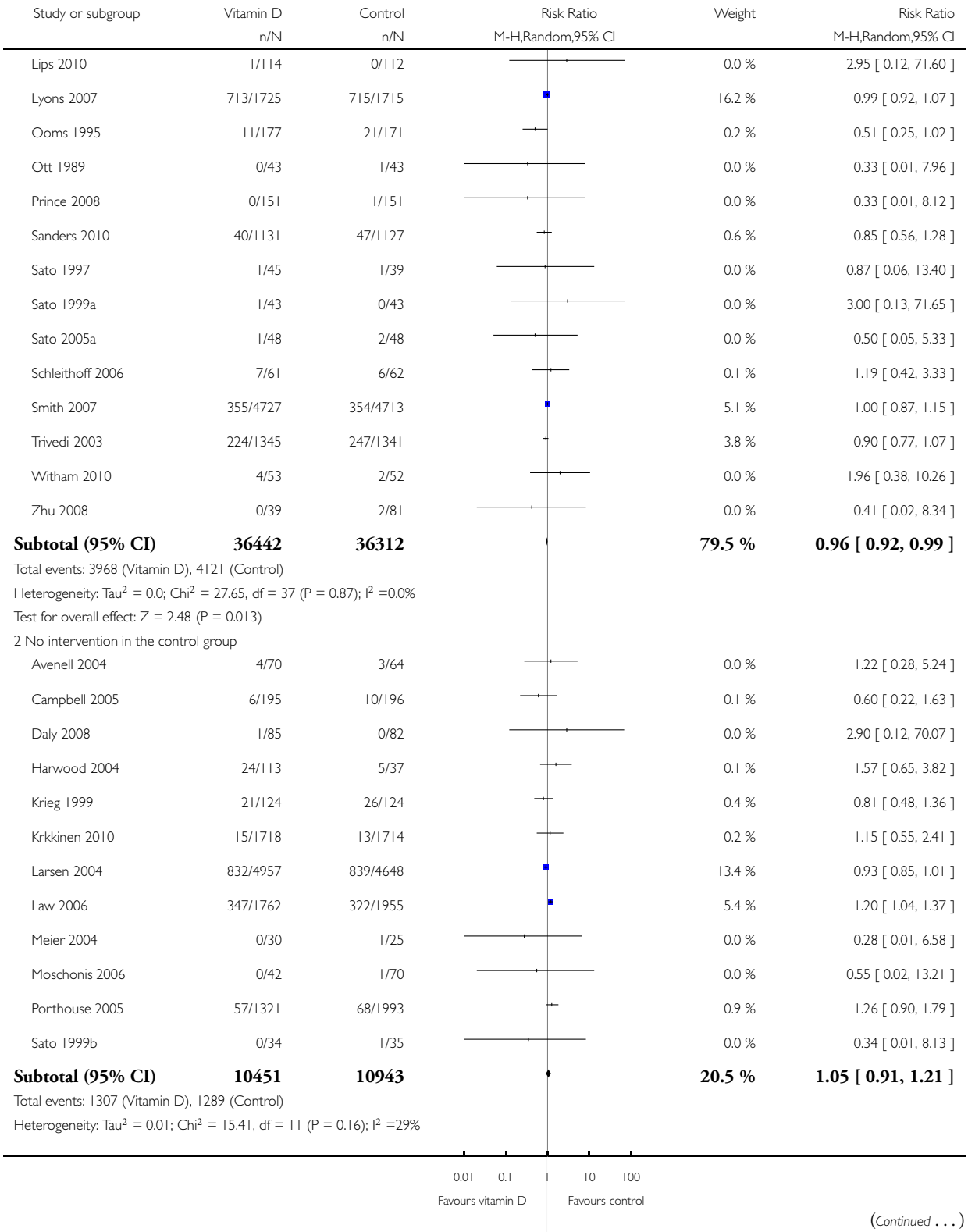

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.67 (P = 0.51)					
Total (95% CI)	**46893**	**47255**		**100.0 %**	**0.97 [0.94, 1.00]**
Total events: 5275 (Vitamin D), 5410 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 44.60, df = 49 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.13 (P = 0.033)					
Test for subgroup differences: Chi^2 = 1.57, df = 1 (P = 0.21), I^2 =36%					

Analysis 1.4. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 4 All-cause mortality in primary and secondary prevention trials.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 4 All-cause mortality in primary and secondary prevention trials

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Primary prevention trials					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Avenell 2004	4/70	3/64		0.0 %	1.22 [0.28, 5.24]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Bjorkman 2007	27/150	9/68		0.2 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Broe 2007	5/99	2/25		0.0 %	0.63 [0.13, 3.07]
Burleigh 2007	16/101	13/104		0.2 %	1.27 [0.64, 2.50]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		26.8 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.9 %	0.76 [0.55, 1.06]

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chel 2008	25/166	33/172		0.5 %	0.78 [0.49, 1.26]
Cooper 2003	0/93	1/94		0.0 %	0.34 [0.01, 8.16]
Corless 1985	8/41	8/41		0.1 %	1.00 [0.42, 2.41]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Dukas 2004	1/192	1/186		0.0 %	0.97 [0.06, 15.37]
Flicker 2005	76/313	85/312		1.4 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Grant 2005	438/2649	460/2643		7.2 %	0.95 [0.84, 1.07]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	807/18106		10.7 %	0.92 [0.83, 1.01]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Krieg 1999	21/124	26/124		0.4 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.2 %	1.15 [0.55, 2.41]
Lappe 2007	4/446	18/733		0.1 %	0.37 [0.12, 1.07]
Larsen 2004	832/4957	839/4648		13.4 %	0.93 [0.85, 1.01]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Law 2006	347/1762	322/1955		5.4 %	1.20 [1.04, 1.37]
Lips 1996	282/1291	306/1287		5.0 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Lyons 2007	713/1725	715/1715		16.2 %	0.99 [0.92, 1.07]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Ooms 1995	11/177	21/171		0.2 %	0.51 [0.25, 1.02]
Ott 1989	0/43	1/43		0.0 %	0.33 [0.01, 7.96]
Porthouse 2005	57/1321	68/1993		0.9 %	1.26 [0.90, 1.79]
Prince 2008	0/151	1/151		0.0 %	0.33 [0.01, 8.12]
Sanders 2010	40/1131	47/1127		0.6 %	0.85 [0.56, 1.28]
Smith 2007	355/4727	354/4713		5.1 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.8 %	0.90 [0.77, 1.07]

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**46609**	**46976**		**99.8 %**	**0.97 [0.94, 1.00]**
Total events: 5261 (Vitamin D), 5398 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 42.54, df = 43 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 2.15 (P = 0.031)					
2 Secondary prevention trials					
Sato 1997	1/45	1/39		0.0 %	0.87 [0.06, 13.40]
Sato 1999a	1/43	0/43		0.0 %	3.00 [0.13, 71.65]
Sato 1999b	0/34	1/35		0.0 %	0.34 [0.01, 8.13]
Sato 2005a	1/48	2/48		0.0 %	0.50 [0.05, 5.33]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Witham 2010	4/53	2/52		0.0 %	1.96 [0.38, 10.26]
Subtotal (95% CI)	**284**	**279**		**0.2 %**	**1.16 [0.55, 2.43]**
Total events: 14 (Vitamin D), 12 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.83, df = 5 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.39 (P = 0.70)					
Total (95% CI)	**46893**	**47255**		**100.0 %**	**0.97 [0.94, 1.00]**
Total events: 5275 (Vitamin D), 5410 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 44.60, df = 49 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.13 (P = 0.033)					
Test for subgroup differences: Chi^2 = 0.23, df = 1 (P = 0.63), I^2 =0.0%					

Analysis 1.5. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 5 All-cause mortality and vitamin D status.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 5 All-cause mortality and vitamin D status

