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

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[Intervention Review]

Vitamin D supplementation for prevention of mortality in adults

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ABSTRACT

Background

Available evidence on the effects of vitamin D on mortality has been inconclusive. In a recent systematic review, we found evidence that vitamin D_3 may decrease mortality in mostly elderly women. The present systematic review updates and reassesses the benefits and harms of vitamin D supplementation used in primary and secondary prophylaxis of mortality.

Objectives

To assess the beneficial and harmful effects of vitamin D supplementation for prevention of mortality in healthy adults and adults in a stable phase of disease.

Search methods

We searched *The Cochrane Library*, MEDLINE, EMBASE, LILACS, the Science Citation Index-Expanded and Conference Proceedings Citation Index-Science (all up to February 2012). We checked references of included trials and pharmaceutical companies for unidentified relevant trials.

Selection criteria

Randomised trials that compared any type of vitamin D in any dose with any duration and route of administration versus placebo or no intervention in adult participants. Participants could have been recruited from the general population or from patients diagnosed with a disease in a stable phase. Vitamin D could have been administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)) or as an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol) or 1,25-dihydroxyvitamin D (calcitriol)).

Data collection and analysis

Six review authors extracted data independently. Random-effects and fixed-effect meta-analyses were conducted. For dichotomous outcomes, we calculated the risk ratios (RRs). To account for trials with zero events, we performed meta-analyses of dichotomous data using risk differences (RDs) and empirical continuity corrections. We used published data and data obtained by contacting trial authors.

To minimise the risk of systematic error, we assessed the risk of bias of the included trials. Trial sequential analyses controlled the risk of random errors possibly caused by cumulative meta-analyses.

Main results

We identified 159 randomised clinical trials. Ninety-four trials reported no mortality, and nine trials reported mortality but did not report in which intervention group the mortality occurred. Accordingly, 56 randomised trials with 95,286 participants provided usable data on mortality. The age of participants ranged from 18 to 107 years. Most trials included women older than 70 years. The mean proportion of women was 77%. Forty-eight of the trials randomly assigned 94,491 healthy participants. Of these, four trials included healthy volunteers, nine trials included postmenopausal women and 35 trials included older people living on their own or in institutional care. The remaining eight trials randomly assigned 795 participants with neurological, cardiovascular, respiratory or rheumatoid diseases. Vitamin D was administered for a weighted mean of 4.4 years. More than half of the trials had a low risk of bias. All trials were conducted in high-income countries. Forty-five trials (80%) reported the baseline vitamin D status of participants based on serum 25-hydroxyvitamin D levels. Participants in 19 trials had vitamin D adequacy (at or above 20 ng/mL). Participants in the remaining 26 trials had vitamin D insufficiency (less than 20 ng/mL).

Vitamin D decreased mortality in all 56 trials analysed together (5,920/47,472 (12.5%) vs 6,077/47,814 (12.7%); RR 0.97 (95% confidence interval (CI) 0.94 to 0.99); P = 0.02; I^2 = 0%). More than 8% of participants dropped out. 'Worst-best case' and 'best-worst case' scenario analyses demonstrated that vitamin D could be associated with a dramatic increase or decrease in mortality. When different forms of vitamin D were assessed in separate analyses, only vitamin D_3 decreased mortality (4,153/37,817 (11.0%) vs 4,340/38,110 (11.4%); RR 0.94 (95% CI 0.91 to 0.98); P = 0.002; I^2 = 0%; 75,927 participants; 38 trials). Vitamin D_2, alfacalcidol and calcitriol did not significantly affect mortality. A subgroup analysis of trials at high risk of bias suggested that vitamin D_2 may even increase mortality, but this finding could be due to random errors. Trial sequential analysis supported our finding regarding vitamin D_3, with the cumulative Z-score breaking the trial sequential monitoring boundary for benefit, corresponding to 150 people treated over five years to prevent one additional death. We did not observe any statistically significant differences in the effect of vitamin D on mortality in subgroup analyses of trials at low risk of bias compared with trials at high risk of bias; of trials using placebo compared with trials using no intervention in the control group; of trials with no risk of industry bias compared with trials with risk of industry bias; of trials assessing primary prevention compared with trials assessing secondary prevention; of trials including participants with vitamin D level below 20 ng/mL at entry compared with trials including participants with vitamin D levels equal to or greater than 20 ng/mL at entry; of trials including ambulatory participants compared with trials including institutionalised participants; of trials using concomitant calcium supplementation compared with trials without calcium; of trials using a dose below 800 IU per day compared with trials using doses above 800 IU per day; and of trials including only women compared with trials including both sexes or only men. Vitamin D_3 statistically significantly decreased cancer mortality (RR 0.88 (95% CI 0.78 to 0.98); P = 0.02; I^2 = 0%; 44,492 participants; 4 trials). Vitamin D_3 combined with calcium increased the risk of nephrolithiasis (RR 1.17 (95% CI 1.02 to 1.34); P = 0.02; I^2 = 0%; 42,876 participants; 4 trials). Alfacalcidol and calcitriol increased the risk of hypercalcaemia (RR 3.18 (95% CI 1.17 to 8.68); P = 0.02; I^2 = 17%; 710 participants; 3 trials).

Authors' conclusions

Vitamin D_3 seemed to decrease mortality in elderly people living independently or in institutional care. Vitamin D_2, alfacalcidol and calcitriol had no statistically significant beneficial effects on mortality. Vitamin D_3 combined with calcium increased nephrolithiasis. Both alfacalcidol and calcitriol increased hypercalcaemia. Because of risks of attrition bias originating from substantial dropout of participants and of outcome reporting bias due to a number of trials not reporting on mortality, as well as a number of other weaknesses in our evidence, further placebo-controlled randomised trials seem warranted.

PLAIN LANGUAGE SUMMARY

Vitamin D supplementation for prevention of mortality in adults

Review question

To assess the beneficial and harmful effects of vitamin D for prevention of mortality in healthy adults and adults in a stable phase of disease.

Background

Numerous observational studies suggest that optimal vitamin D status may be associated with fewer occurrences of cancer and cardiovascular disease (such as heart attack or stroke). Vitamin D is synthesised in the skin as vitamin D_3 (cholecalciferol) or is obtained from dietary sources or supplements as vitamin D_3 or vitamin D_2 (ergocalciferol). Our Cochrane systematic review from 2011, which analysed the influence of different forms of vitamin D on mortality, showed that vitamin D_3 (cholecalciferol) decreased mortality. This systematic review is now updated, and all included trials have been reassessed in accordance with improved Cochrane methodology, developed to enhance the validity of the conclusions.

Study characteristics

In the 56 trials that provided data for the analyses, a total of 95,286 participants were randomly assigned to vitamin D versus no treatment or placebo. More than half of the trials were considered to have low risk of bias. All trials were conducted in high-income countries. The age of participants ranged from 18 to 107 years. The mean proportion of women was 77%. Vitamin D was administered for an average of 4.4 years.

This plain language summary is as current as of February 2012.

Key results

This review suggests that vitamin D_3 may reduce mortality, showing that about 150 participants need to be treated over five years for one additional life to be saved. We found comparable effects of vitamin D_3 in studies that included only women compared with studies including both women and men. Vitamin D_3 also seemed to decrease cancer mortality, showing a reduction in mortality of 4 per 1000 persons treated for five to seven years. We also observed adverse effects to vitamin D such as 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 some evidence that vitamin D_3 seems to decrease mortality in elderly people not dependent on help or living in institutional care.