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D insufficiency					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Chapuy 1992	893/1634	917/1636		26.8 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.9 %	0.76 [0.55, 1.06]
Corless 1985	8/41	8/41		0.1 %	1.00 [0.42, 2.41]
Grant 2005	438/2649	460/2643		7.2 %	0.95 [0.84, 1.07]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	807/18106		10.7 %	0.92 [0.83, 1.01]
Krieg 1999	21/124	26/124		0.4 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.2 %	1.15 [0.55, 2.41]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		5.0 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Ooms 1995	11/177	21/171		0.2 %	0.51 [0.25, 1.02]
Prince 2008	0/151	1/151		0.0 %	0.33 [0.01, 8.12]
Sanders 2010	40/1131	47/1127		0.6 %	0.85 [0.56, 1.28]
Sato 1999a	1/43	0/43		0.0 %	3.00 [0.13, 71.65]
Sato 1999b	0/34	1/35		0.0 %	0.34 [0.01, 8.13]
Sato 2005a	1/48	2/48		0.0 %	0.50 [0.05, 5.33]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Witham 2010	4/53	2/52		0.0 %	1.96 [0.38, 10.26]
Subtotal (95% CI)	**28329**	**27966**		**52.6 %**	**0.95 [0.91, 0.99]**
Total events: 2576 (Vitamin D), 2678 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 18.95, df = 21 (P = 0.59); I^2 =0.0%					

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 2.36 (P = 0.018)					
2 Vitamin D adequacy					
Bjorkman 2007	27/150	9/68		0.2 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Broe 2007	5/99	2/25		0.0 %	0.63 [0.13, 3.07]
Burleigh 2007	16/101	13/104		0.2 %	1.27 [0.64, 2.50]
Chel 2008	25/166	33/172		0.5 %	0.78 [0.49, 1.26]
Cooper 2003	0/93	1/94		0.0 %	0.34 [0.01, 8.16]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Dukas 2004	1/192	1/186		0.0 %	0.97 [0.06, 15.37]
Flicker 2005	76/313	85/312		1.4 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Ott 1989	0/43	1/43		0.0 %	0.33 [0.01, 7.96]
Smith 2007	355/4727	354/4713		5.1 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.8 %	0.90 [0.77, 1.07]
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**7847**	**7750**		**11.3 %**	**0.95 [0.86, 1.04]**
Total events: 735 (Vitamin D), 754 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 7.23, df = 17 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 1.07 (P = 0.29)					
3 Unknown vitamin D status					
Avenell 2004	4/70	3/64		0.0 %	1.22 [0.28, 5.24]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Lappe 2007	4/446	18/733		0.1 %	0.37 [0.12, 1.07]
Larsen 2004	832/4957	839/4648		13.4 %	0.93 [0.85, 1.01]
Law 2006	347/1762	322/1955		5.4 %	1.20 [1.04, 1.37]
Lyons 2007	713/1725	715/1715		16.2 %	0.99 [0.92, 1.07]
Porthouse 2005	57/1321	68/1993		0.9 %	1.26 [0.90, 1.79]

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Sato 1997	1/45	1/39		0.0 %	0.87 [0.06, 13.40]
Subtotal (95% CI)	**10717**	**11539**		**36.1 %**	**1.02 [0.91, 1.14]**
Total events: 1964 (Vitamin D), 1978 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 16.35, df = 9 (P = 0.06); I^2 =45%					
Test for overall effect: Z = 0.33 (P = 0.74)					
Total (95% CI)	**46893**	**47255**		**100.0 %**	**0.97 [0.94, 1.00]**
Total events: 5275 (Vitamin D), 5410 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 44.60, df = 49 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.13 (P = 0.033)					
Test for subgroup differences: Chi^2 = 1.39, df = 2 (P = 0.50), I^2 =0.0%					

Analysis 1.6. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 6 All-cause mortality in trials using vitamin D_3 (cholecalciferol)).

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 6 All-cause mortality in trials using vitamin D_3 (cholecalciferol))

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D_3 trials with low risk of bias					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Bjorkman 2007	27/150	9/68		0.3 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Burleigh 2007	16/101	13/104		0.3 %	1.27 [0.64, 2.50]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Grant 2005	438/2649	460/2643		10.0 %	0.95 [0.84, 1.07]
Jackson 2006	744/18176	807/18106		15.0 %	0.92 [0.83, 1.01]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]

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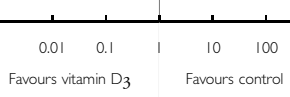
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		7.0 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Ooms 1995	11/177	21/171		0.3 %	0.51 [0.25, 1.02]
Sanders 2010	40/1131	47/1127		0.8 %	0.85 [0.56, 1.28]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Trivedi 2003	224/1345	247/1341		5.3 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**25880**	**25723**		**39.3 %**	**0.93 [0.87, 0.99]**
Total events: 1807 (Vitamin D), 1926 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 12.93, df = 15 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 2.44 (P = 0.015)					
2 Vitamin D_3 trials with high risk of bias					
Avenell 2004	4/70	3/64		0.1 %	1.22 [0.28, 5.24]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		37.5 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		1.3 %	0.76 [0.55, 1.06]
Chel 2008	25/166	33/172		0.6 %	0.78 [0.49, 1.26]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Harwood 2004	6/39	5/37		0.1 %	1.14 [0.38, 3.41]
Krieg 1999	21/124	26/124		0.5 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.3 %	1.15 [0.55, 2.41]
Lappe 2007	4/446	18/733		0.1 %	0.37 [0.12, 1.07]
Larsen 2004	832/4957	839/4648		18.7 %	0.93 [0.85, 1.01]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Porthouse 2005	57/1321	68/1993		1.2 %	1.26 [0.90, 1.79]
Subtotal (95% CI)	**11358**	**11828**		**60.7 %**	**0.95 [0.91, 1.00]**
Total events: 1935 (Vitamin D), 1985 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 13.87, df = 15 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 1.91 (P = 0.056)					
Total (95% CI)	**37238**	**37551**		**100.0 %**	**0.94 [0.91, 0.98]**
Total events: 3742 (Vitamin D), 3911 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 27.29, df = 31 (P = 0.66); I^2 =0.0%					



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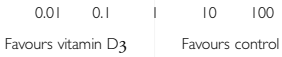
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 3.02 (P = 0.0026)					
Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² =0.0%					



Analysis 1.7. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 7 All-cause mortality in trials using vitamin D_3 singly or combined with calcium.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 7 All-cause mortality in trials using vitamin D_3 singly or combined with calcium

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D_3 singly					
Avenell 2004	1/35	2/35		0.2 %	0.50 [0.05, 5.27]
Campbell 2005	6/195	10/196		1.2 %	0.60 [0.22, 1.63]
Chel 2008	25/166	33/172		5.1 %	0.78 [0.49, 1.26]
Grant 2005	217/1343	217/1332		25.4 %	0.99 [0.83, 1.18]
Latham 2003	11/121	3/122		0.8 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		31.5 %	0.92 [0.80, 1.06]
Ooms 1995	11/177	21/171		2.4 %	0.51 [0.25, 1.02]
Sanders 2010	40/1131	47/1127		6.5 %	0.85 [0.56, 1.28]
Trivedi 2003	224/1345	247/1341		26.9 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**5804**	**5783**		**100.0 %**	**0.91 [0.82, 1.02]**
Total events: 817 (Vitamin D), 886 (Control)					
Heterogeneity: Tau² = 0.00; Chi² = 9.86, df = 8 (P = 0.27); I² =19%					
Test for overall effect: Z = 1.64 (P = 0.10)					
2 Vitamin D_3 combined with calcium					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Avenell 2004	3/35	1/29		0.0 %	2.49 [0.27, 22.64]

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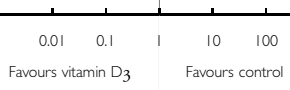
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Bjorkman 2007	27/150	9/68		0.4 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Burleigh 2007	16/101	13/104		0.4 %	1.27 [0.64, 2.50]
Chapuy 1992	893/1634	917/1636		46.4 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		1.6 %	0.76 [0.55, 1.06]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Grant 2005	221/1306	243/1311		6.4 %	0.91 [0.77, 1.08]
Harwood 2004	6/39	5/37		0.1 %	1.14 [0.38, 3.41]
Jackson 2006	744/18176	807/18106		18.5 %	0.92 [0.83, 1.01]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Krieg 1999	21/124	26/124		0.7 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.3 %	1.15 [0.55, 2.41]
Lappe 2007	4/446	12/445		0.1 %	0.33 [0.11, 1.02]
Larsen 2004	832/4957	839/4648		23.1 %	0.93 [0.85, 1.01]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Porthouse 2005	57/1321	68/1993		1.5 %	1.26 [0.90, 1.79]
Schleithoff 2006	7/61	6/62		0.2 %	1.19 [0.42, 3.33]
Subtotal (95% CI)	**31434**	**31480**		**100.0 %**	**0.95 [0.91, 0.99]**
Total events: 2925 (Vitamin D), 3019 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 18.63$, df = 24 (P = 0.77); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.42 (P = 0.016)					