Quality of the evidence

A large number of study participants left the trial before completion, and this raises concerns regarding the validity of the results. More randomised clinical trials are needed on the effects of vitamin D_3 on mortality in younger, healthy persons, as well as in elderly community-dwelling and institutionalised persons without apparent vitamin D deficiency.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Vitamin D supplementation for prevention of mortality in adults

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 D_3 (cholecalciferol) (Follow-up: 0.08 to 7 years)	**Study population**		**RR 0.94** (0.91 to 0.98)	75,927 (38)	⊕⊕⊕◯ **moderate**[a]	Trial sequential analysis of all trials irrespective of bias risks showed that the required information size had not yet been reached and that the cumulative Z-curve crossed the trial sequential monitoring boundary for benefit. If this is correct, the intervention effect corresponds to a number needed to treat for a beneficial outcome (NNTB) of 150 participants over five years to save one additional life
	114 per 1000	**107 per 1000** (104 to 112)				
	Moderate risk					
	46 per 1000	**43 per 1000** (42 to 45)				

Cardiovascular mortality in trials using vitamin D_3 (cholecalciferol) (Follow-up: 0.31 to 6.2 years)	**Study population**		**RR 0.98** (0.90 to 1.07)	47,267 (10)	⊕⊕◯◯ **low**[b]	Trial sequential analysis showed that the cumulative Z-curve did not cross the conventional monitoring boundary for benefit. The required information size was 2,539,845 participants
	42 per 1000	**41 per 1000** (38 to 45)				
	Moderate risk					
	13 per 1000	**11 per 1000** (12 to 15)				
Cancer mortality in trials using vitamin D_3 (cholecalciferol) (Follow-up: 5 to 7 years)	**Study population**		**RR 0.88** (0.78 to 0.98)	44,492 (4)	⊕⊕⊕◯ **moderate**[a]	Trial sequential analysis showed that the cumulative Z-curve did not cross the conventional monitoring boundary for benefit. The required information size was 66,724 participants
	29 per 1000	**25 per 1000** (22 to 31)				
	Moderate risk					
	21 per 1000	**19 per 1000** (16 to 21)				
Adverse events: nephrolithiasis in trials using vitamin D_3 combined with calcium (Follow-up: 1.25 to 7 years)	**Study population**		**RR 1.17** (1.02 to 1.34)	42,876 (4)	⊕⊕⊕◯ **moderate**[a]	
	18 per 1000	**21 per 1000** (18 to 24)				
	Moderate risk					
	9 per 1000	**11 per 1000** (9 to 12)				
Adverse events: hypercalcaemia in trials using the active forms of vitamin D (alfacalcidol and calcitriol) (Follow-up: 0.75 to 3 years)	**Study population**		**RR 3.18** (1.17 to 8.68)	710 (3)	⊕⊕◯◯ **low**[b]	

	23 per 1000	**72 per 1000** (27 to 197)				
	Moderate risk					
	11 per 1000	**15 per 1000** (4 to 23)				
Health-related quality of life (Follow-up: 0.38 years)	See comment	See comment	Not estimable	105 (1)	See comment	Insufficient information: significant worsening in disease-specific quality of life in the vitamin D_2 group compared with the placebo group was reported. The between-group difference at 20 weeks was 5.3 (0.5 to 10.2), and the minimally important difference (MID) is estimated to be 5 points in either direction
Health economics (Follow-up: 4 years)	See comment	See comment	Not estimable	3270 (1)	See comment	Insufficient information: authors reported that vitamin D_3 and calcium supplementation prevented 46 hip fractures in every 1000 women treated

*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; **RRR**: relative risk reduction

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.

[a] Downgraded by one level because of risk of attrition bias
[b] Downgraded by two levels because of risk of attrition bias and imprecision

BACKGROUND

Description of the condition

Vitamin D is synthesised in the skin as vitamin D_3 (cholecalciferol) or is 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 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 in the cells (Wesley Pike 2005). Renal production of 1,25-dihydroxyvitamin D is regulated by parathyroid hormone levels, by serum calcium and phosphorus levels and by the phosphaturic hormone fibroblast growth factor-23 (Kovesdy 2013).

Under conditions of hypocalcaemia, 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). During past decades, 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 measurement of the serum 25-hydroxyvitamin D level, which is a functional indicator of 'vitamin D status' (Bischoff-Ferrari 2009c; Dawson-Hughes 2005; Lips 2004). The US 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). Major causes of vitamin D deficiency include 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 its 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)) seems to prevent osteoporosis, osteomalacia and fractures (Holick 2007a; Lamberg-Allardt 2006). It has been speculated that vitamin D may confer benefits beyond the skeletal system (Davis 2007). Evidence on whether vitamin D may prevent cancer, cardiovascular disease and mortality is contradictory (Bjelakovic 2011; Davis 2007; Giovannucci 2005; Michos 2008; Pittas 2010; Wang 2010; Zittermann 2006).

Adverse effects of the intervention

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

Why it is important to do this review

Available evidence on vitamin D and mortality is intriguing and for the most inconclusive. Most observational studies have associated low vitamin D status with increased risk of death (Johansson 2012; Zittermann 2012). Several systematic reviews and meta-analyses found beneficial effects of vitamin D in elderly people with vitamin deficiency or in people who received vitamin D as monotherapy or in combination with calcium for osteoporosis, fractures and falls (Bischoff-Ferrari 2005; Bischoff-Ferrari 2009a; Jackson 2007; Latham 2003b; Richy 2005; Tang 2007). Vitamin D supplementation revealed positive effects in maintaining glucose homeostasis (Pittas 2007a) and in preventing tuberculosis (Nnoaham 2008). However, Izaks et al (Izaks 2007) and Boonen et al (Boonen 2006) found no statistically significant effects of vitamin D supplementation on these outcomes in the general population. A meta-analysis by Autier and Gandini (Autier 2007) of 18 randomised clinical trials found significantly lower mortality among vitamin D-supplemented participants (Autier 2007). A Cochrane systematic review of 16 randomised trials on prevention of fractures found only a non-significant tendency of vitamin D to reduce mortality (Avenell 2009). In our published Cochrane review in 2011, data from 50 randomised clinical trials with 94,148 participants suggested a beneficial effect of vitamin D_3 on mortality (Bjelakovic 2011). Since the time of that review (Bjelakovic 2011), the results of several new randomised trials conducted to test the influence of vitamin D supplementation on mortality have become available. Also, we wanted to analyse further the influence of participants' sex on the effects of vitamin D_3 and to implement the improved Cochrane methodology in performing data assessment. The present review is an update of the former review (Bjelakovic 2011).

OBJECTIVES

To assess the beneficial and harmful effects of vitamin D supplementation for prevention of mortality in healthy adults and adults in a stable phase of disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials, irrespective of blinding, publication status or language, that have 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 seek to prevent disease before it occurs) and secondary prevention trials (defined as trials undertaken to prevent recurrences or exacerbations of a disease that has already been diagnosed) (Starfield 2008).

Types of participants

We included adult participants (18 years of age or older) who were.

- Healthy or were recruited from the general population (primary prevention), irrespective of vitamin D status in the blood.
- Diagnosed with a specific disease and in a stable phase (secondary prevention), irrespective of vitamin D status in the blood.
- 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, gastrointestinal bypass 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 and for any duration, administered as monotherapy or in combination with calcium. The route of administration could have been enteral or parenteral.

Vitamin D could have been administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)) or as an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol) or 1,25-dihydroxyvitamin D (calcitriol)).

Control

Identical placebo or no intervention.

Calcium in the control group was allowed if used equally in the vitamin D groups 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 and non-serious. A serious adverse event was defined as any untoward medical occurrence that was life threatening; resulted in death, or in persistent or significant disability or incapacity; or was a congenital anomaly/birth defect; or any medical event that might have jeopardised the participant or required intervention to prevent it (ICH-GCP 1997). All other adverse events (i.e. medical occurrences not necessarily having a causal relationship to the treatment but causing a dose reduction or discontinuation of 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.

Co-variates, effect modifiers and confounders

We recorded any possible co-variates, effect modifiers and confounders such as 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 and attrition.

Timing of outcome measurement

We applied no restrictions regarding duration of the intervention or length of follow-up. We assessed outcome data at the end of the trial follow-up period.

Search methods for identification of studies

Electronic searches

We searched the following sources from inception to the specified date to identify trials that met our criteria.