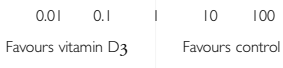
Analysis 1.8. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 8 All-cause mortality in trials using low- or high dose of vitamin D_3.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 8 All-cause mortality in trials using low- or high dose of vitamin D_3

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-dose of vitamin D_3 (< 800 IU a day)					
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bjorkman 2007	17/77	9/68		0.6 %	1.67 [0.80, 3.49]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Chel 2008	25/166	33/172		1.5 %	0.78 [0.49, 1.26]
Dawson-Hughes 1997	2/187	2/202		0.1 %	1.08 [0.15, 7.59]
Jackson 2006	744/18176	807/18106		35.6 %	0.92 [0.83, 1.01]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Larsen 2004	832/4957	839/4648		44.6 %	0.93 [0.85, 1.01]
Lips 1996	282/1291	306/1287		16.7 %	0.92 [0.80, 1.06]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Ooms 1995	11/177	21/171		0.7 %	0.51 [0.25, 1.02]
Subtotal (95% CI)	**25361**	**25006**		**100.0 %**	**0.92 [0.87, 0.97]**
Total events: 1913 (Vitamin D), 2022 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.65$, df = 11 (P = 0.74); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.82 (P = 0.0047)					
2 High-dose of vitamin D_3 ($\geq$ 800 IU a day)					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Avenell 2004	4/70	3/64		0.1 %	1.22 [0.28, 5.24]
Bischoff 2003	1/62	4/60		0.1 %	0.24 [0.03, 2.10]
Bjorkman 2007	10/73	9/68		0.3 %	1.04 [0.45, 2.39]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Burleigh 2007	16/101	13/104		0.5 %	1.27 [0.64, 2.50]
Campbell 2005	6/195	10/196		0.2 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		64.4 %	0.98 [0.92, 1.04]



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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chapuy 2002	70/389	46/194		2.2 %	0.76 [0.55, 1.06]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Grant 2005	438/2649	460/2643		17.2 %	0.95 [0.84, 1.07]
Harwood 2004	6/39	5/37		0.2 %	1.14 [0.38, 3.41]
Krieg 1999	21/124	26/124		0.9 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.4 %	1.15 [0.55, 2.41]
Lappe 2007	4/446	18/733		0.2 %	0.37 [0.12, 1.07]
Latham 2003	11/121	3/122		0.2 %	3.70 [1.06, 12.92]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Porthouse 2005	57/1321	68/1993		2.1 %	1.26 [0.90, 1.79]
Sanders 2010	40/1131	47/1127		1.4 %	0.85 [0.56, 1.28]
Schleithoff 2006	7/61	6/62		0.2 %	1.19 [0.42, 3.33]
Trivedi 2003	224/1345	247/1341		9.1 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**11877**	**12613**		**100.0 %**	**0.96 [0.92, 1.01]**

Total events: 1829 (Vitamin D), 1898 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 19.44$, df = 20 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 1.52 (P = 0.13)

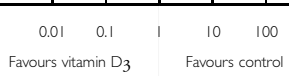
Analysis 1.9. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 9 All-cause mortality in trials applying vitamin D_3 daily or intermittently.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 9 All-cause mortality in trials applying vitamin D_3 daily or intermittently

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D_3 daily					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Avenell 2004	4/70	3/64		0.1 %	1.22 [0.28, 5.24]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Bjorkman 2007	27/150	9/68		0.3 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Burleigh 2007	16/101	13/104		0.3 %	1.27 [0.64, 2.50]
Chapuy 1992	893/1634	917/1636		40.2 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		1.4 %	0.76 [0.55, 1.06]
Chel 2008	8/55	12/57		0.2 %	0.69 [0.31, 1.56]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Grant 2005	438/2649	460/2643		10.7 %	0.95 [0.84, 1.07]
Harwood 2004	6/39	5/37		0.1 %	1.14 [0.38, 3.41]
Jackson 2006	744/18176	807/18106		16.0 %	0.92 [0.83, 1.01]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Krieg 1999	21/124	26/124		0.6 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.3 %	1.15 [0.55, 2.41]
Lappe 2007	4/446	18/733		0.1 %	0.37 [0.12, 1.07]
Larsen 2004	832/4957	839/4648		20.1 %	0.93 [0.85, 1.01]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		7.5 %	0.92 [0.80, 1.06]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]



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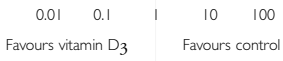
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Ooms 1995	11/177	21/171		0.3 %	0.51 [0.25, 1.02]
Porthouse 2005	57/1321	68/1993		1.3 %	1.26 [0.90, 1.79]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Subtotal (95% CI)	**34342**	**34660**		**100.0 %**	**0.95 [0.91, 0.99]**
Total events: 3454 (Vitamin D), 3586 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 25.41$, df = 27 (P = 0.55); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.69 (P = 0.0071)					
2 Vitamin D_3 intermittently					
Campbell 2005	6/195	10/196		2.1 %	0.60 [0.22, 1.63]
Chel 2008	25/166	33/172		9.2 %	0.78 [0.49, 1.26]
Lips 2010	1/114	0/112		0.2 %	2.95 [0.12, 71.60]
Sanders 2010	40/1131	47/1127		12.1 %	0.85 [0.56, 1.28]
Trivedi 2003	224/1345	247/1341		76.5 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**2951**	**2948**		**100.0 %**	**0.88 [0.76, 1.02]**
Total events: 296 (Vitamin D), 337 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.47$, df = 4 (P = 0.83); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.74 (P = 0.082)					



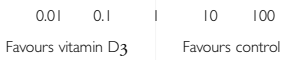
Analysis 1.10. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 10 All-cause mortality in trials using vitamin D_3 and vitamin D status.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 10 All-cause mortality in trials using vitamin D_3 and vitamin D status

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D insufficiency					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Chapuy 1992	893/1634	917/1636		37.5 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		1.3 %	0.76 [0.55, 1.06]
Grant 2005	438/2649	460/2643		10.0 %	0.95 [0.84, 1.07]
Harwood 2004	6/39	5/37		0.1 %	1.14 [0.38, 3.41]
Jackson 2006	744/18176	807/18106		15.0 %	0.92 [0.83, 1.01]
Krieg 1999	21/124	26/124		0.5 %	0.81 [0.48, 1.36]
Krkkinen 2010	15/1718	13/1714		0.3 %	1.15 [0.55, 2.41]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		7.0 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Ooms 1995	11/177	21/171		0.3 %	0.51 [0.25, 1.02]
Sanders 2010	40/1131	47/1127		0.8 %	0.85 [0.56, 1.28]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Subtotal (95% CI)	**27885**	**27596**		**73.1 %**	**0.94 [0.90, 0.99]**
Total events: 2544 (Vitamin D), 2664 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 15.48$, df = 15 (P = 0.42); $I^2 = 3\%$					
Test for overall effect: Z = 2.32 (P = 0.020)					
2 Vitamin D adequacy					
Bjorkman 2007	27/150	9/68		0.3 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Burleigh 2007	16/101	13/104		0.3 %	1.27 [0.64, 2.50]
Chel 2008	25/166	33/172		0.6 %	0.78 [0.49, 1.26]



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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Dawson-Hughes 1997	2/187	2/202		0.0 %	1.08 [0.15, 7.59]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Trivedi 2003	224/1345	247/1341		5.3 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**2168**	**2125**		**6.6 %**	**0.92 [0.79, 1.07]**
Total events: 295 (Vitamin D), 307 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.11, df = 8 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 1.10 (P = 0.27)					
3 Unknown vitamin D status					
Avenell 2004	4/70	3/64		0.1 %	1.22 [0.28, 5.24]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Lappe 2007	4/446	18/733		0.1 %	0.37 [0.12, 1.07]
Larsen 2004	832/4957	839/4648		18.7 %	0.93 [0.85, 1.01]
Porthouse 2005	57/1321	68/1993		1.2 %	1.26 [0.90, 1.79]
Subtotal (95% CI)	**7185**	**7830**		**20.3 %**	**0.95 [0.75, 1.19]**
Total events: 903 (Vitamin D), 940 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 7.56, df = 6 (P = 0.27); I^2 =21%					
Test for overall effect: Z = 0.48 (P = 0.63)					
Total (95% CI)	**37238**	**37551**		**100.0 %**	**0.94 [0.91, 0.98]**
Total events: 3742 (Vitamin D), 3911 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 27.29, df = 31 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 3.02 (P = 0.0026)					
Test for subgroup differences: Chi^2 = 0.10, df = 2 (P = 0.95), I^2 =0.0%					

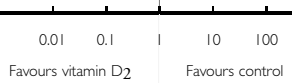
Analysis 1.11. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 11 All-cause mortality in trials using vitamin D_2 (ergocalciferol).