- *The Cochrane Library* (Issue 2, February 2012).
- MEDLINE (until February 2012).
- EMBASE (until February 2012).
- LILACS (until February 2012).
- Science Citation Index-Expanded (until February 2012).
- Conference Proceedings Citation Index-Science (until February 2012).

We also searched Clinicaltrials.gov (http://clinicaltrials.gov/) and the World Health Organization International Clinical Trials Registry Platform (ICTRP 2011) to look for ongoing trials.
The search strategies for the databases we have searched are given in Appendix 1.

Searching other resources

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

Data collection and analysis

The present updated review expands on the previously published review in 2011 (Bjelakovic 2011) and the protocol published in 2008 (Bjelakovic 2008a).

Selection of studies

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

Data extraction and management

Six review authors (GB, LLG, DN, KW, RGS and MB) independently extracted data on the relevant population and intervention characteristics, as well as on the risk of bias components, from trials that fulfilled the inclusion criteria of our review protocol. We used standard templates for data extraction. We searched for duplicate publications. Disagreements were resolved by discussion or, when needed, by the review author CG.

Assessment of risk of bias in included studies

Because of the risk of overestimation of beneficial intervention effects in randomised clinical trials with unclear or inadequate methodological quality (Kjaergard 2001; Lundh 2012; Moher 1998; Savovic 2012; 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, incomplete outcome data, selective outcome reporting, industry bias and other apparent biases (Higgins 2011). The following definitions were used.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent person not otherwise involved in the trial.
- Uncertain risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. if the allocation sequence was hidden in sequentially numbered, opaque and sealed envelopes).
- Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants, personnel and outcome assessors

- Low risk of bias: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.

- Uncertain risk of bias: information was insufficient to allow assessment of whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding was provided, and assessment of outcomes was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, have been employed to handle missing data.
- Uncertain risk of bias: information was insufficient to allow assessment of whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased because of missing data.

Selective outcome reporting

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

To be assessed with low risk of bias in the selective outcome reporting domain, the trial should have been registered on the www.clinicaltrials.gov website or a similar register, or a protocol should exist (e.g. published in a paper journal). In cases where the trial was run and published during the years when trial registration was not required, we tried to carefully scrutinise the publication reporting on the trial to identify the trial objectives and outcomes. If usable data on all outcomes specified in the trial objectives were provided in the publication's results section, the trial was considered to have low risk of bias in the 'Selective outcome reporting' domain.

Industry bias

- Low risk of bias: the trial is not funded by a manufacturer of vitamin D.
- Uncertain risk of bias: the source of funding is not clear.
- High risk of bias: the trial is funded by a manufacturer of vitamin D.

Other bias

- Low risk of bias: the trial appears to be free of other components that could put it at risk of bias.
- Uncertain risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: other factors in the trial could put it at risk of bias (e.g. authors have conducted trials on the same topic, etc).

Trials assessed as having 'low risk of bias' in all of the individual domains specified above were considered 'trials with low risk of bias'. Trials assessed as having 'uncertain risk of bias' or 'high risk of bias' in one or more of the specified individual domains were considered trials with 'high risk of bias' (Gluud 2011).

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 randomly assigned participants, as well as intention-to-treat (ITT) and per-protocol (PP) populations. We investigated attrition (i.e. 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 simultaneously evaluating all available data. When doubts arose, the publication that reported the longest follow-up (usually the most recent publication) was given priority.

Assessment of heterogeneity

We identified heterogeneity through visual inspection of the forest plots by using a standard Chi^2 test and a significance level of $\alpha = 0.1$. In view of the low power of such tests, we also examined heterogeneity by using the I^2 statistic (Higgins 2002); I^2 values of 50% or 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. For heterogeneity adjustment of the required information size, we used diversity, the D^2 statistic (Wetterslev 2009).

Assessment of reporting biases

Funnel plots were used to assess the potential existence of bias (Lau 2006). Several explanations can be offered 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 in accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

For the statistical analyses, we used Review Manager 5.2 (RevMan 2012), Trial Sequential Analysis version 0.9 beta (TSA 2011), STATA 8.2 (STATA Corp, College Station, Texas) and Sigma Stat 3.0 (SPSS Inc, Chicago, Illinois). For dichotomous outcomes, we calculated the Mantel-Haenszel risk ratios (RRs) (Gluud 2008). For all association measures, 95% confidence intervals (CIs) were used. We analysed the data with both fixed-effect (DeMets 1987) and random-effects (DerSimonian 1986) model meta-analyses. In cases where no difference in statistical significance was observed between the results obtained with the two models, we presented the result of the random-effects model analysis. Otherwise, we presented the results of both analyses.

We calculated weighted averages for factors related to the trials such as duration of the intervention and length of the follow-up period.

Analyses were performed using the intention-to-treat (ITT) principle, including all randomly assigned participants, irrespective of completeness of data. Participants with missing data were included in the analyses using a carry forward of the last observed response. Accordingly, participants who had been lost to follow-up were counted as being alive.

Review Manager 5.2 does not include trials with zero events in both intervention groups when calculating RR (RevMan 2012). To account for trials with zero events, meta-analyses of dichotomous data were repeated using risk differences (RDs) (Friedrich 2007; Keus 2009). The influence of trials with zero events in the treatment, control or both groups was also assessed by recalculating the random-effects model meta-analyses with 0.5, 0.01 and 0.001 as empirical continuity corrections (Bradburn 2007; Sweeting 2004) using Trial Sequential Analysis version 0.9 beta (TSA 2011; www.ctu.dk/tsa).

For trials using a factorial design that tested vitamin D parallel to any other intervention (i.e. hormone replacement therapy, other vitamins, etc), we used 'inside the table' analysis in which we compared only the vitamin D intervention group versus the placebo or no intervention group. Otherwise, we used 'at margins' analysis (McAlister 2003). In trials with parallel-group design with more than two intervention groups and additional therapy, we compared the vitamin D singly administered group versus the placebo or no intervention group.

We included in the analyses individually randomised trials as well as cluster-randomised trials. Data from cluster-randomised trials were incorporated using the generic inverse variance method. We explored the association between intervention effects of vitamin D and the subgrouping of individually randomised and cluster-randomised trials. The influence of cluster-randomised trials on our results was also explored in sensitivity analyses, which either included or excluded them.

We compared the intervention effects in subgroups of trials using the method described by Bornstein et al (Borenstein 2009) and implemented in RevMan 5.2 for all types of meta-analyses.

Trial sequential analysis

A cumulative meta-analysis runs the risk of random errors due to analysis of sparse data and repetitive testing of data (Thorlund 2009; Thorlund 2011a; Thorlund 2011b; Wetterslev 2008). We conducted trial sequential analyses to control the risk of random errors and to prevent premature statements of superiority of the experimental or control intervention or probably falsely declarations of absence of effect in cases for which we have too few data (Thorlund 2011a; Thorlund 2011b; Wetterslev 2008). We performed trial sequential analyses with a type I error of 5%, a type II error of 20% (80% power) and a 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 control group (Autier 2007) and an anticipated intervention effect of 5% relative risk reduction or otherwise as stated. Trials were entered into trial sequential analyses according to year of publication, and in cases where more than one trial was published in a year, trial entrance followed alphabetically the family name of the first author.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses in cases where one of the primary outcome measures showed statistically significant differences between intervention groups.

We performed the following subgroup analyses.

- Trials at low risk of bias compared with trials at high risk of bias.
- Placebo-controlled trials compared with trials with no intervention in the control group.
- Individually randomised trials compared with cluster-randomised trials.
- Primary prevention trials compared with secondary prevention trials.
- Vitamin D_3 compared with placebo or no intervention.
- Trials that administered vitamin D_3 singly compared with trials that administered vitamin D_3 combined with calcium.
- Trials that administered low-dose vitamin D_3 compared with trials that administered high-dose vitamin D_3.
- Trials that administered vitamin D_3 daily compared with trials that administered vitamin D_3 intermittently.
- Trials that administered vitamin D_3 to vitamin D-sufficient participants compared with trials that administered vitamin D_3 to vitamin D-insufficient participants.
- Vitamin D_2 compared with placebo or no intervention.
- Trials that administered vitamin D_2 singly compared with trials that administered vitamin D_2 combined with calcium.