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 11 All-cause mortality in trials using vitamin D_2 (ergocalciferol)

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D_2 trials with low risk of bias					
Broe 2007	5/99	2/25		0.1 %	0.63 [0.13, 3.07]
Cooper 2003	0/93	1/94		0.0 %	0.34 [0.01, 8.16]
Flicker 2005	76/313	85/312		5.0 %	0.89 [0.68, 1.16]
Lyons 2007	713/1725	715/1715		56.8 %	0.99 [0.92, 1.07]
Prince 2008	0/151	1/151		0.0 %	0.33 [0.01, 8.12]
Sato 2005a	1/48	2/48		0.1 %	0.50 [0.05, 5.33]
Smith 2007	355/4727	354/4713		17.8 %	1.00 [0.87, 1.15]
Witham 2010	4/53	2/52		0.1 %	1.96 [0.38, 10.26]
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**7248**	**7191**		**80.1 %**	**0.99 [0.92, 1.05]**
Total events: 1154 (Vitamin D), 1164 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.10, df = 8 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
2 Vitamin D_2 trials with high risk of bias					
Corless 1985	8/41	8/41		0.5 %	1.00 [0.42, 2.41]
Harwood 2004	18/74	5/37		0.4 %	1.80 [0.73, 4.47]
Law 2006	347/1762	322/1955		19.0 %	1.20 [1.04, 1.37]
Subtotal (95% CI)	**1877**	**2033**		**19.9 %**	**1.20 [1.05, 1.37]**
Total events: 373 (Vitamin D), 335 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.93, df = 2 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 2.68 (P = 0.0074)					
Total (95% CI)	**9125**	**9224**		**100.0 %**	**1.02 [0.97, 1.09]**
Total events: 1527 (Vitamin D), 1499 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 10.81, df = 11 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Chi^2 = 6.74, df = 1 (P = 0.01), I^2 =85%					



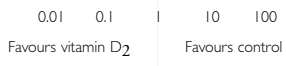
Analysis 1.12. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 12 All-cause mortality in trials using vitamin D_2 singly or combined with calcium.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 12 All-cause mortality in trials using vitamin D_2 singly or combined with calcium

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D_2 singly					
Broe 2007	5/99	2/25		0.2 %	0.63 [0.13, 3.07]
Corless 1985	8/41	8/41		0.6 %	1.00 [0.42, 2.41]
Harwood 2004	7/38	5/37		0.4 %	1.36 [0.47, 3.91]
Law 2006	347/1762	322/1955		21.7 %	1.20 [1.04, 1.37]
Lyons 2007	713/1725	715/1715		56.5 %	0.99 [0.92, 1.07]
Sato 2005a	1/48	2/48		0.1 %	0.50 [0.05, 5.33]
Smith 2007	355/4727	354/4713		20.5 %	1.00 [0.87, 1.15]
Witham 2010	4/53	2/52		0.2 %	1.96 [0.38, 10.26]
Subtotal (95% CI)	**8493**	**8586**		**100.0 %**	**1.04 [0.97, 1.11]**
Total events: 1440 (Vitamin D), 1410 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.23$, df = 7 (P = 0.41); $I^2 = 3\%$					
Test for overall effect: Z = 1.03 (P = 0.30)					
2 Vitamin D_2 combined with calcium					
Cooper 2003	0/93	1/94		1.9 %	0.34 [0.01, 8.16]
Flicker 2005	76/313	85/312		75.7 %	0.89 [0.68, 1.16]
Harwood 2004	11/36	5/37		18.3 %	2.26 [0.87, 5.86]
Prince 2008	0/151	1/151		1.9 %	0.33 [0.01, 8.12]
Zhu 2008	0/39	2/81		2.2 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**632**	**675**		**100.0 %**	**1.00 [0.64, 1.57]**
Total events: 87 (Vitamin D), 94 (Control)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 4.51$, df = 4 (P = 0.34); $I^2 = 11\%$					
Test for overall effect: Z = 0.00 (P = 1.0)					



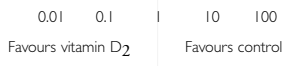
Analysis 1.13. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 13 All-cause mortality in trials using low- or high dose of vitamin D_2.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 13 All-cause mortality in trials using low- or high dose of vitamin D_2

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-dose of vitamin D_2					
Broe 2007	5/76	2/25		100.0 %	0.82 [0.17, 3.98]
Subtotal (95% CI)	**76**	**25**		**100.0 %**	**0.82 [0.17, 3.98]**
Total events: 5 (Vitamin D), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.24 (P = 0.81)					
2 High-dose of vitamin D_2					
Broe 2007	0/23	2/25		0.1 %	0.22 [0.01, 4.29]
Cooper 2003	0/93	1/94		0.0 %	0.34 [0.01, 8.16]
Corless 1985	8/41	8/41		0.6 %	1.00 [0.42, 2.41]
Flicker 2005	76/313	85/312		6.3 %	0.89 [0.68, 1.16]
Harwood 2004	18/74	5/37		0.6 %	1.80 [0.73, 4.47]
Law 2006	347/1762	322/1955		21.3 %	1.20 [1.04, 1.37]
Lyons 2007	713/1725	715/1715		50.6 %	0.99 [0.92, 1.07]
Prince 2008	0/151	1/151		0.0 %	0.33 [0.01, 8.12]
Sato 2005a	1/48	2/48		0.1 %	0.50 [0.05, 5.33]
Smith 2007	355/4727	354/4713		20.2 %	1.00 [0.87, 1.15]
Witham 2010	4/53	2/52		0.2 %	1.96 [0.38, 10.26]
Zhu 2008	0/39	2/81		0.1 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**9049**	**9224**		**100.0 %**	**1.03 [0.96, 1.10]**
Total events: 1522 (Vitamin D), 1499 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.48$, df = 11 (P = 0.40); $I^2 = 4\%$					
Test for overall effect: Z = 0.81 (P = 0.42)					



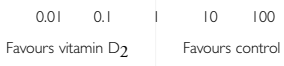
Analysis 1.14. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 14 All-cause mortality in trials applying vitamin D_2 daily or intermittently.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 14 All-cause mortality in trials applying vitamin D_2 daily or intermittently

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D_2 daily					
Broe 2007	5/99	2/25		2.5 %	0.63 [0.13, 3.07]
Corless 1985	8/41	8/41		8.0 %	1.00 [0.42, 2.41]
Flicker 2005	76/313	85/312		87.1 %	0.89 [0.68, 1.16]
Prince 2008	0/151	1/151		0.6 %	0.33 [0.01, 8.12]
Sato 2005a	1/48	2/48		1.1 %	0.50 [0.05, 5.33]
Zhu 2008	0/39	2/81		0.7 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**691**	**658**		**100.0 %**	**0.88 [0.68, 1.12]**
Total events: 90 (Vitamin D), 100 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.09$, df = 5 (P = 0.96); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Vitamin D_2 intermittently					
Cooper 2003	0/93	1/94		0.1 %	0.34 [0.01, 8.16]
Harwood 2004	18/74	5/37		1.4 %	1.80 [0.73, 4.47]
Law 2006	347/1762	322/1955		28.6 %	1.20 [1.04, 1.37]
Lyons 2007	713/1725	715/1715		41.7 %	0.99 [0.92, 1.07]
Smith 2007	355/4727	354/4713		27.8 %	1.00 [0.87, 1.15]
Witham 2010	4/53	2/52		0.4 %	1.96 [0.38, 10.26]
Subtotal (95% CI)	**8434**	**8566**		**100.0 %**	**1.06 [0.95, 1.18]**
Total events: 1437 (Vitamin D), 1399 (Control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.15$, df = 5 (P = 0.15); $I^2 = 39\%$					
Test for overall effect: Z = 1.04 (P = 0.30)					



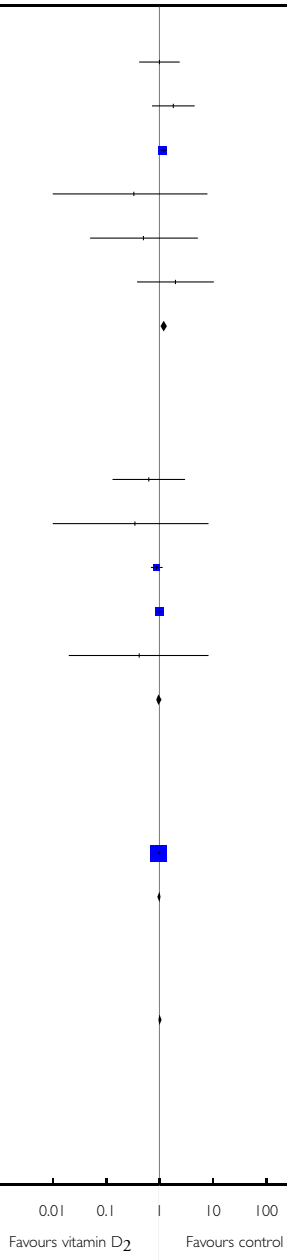
Analysis 1.15. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 15 All-cause mortality in trials using vitamin D_2 and vitamin D status.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 15 All-cause mortality in trials using vitamin D_2 and vitamin D status

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D insufficiency					
Corless 1985	8/41	8/41		0.5 %	1.00 [0.42, 2.41]
Harwood 2004	18/74	5/37		0.4 %	1.80 [0.73, 4.47]
Law 2006	347/1762	322/1955		19.0 %	1.20 [1.04, 1.37]
Prince 2008	0/151	1/151		0.0 %	0.33 [0.01, 8.12]
Sato 2005a	1/48	2/48		0.1 %	0.50 [0.05, 5.33]
Witham 2010	4/53	2/52		0.1 %	1.96 [0.38, 10.26]
Subtotal (95% CI)	**2129**	**2284**		**20.1 %**	**1.20 [1.05, 1.37]**
Total events: 378 (Vitamin D), 340 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.42$, df = 5 (P = 0.79); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.67 (P = 0.0076)					
2 Vitamin D adequacy					
Broe 2007	5/99	2/25		0.1 %	0.63 [0.13, 3.07]
Cooper 2003	0/93	1/94		0.0 %	0.34 [0.01, 8.16]
Flicker 2005	76/313	85/312		5.0 %	0.89 [0.68, 1.16]
Smith 2007	355/4727	354/4713		17.8 %	1.00 [0.87, 1.15]
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**5271**	**5225**		**23.1 %**	**0.97 [0.86, 1.10]**
Total events: 436 (Vitamin D), 444 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.59$, df = 4 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.49 (P = 0.62)					
3 Unknown vitamin D status					
Lyons 2007	713/1725	715/1715		56.8 %	0.99 [0.92, 1.07]
Subtotal (95% CI)	**1725**	**1715**		**56.8 %**	**0.99 [0.92, 1.07]**
Total events: 713 (Vitamin D), 715 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					
Total (95% CI)	**9125**	**9224**		**100.0 %**	**1.02 [0.97, 1.09]**
Total events: 1527 (Vitamin D), 1499 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 10.81$, df = 11 (P = 0.46); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: $Chi^2 = 6.77$, df = 2 (P = 0.03), $I^2 = 70\%$					



Analysis 1.16. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 16 All-cause mortality in trials using alfacalcidol (1-α hydroxyvitamin D).

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 16 All-cause mortality in trials using alfacalcidol (1- hydroxyvitamin D)

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dukas 2004	1/192	1/186		28.2 %	0.97 [0.06, 15.37]
Sato 1997	1/45	1/39		28.8 %	0.87 [0.06, 13.40]
Sato 1999a	1/43	0/43		21.4 %	3.00 [0.13, 71.65]
Sato 1999b	0/34	1/35		21.5 %	0.34 [0.01, 8.13]
Total (95% CI)	**314**	**303**		**100.0 %**	**0.96 [0.22, 4.15]**

Total events: 3 (Vitamin D), 3 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.91$, df = 3 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 0.06 (P = 0.95)

Analysis 1.17. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 17 All-cause mortality in trials using alfacalcidol and vitamin D status.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 17 All-cause mortality in trials using alfacalcidol and vitamin D status

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D insufficiency					
Sato 1999a	1/43	0/43		21.4 %	3.00 [0.13, 71.65]
Sato 1999b	0/34	1/35		21.5 %	0.34 [0.01, 8.13]
Subtotal (95% CI)	**77**	**78**		**43.0 %**	**1.01 [0.11, 9.52]**
Total events: 1 (Vitamin D), 1 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.90$, df = 1 (P = 0.34); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.01 (P = 0.99)					
2 Vitamin D adequacy					
Dukas 2004	1/192	1/186		28.2 %	0.97 [0.06, 15.37]
Subtotal (95% CI)	**192**	**186**		**28.2 %**	**0.97 [0.06, 15.37]**
Total events: 1 (Vitamin D), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
3 Unknown vitamin D status					
Sato 1997	1/45	1/39		28.8 %	0.87 [0.06, 13.40]
Subtotal (95% CI)	**45**	**39**		**28.8 %**	**0.87 [0.06, 13.40]**
Total events: 1 (Vitamin D), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					
Total (95% CI)	**314**	**303**		**100.0 %**	**0.96 [0.22, 4.15]**
Total events: 3 (Vitamin D), 3 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.91$, df = 3 (P = 0.82); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.06 (P = 0.95)					
Test for subgroup differences: $Chi^2 = 0.01$, df = 2 (P = 1.00), $I^2 = 0.0\%$					

Analysis 1.18. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 18 All-cause mortality in trials using calcitriol (1,25-dihydroxyvitamin D).

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 18 All-cause mortality in trials using calcitriol (1,25-dihydroxyvitamin D)

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Gallagher 2001	2/123	1/123		46.9 %	2.00 [0.18, 21.77]
Grady 1991	1/50	0/48		26.5 %	2.88 [0.12, 69.07]
Ott 1989	0/43	1/43		26.6 %	0.33 [0.01, 7.96]
Total (95% CI)	**216**	**214**		**100.0 %**	**1.37 [0.27, 7.03]**

Total events: 3 (Vitamin D), 2 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.07$, df = 2 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 0.38 (P = 0.71)

Analysis 1.19. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 19 All-cause mortality in trials using calcitriol and vitamin D status.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 19 All-cause mortality in trials using calcitriol and vitamin D status

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D insufficiency					
Ott 1989	0/43	1/43		26.6 %	0.33 [0.01, 7.96]
Subtotal (95% CI)	**43**	**43**		**26.6 %**	**0.33 [0.01, 7.96]**
Total events: 0 (Vitamin D), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
2 Vitamin D adequacy					
Gallagher 2001	2/123	1/123		46.9 %	2.00 [0.18, 21.77]
Grady 1991	1/50	0/48		26.5 %	2.88 [0.12, 69.07]
Subtotal (95% CI)	**173**	**171**		**73.4 %**	**2.28 [0.34, 15.39]**
Total events: 3 (Vitamin D), 1 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 0.85 (P = 0.40)					
Total (95% CI)	**216**	**214**		**100.0 %**	**1.37 [0.27, 7.03]**
Total events: 3 (Vitamin D), 2 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.07, df = 2 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 0.38 (P = 0.71)					
Test for subgroup differences: Chi^2 = 1.04, df = 1 (P = 0.31), I^2 =4%					

Analysis 1.20. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 20 Cardiovascular mortality.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 20 Cardiovascular mortality

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bolton-Smith 2007	0/62	1/61		0.1 %	0.33 [0.01, 7.90]
Brazier 2005	3/95	1/97		0.2 %	3.06 [0.32, 28.93]
Jackson 2006	499/18176	475/18106		78.5 %	1.05 [0.92, 1.18]
Lips 2010	1/114	0/112		0.1 %	2.95 [0.12, 71.60]
Moschonis 2006	0/42	1/70		0.1 %	0.55 [0.02, 13.21]
Sanders 2010	17/1131	13/1127		2.3 %	1.30 [0.64, 2.67]
Trivedi 2003	101/1345	117/1341		18.5 %	0.86 [0.67, 1.11]
Total (95% CI)	**20965**	**20914**		**100.0 %**	**1.02 [0.91, 1.13]**

Total events: 621 (Vitamin D), 608 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.29$, df = 6 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 0.29 (P = 0.77)