- Trials that administered low-dose vitamin D_2 compared with trials that administered high-dose vitamin D_2.
- Trials that administered vitamin D_2 daily compared with trials that administered vitamin D_2 intermittently.
- Trials that administered vitamin D_2 to vitamin D-sufficient participants compared with trials that administered vitamin D_2 to vitamin D-insufficient participants.
- Alfacalcidol compared with placebo or no intervention.
- Trials that administered alfacalcidol to vitamin D-sufficient participants compared with trials that administered alfacalcidol to vitamin D-insufficient participants.
- Calcitriol compared with placebo or no intervention.
- Trials that administered calcitriol to vitamin D-sufficient participants compared with trials that administered calcitriol to vitamin D-insufficient participants.

Sensitivity analysis

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

- Repeating the analysis while excluding cluster-randomised trials.
- Repeating the analysis while including trials with zero mortality in both intervention groups.
- Repeating the analysis while taking attrition bias into consideration.

RESULTS

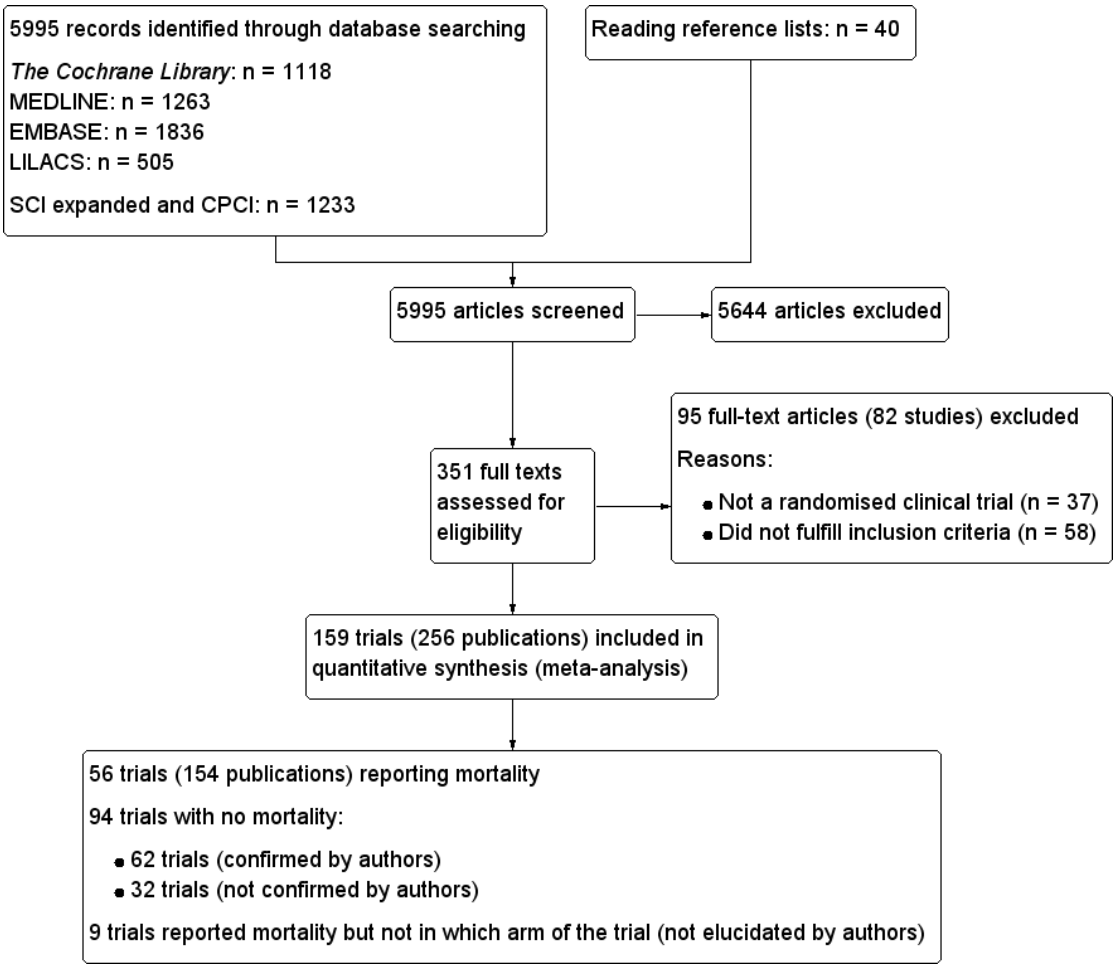
Description of studies

Results of the search

We identified a total of 5995 references of possible interest by searching *The Cochrane Library* (n = 1118), MEDLINE (n = 1263), EMBASE (n = 1836), LILACS (n = 505), Science Citation Index-Expanded (n = 1205), Conference Proceedings Citation Index-Science (n = 28) and reference lists (n = 40). We excluded 4802 duplicates and 842 clearly irrelevant references by reading the abstracts. Accordingly, 351 references were retrieved for further assessment. Of these, we excluded 95 references describing 82 studies because they were not randomised clinical trials or did not fulfil our review protocol inclusion criteria. Reasons for exclusion are listed in the table Characteristics of excluded studies.