Analysis 1.21. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 21 Cancer mortality.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 21 Cancer mortality

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Jackson 2006	344/18176	383/18106		83.8 %	0.89 [0.77, 1.03]
Komulainen 1999	0/116	1/116		0.2 %	0.33 [0.01, 8.10]
Trivedi 2003	63/1345	72/1341		16.0 %	0.87 [0.63, 1.21]
Total (95% CI)	**19637**	**19563**		**100.0 %**	**0.89 [0.78, 1.02]**

Total events: 407 (Vitamin D), 456 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.38$, df = 2 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 1.74 (P = 0.082)

Analysis 1.22. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 22 Adverse events.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 22 Adverse events

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Hypercalcemia in trials using supplemental forms of vitamin D					
Aloia 2005	6/104	3/104		12.7 %	2.00 [0.51, 7.78]
Bjorkman 2007	1/150	0/68		2.3 %	1.37 [0.06, 33.23]
Bolton-Smith 2007	0/62	1/61		2.3 %	0.33 [0.01, 7.90]
Brazier 2005	7/95	11/97		28.7 %	0.65 [0.26, 1.61]
Chapuy 1992	1/1634	0/1636		2.3 %	3.00 [0.12, 73.68]
Chapuy 2002	3/389	0/194		2.7 %	3.50 [0.18, 67.42]
Corless 1985	1/41	0/41		2.3 %	3.00 [0.13, 71.56]

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Grant 2005	13/2649	8/2643		30.4 %	1.62 [0.67, 3.91]
Krieg 1999	1/124	0/124		2.3 %	3.00 [0.12, 72.94]
Ooms 1995	1/177	0/171		2.3 %	2.90 [0.12, 70.67]
Prince 2008	1/151	0/151		2.3 %	3.00 [0.12, 73.06]
Witham 2010	2/53	1/52		4.2 %	1.96 [0.18, 20.99]
Zhu 2008	1/39	5/81		5.3 %	0.42 [0.05, 3.44]
Subtotal (95% CI)	**5668**	**5423**		**100.0 %**	**1.26 [0.78, 2.05]**
Total events: 38 (Vitamin D), 29 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.57, df = 12 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 0.95 (P = 0.34)					
2 Hypercalcemia in trials using active forms of vitamin D					
Dukas 2004	5/192	1/186		19.1 %	4.84 [0.57, 41.07]
Gallagher 2001	15/123	7/123		69.3 %	2.14 [0.91, 5.07]
Ott 1989	8/43	0/43		11.6 %	17.00 [1.01, 285.60]
Subtotal (95% CI)	**358**	**352**		**100.0 %**	**3.18 [1.17, 8.68]**
Total events: 28 (Vitamin D), 8 (Control)					
Heterogeneity: Tau^2 = 0.18; Chi^2 = 2.41, df = 2 (P = 0.30); I^2 =17%					
Test for overall effect: Z = 2.26 (P = 0.024)					
3 Nephrolithiasis in trials using vitamin D_3 combined with calcium					
Grant 2005	2/2649	2/2643		0.5 %	1.00 [0.14, 7.08]
Jackson 2006	449/18176	381/18106		99.1 %	1.17 [1.03, 1.34]
Lappe 2007	1/446	1/733		0.2 %	1.64 [0.10, 26.21]
Schleithoff 2006	0/61	1/62		0.2 %	0.34 [0.01, 8.16]
Subtotal (95% CI)	**21332**	**21544**		**100.0 %**	**1.17 [1.02, 1.34]**
Total events: 452 (Vitamin D), 385 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.67, df = 3 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 2.31 (P = 0.021)					
4 Nephrolithiasis in trials using calcitriol					
Gallagher 2001	0/123	1/123		100.0 %	0.33 [0.01, 8.10]
Subtotal (95% CI)	**123**	**123**		**100.0 %**	**0.33 [0.01, 8.10]**
Total events: 0 (Vitamin D), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
5 Hypercalciuria					
Aloia 2005	3/104	1/104		47.3 %	3.00 [0.32, 28.37]
Dawson-Hughes 1997	1/187	0/202		23.4 %	3.24 [0.13, 79.03]
Grady 1991	6/50	0/48		29.4 %	12.49 [0.72, 215.84]
Subtotal (95% CI)	**341**	**354**		**100.0 %**	**4.64 [0.99, 21.76]**

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 10 (Vitamin D), 1 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.70, df = 2 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 1.95 (P = 0.051)					
6 Renal insufficiency					
Grady 1991	2/50	0/48		23.5 %	4.80 [0.24, 97.55]
Grant 2005	2/2649	5/2643		42.1 %	0.40 [0.08, 2.06]
Witham 2010	5/53	1/52		34.5 %	4.91 [0.59, 40.57]
Subtotal (95% CI)	**2752**	**2743**		**100.0 %**	**1.70 [0.27, 10.70]**
Total events: 9 (Vitamin D), 6 (Control)					
Heterogeneity: Tau^2 = 1.40; Chi^2 = 4.26, df = 2 (P = 0.12); I^2 =53%					
Test for overall effect: Z = 0.56 (P = 0.57)					
7 Cardiovascular disorders					
Brazier 2005	6/95	5/97		0.7 %	1.23 [0.39, 3.88]
Gallagher 2001	8/123	7/123		1.0 %	1.14 [0.43, 3.05]
Komulainen 1999	2/116	0/116		0.1 %	5.00 [0.24, 103.02]
Prince 2008	5/151	6/151		0.7 %	0.83 [0.26, 2.67]
Trivedi 2003	477/1345	503/1341		96.8 %	0.95 [0.86, 1.04]
Witham 2010	5/53	5/52		0.7 %	0.98 [0.30, 3.19]
Subtotal (95% CI)	**1883**	**1880**		**100.0 %**	**0.95 [0.86, 1.05]**
Total events: 503 (Vitamin D), 526 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.55, df = 5 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 1.02 (P = 0.31)					
8 Gastrointestinal disorders					
Baeksgaard 1998	2/80	2/80		4.2 %	1.00 [0.14, 6.93]
Bischoff 2003	2/62	0/60		2.0 %	4.84 [0.24, 98.80]
Bolton-Smith 2007	2/62	0/61		2.0 %	4.92 [0.24, 100.43]
Brazier 2005	22/95	21/97		13.4 %	1.07 [0.63, 1.81]
Burleigh 2007	4/101	3/104		6.1 %	1.37 [0.32, 5.98]
Chapuy 1992	40/1634	28/1636		13.8 %	1.43 [0.89, 2.31]
Chapuy 2002	24/389	16/194		12.6 %	0.75 [0.41, 1.37]
Daly 2008	5/85	0/82		2.2 %	10.62 [0.60, 188.99]
Dawson-Hughes 1997	4/187	2/202		5.1 %	2.16 [0.40, 11.66]
Gallagher 2001	23/123	22/123		13.4 %	1.05 [0.62, 1.77]
Krieg 1999	6/124	0/124		2.2 %	13.00 [0.74, 228.31]
Krkkinen 2010	64/1718	0/1714		2.3 %	128.70 [7.97, 2078.10]
Moschonis 2006	0/42	4/70		2.2 %	0.18 [0.01, 3.32]

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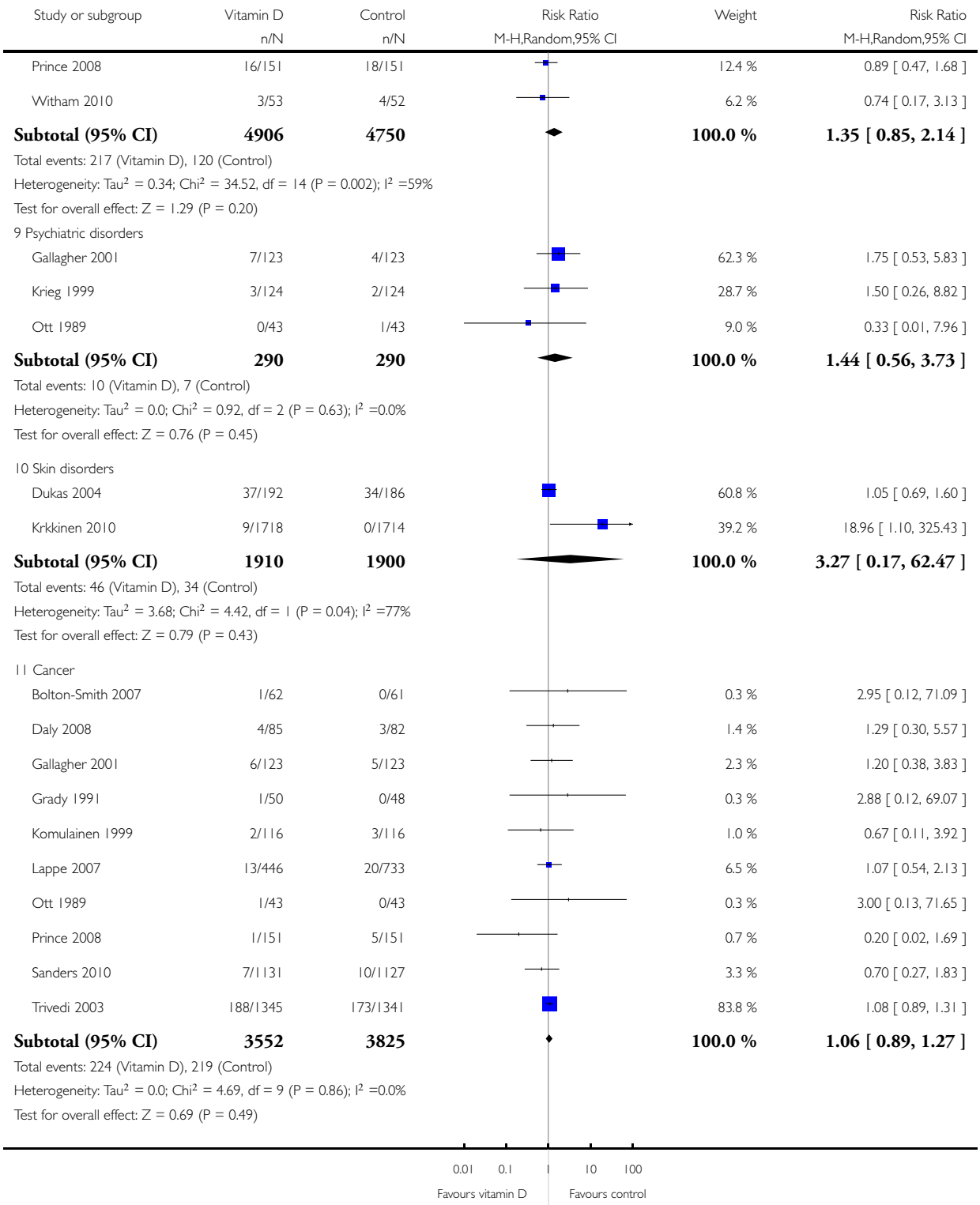

Analysis 1.23. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 23 All-cause mortality ('best-worst-case' and 'worst-best-case' scenario).

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 23 All-cause mortality ('best-worst-case' and 'worst-best-case' scenario)

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Best-worst-case scenario					
Aloia 2005	1/104	30/104		1.1 %	0.03 [0.00, 0.24]
Avenell 2004	4/70	10/64		2.1 %	0.37 [0.12, 1.11]
Baeksgaard 1998	0/80	16/80		0.7 %	0.03 [0.00, 0.50]
Bischoff 2003	1/62	15/60		1.1 %	0.06 [0.01, 0.47]
Bjorkman 2007	27/150	9/68		2.9 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	5/61		0.6 %	0.09 [0.01, 1.58]
Brazier 2005	3/95	29/97		2.1 %	0.11 [0.03, 0.34]
Broe 2007	5/99	2/25		1.5 %	0.63 [0.13, 3.07]
Burleigh 2007	16/101	23/104		3.1 %	0.72 [0.40, 1.27]
Campbell 2005	6/195	12/196		2.4 %	0.50 [0.19, 1.31]
Chapuy 1992	258/1634	337/1636		3.6 %	0.77 [0.66, 0.89]
Chapuy 2002	70/389	70/194		3.5 %	0.50 [0.38, 0.66]
Chel 2008	25/166	33/172		3.3 %	0.78 [0.49, 1.26]
Cooper 2003	0/93	14/94		0.7 %	0.03 [0.00, 0.58]
Corless 1985	8/41	15/41		2.8 %	0.53 [0.25, 1.12]
Daly 2008	1/85	28/82		1.1 %	0.03 [0.00, 0.25]
Dawson-Hughes 1997	2/187	32/202		1.7 %	0.07 [0.02, 0.28]
Dukas 2004	1/192	31/186		1.1 %	0.03 [0.00, 0.23]
Flicker 2005	76/313	128/312		3.6 %	0.59 [0.47, 0.75]
Gallagher 2001	2/123	11/123		1.6 %	0.18 [0.04, 0.80]
Grady 1991	1/50	1/48		0.7 %	0.96 [0.06, 14.92]
Grant 2005	438/2649	496/2643		3.6 %	0.88 [0.78, 0.99]
Harwood 2004	24/113	5/37		2.5 %	1.57 [0.65, 3.82]

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Jackson 2006	744/18176	1291/18106		3.7 %	0.57 [0.53, 0.63]
Komulainen 1999	0/116	4/116		0.6 %	0.11 [0.01, 2.04]
Krieg 1999	21/124	71/124		3.3 %	0.30 [0.19, 0.45]
Krkkinen 2010	15/1718	36/1714		3.0 %	0.42 [0.23, 0.76]
Latham 2003	11/121	8/122		2.5 %	1.39 [0.58, 3.33]
Law 2006	347/1762	386/1955		3.6 %	1.00 [0.88, 1.14]
Lips 1996	282/1291	315/1287		3.6 %	0.89 [0.78, 1.03]
Lips 2010	1/114	15/112		1.1 %	0.07 [0.01, 0.49]
Lyons 2007	713/1725	801/1715		3.7 %	0.88 [0.82, 0.95]
Meier 2004	0/30	9/25		0.7 %	0.04 [0.00, 0.72]
Moschonis 2006	0/42	8/70		0.6 %	0.10 [0.01, 1.64]
Ooms 1995	11/177	53/171		3.0 %	0.20 [0.11, 0.37]
Ott 1989	0/43	7/43		0.6 %	0.07 [0.00, 1.13]
Porthouse 2005	57/1321	131/1993		3.5 %	0.66 [0.48, 0.89]
Prince 2008	0/151	7/151		0.6 %	0.07 [0.00, 1.16]
Sanders 2010	40/1131	110/1127		3.4 %	0.36 [0.25, 0.52]
Sato 1999a	1/43	3/43		0.9 %	0.33 [0.04, 3.08]
Sato 1999b	0/34	3/35		0.6 %	0.15 [0.01, 2.74]
Sato 2005a	1/48	6/48		1.0 %	0.17 [0.02, 1.33]
Schleithoff 2006	7/61	11/62		2.5 %	0.65 [0.27, 1.56]
Smith 2007	355/4727	2423/4713		3.7 %	0.15 [0.13, 0.16]
Trivedi 2003	224/1345	324/1341		3.6 %	0.69 [0.59, 0.80]
Witham 2010	4/53	4/52		1.8 %	0.98 [0.26, 3.72]
Zhu 2008	0/39	7/81		0.6 %	0.14 [0.01, 2.33]
Subtotal (95% CI)	**41445**	**41835**	◆	**100.0 %**	**0.41 [0.32, 0.53]**
Total events: 3803 (Vitamin D), 7385 (Control)					
Heterogeneity: Tau^2 = 0.45; Chi^2 = 1171.50, df = 46 (P<0.00001); I^2 =96%					
Test for overall effect: Z = 6.97 (P < 0.00001)					
2 Worst-best-case scenario					
Aloia 2005	30/104	2/104		1.8 %	15.00 [3.68, 61.15]
Avenell 2004	18/70	3/64		2.1 %	5.49 [1.70, 17.75]
Baeksgaard 1998	15/80	1/80		1.3 %	15.00 [2.03, 110.88]
Bischoff 2003	19/62	4/60		2.3 %	4.60 [1.66, 12.72]

0.002 0.1 1 10 500

Favours vitamin D Favours control

(*Continued* . . .)

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bjorkman 2007	27/150	9/68		2.7 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	8/62	1/61		1.2 %	7.87 [1.01, 61.05]
Brazier 2005	21/95	1/97		1.3 %	21.44 [2.94, 156.24]
Broe 2007	8/99	2/25		1.7 %	1.01 [0.23, 4.46]
Burleigh 2007	20/101	13/104		2.8 %	1.58 [0.83, 3.01]
Campbell 2005	45/195	10/196		2.8 %	4.52 [2.35, 8.72]
Chapuy 1992	302/1634	917/1636		3.2 %	0.33 [0.30, 0.37]
Chapuy 2002	109/389	46/194		3.1 %	1.18 [0.88, 1.59]
Chel 2008	25/166	33/172		3.0 %	0.78 [0.49, 1.26]
Cooper 2003	20/93	1/94		1.3 %	20.22 [2.77, 147.56]
Corless 1985	25/41	8/41		2.7 %	3.13 [1.60, 6.10]
Daly 2008	30/85	0/82		0.8 %	58.87 [3.66, 947.17]
Dawson-Hughes 1997	39/187	2/202		1.8 %	21.06 [5.16, 86.02]
Dukas 2004	26/192	1/186		1.3 %	25.19 [3.45, 183.73]
Flicker 2005	130/313	85/312		3.1 %	1.52 [1.22, 1.91]
Gallagher 2001	22/123	1/123		1.3 %	22.00 [3.01, 160.68]
Grady 1991	1/50	0/48		0.7 %	2.88 [0.12, 69.07]
Grant 2005	469/2649	460/2643		3.2 %	1.02 [0.91, 1.14]
Harwood 2004	42/113	5/37		2.5 %	2.75 [1.18, 6.43]
Jackson 2006	1240/18176	807/18106		3.2 %	1.53 [1.40, 1.67]
Komulainen 1999	3/116	1/116		1.1 %	3.00 [0.32, 28.42]
Krieg 1999	74/124	26/124		3.0 %	2.85 [1.96, 4.12]
Krkkinen 2010	20/1718	13/1714		2.7 %	1.53 [0.77, 3.08]
Latham 2003	13/121	3/122		2.0 %	4.37 [1.28, 14.95]
Law 2006	396/1762	322/1955		3.2 %	1.36 [1.20, 1.56]
Lips 1996	289/1291	306/1287		3.2 %	0.94 [0.82, 1.08]
Lips 2010	9/114	0/112		0.8 %	18.67 [1.10, 316.98]
Lyons 2007	805/1725	715/1715		3.2 %	1.12 [1.04, 1.21]
Meier 2004	3/30	1/25		1.1 %	2.50 [0.28, 22.56]
Moschonis 2006	3/42	1/70		1.1 %	5.00 [0.54, 46.53]
Ooms 1995	51/177	21/171		3.0 %	2.35 [1.48, 3.73]

(*Continued* . . .)

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Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ott 1989	7/43	1/43		1.2 %	7.00 [0.90, 54.50]
Porthouse 2005	109/1321	68/1993		3.1 %	2.42 [1.80, 3.25]
Prince 2008	7/151	1/151		1.2 %	7.00 [0.87, 56.21]
Sanders 2010	116/1131	47/1127		3.1 %	2.46 [1.77, 3.42]
Sato 1999a	3/43	0/43		0.8 %	7.00 [0.37, 131.56]
Sato 1999b	2/34	1/35		1.0 %	2.06 [0.20, 21.67]
Sato 2005a	5/48	2/48		1.6 %	2.50 [0.51, 12.26]
Schleithoff 2006	19/61	6/62		2.5 %	3.22 [1.38, 7.51]
Smith 2007	2447/4727	354/4713		3.2 %	6.89 [6.21, 7.65]
Trivedi 2003	307/1345	247/1341		3.2 %	1.24 [1.07, 1.44]
Witham 2010	5/53	2/52		1.6 %	2.45 [0.50, 12.08]
Zhu 2008	6/39	2/81		1.7 %	6.23 [1.32, 29.47]
Subtotal (95% CI)	**41445**	**41835**	◆	**100.0 %**	**2.73 [2.04, 3.65]**
Total events: 7390 (Vitamin D), 4552 (Control)					
Heterogeneity: $Tau^2 = 0.69$; $Chi^2 = 1913.80$, df = 46 (P<0.00001); $I^2 = 98\%$					
Test for overall effect: Z = 6.75 (P < 0.00001)					

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Favours vitamin D Favours control

APPENDICES

Appendix 1. Search strategies

Search terms for various databases
The Cochrane Library
1. MeSH descriptor Vitamin D explode all trees 2. MeSH descriptor Cholecalciferol explode all trees 3. MeSH descriptor Ergocalciferols explode all trees 4. MeSH descriptor Dihydrotachysterol explode all trees 5. MeSH descriptor 25-hydroxyvitamin D 2 explode all trees

(*Continued*)

6. MeSH descriptor Hydroxycholecalciferols explode all trees
7. ((vitamin* in All Text and d in All Text and 2 in All Text) or (vitamin* in All Text and d2 in All Text))
8. (cholecalciferol* in All Text or calciferol* in All Text or calcitriol* in All Text or dihydrotachysterol* in All Text or (hydroxyvitamin* in All Text and d* in All Text))
9. (alfacalcidol* in All Text or alphacalcidol* in All Text or colecalciferol* in All Text)
10. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
11. MeSH descriptor Mortality explode all trees
12. (mortality in All Text or mortaliti* in All Text)
13. (#11 or #12)
14. MeSH descriptor Primary Prevention explode all trees
15. prevent* in All Text
16. MeSH descriptor Neoplasms explode all trees
17. (cancer* in All Text or neoplasm* in All Text or tumo?r* in All Text)
18. (#14 or #15 or #16 or #17)
19. (#10 and #13)
20. (#10 and #18)
21. (#19 or #20)

MEDLINE

1. exp Vitamin D/
2. exp Cholecalciferol/
3. exp ergocalciferols/ or exp dihydrotachysterol/ or exp 25-hydroxyvitamin d 2/
4. exp Hydroxycholecalciferols/
5. vitamin D?.tw,ot.
6. (cholecalciferol$ or calcifediol$ or calcitriol$ or dihydrotachysterol$ or hydroxyvitamin$ d?).tw,ot.
7. (alfacalcidol$ or alphacalcidol$ or colecalciferol$).tw,ot.
8. or/1-7
9. exp Mortality/
10. mortality.tw,ot.
11. mortaliti$.tw,ot.
12. or/9-11
13. exp Primary Prevention/
14. (prevention$ or prevent$).tw,ot.
15. exp Neoplasm/
16. (cancer$ or neoplasm$ or tumo?r$).tw,ot.
17. or/13-16
18. exp Randomized Controlled Trials as topic/
19. Randomized Controlled Trial.pt.
20. exp Controlled Clinical Trials as topic/
21. Controlled Clinical Trial.pt.
22. exp Random Allocation/
23. exp Double-Blind Method/
24. exp Single-Blind Method/
25. or/18-24
26. exp "Review Literature as topic"/
27. exp Technology Assessment, Biomedical/
28. exp Meta-analysis as topic/
29. Meta-analysis.pt.

(*Continued*)

30. hta.tw,ot.
31. (health technology adj6 assessment$).tw,ot.
32. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
33. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current
content$ or systemat$)).tw,ot.
34. or/26-33
35. 25 or 34
36. 8 and 17 and 35
37. 8 and 12 and 35
38 36 or 37
39. limit 38 to animals
40. limit 38 to humans
41. 39 not 40
42 38 not 41

EMBASE

1. exp ergocalciferol/ or exp vitamin D/
2. exp colecalciferol/
3. exp dihydrotachysterol/
4. exp 25 hydroxyvitamin D/
5. exp hydroxycolecalciferol/
6. (vitamin* D? or vitamin*D?).tw,ot.
7. (cholecalciferol* or colecalciferol* or calcifediol* or calcitriol* or dihydrotachysterol* or hydroxyvitamin* d?).tw,ot.
8. exp alfacalcidol/
9. (alfacalcidol* or alphacalcidol*).tw,ot.
10. or/1-9
11. exp mortality/
12. (mortality or mortaliti*).tw,ot.
13. 11 or 12
14. exp prevention/
15. prevent*.tw,ot.
16. exp neoplasm/
17. or/14-16
18. randomized controlled trial/
19. double blind procedure/
20. single blind procedure/
21. exp randomization/
22. exp controlled clinical trial/
23. or/18-22
24. exp meta analysis/
25. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
26. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systematic$)).ab,ti,ot.
27. exp Literature/
28. exp Biomedical Technology Assessment/
29. hta.tw,ot.
30. (health technology adj6 assessment$).tw,ot.