In total, 159 randomised trials described in 256 publications fulfilled our inclusion criteria (Figure 1). They included a total of 105,992 participants. In total, 94 trials described in 114 publications reported no deaths (Abu-Mouch 2011; Aloia 1988; Aloia 1990; Aloia 2008; Aloia 2010; Andersen 2009; Angeles-Agdeppa 2010; Armas 2004b; Arvold 2009; Bang 2011; Barnes 2006; Barnes 2011; Biancuzzo 2010; Braam 2004; Bunout 2006; Burton 2010; Caniggia 1984; Cashman 2008; Chen 1997; Christiansen 1980; Christiansen 1981; Dawson-Hughes 1991; Deroisy 2002; Dhesi 2004; Di 2004; Domrongkitchaiporn 2000; Ebeling 2001; Fliser 1997; Forsythe 2012; Gallagher 1982; Gorai 1999; Green 2010; Harris 1999; Harris 2002; Himeno 2009; Himmelstein 1990; Holick 2008c; Hulshof 2000; Hunter 2000; Ishida 2004; Islam 2010; Jensen 1982a; Jensen 1982b; Jensen 1985; Johnson 1980; Jorde 2008; Jorde 2009; Jorde 2010a; Jorde 2010b; Jorde 2010c; Jorde 2010d; Jorde 2010e; Kenny 2003; Khaw 1994; Kimball 2011; Kruger 2010; Kuwabara 2009; Laaksi 2010; Lambrinoudaki 2000; Lappe 2008; Li-Ng 2009; Lind 1989; Lind 1992; Lips 1988; Ljunghall 1987; Major 2007; Major 2009; Maki 2011; Malhotra 2009; Martin-Bautista 2010; Menczel 1994; Mitri 2011; Nagpal 2009; Nelson 2009; Nordin 1985; Ongphiphadhanakul 2000; Orimo 1994; Orwoll 1988; Orwoll 1994; Patel 2001; Pfeifer 2000; Pfeifer 2001; Pfeifer 2009; Pignotti 2010; Pilz 2011; Schaafsma 2000; Scragg 1995a; Scragg 1995b; Shiomi 1999a; Shiomi 1999b; Shiraki 1985; Shiraki 1996; Shiraki 2004; Sneve 2008; Son 2001; Songpatanasilp 2009; Sorva 1991; Sugden 2008; Urbain 2011; Ushiroyama 1995; Ushiroyama 2001; Ushiroyama 2002; Van Der Klis 1996; Viljakainen 2006; Viljakainen 2009; von Hurst 2008; von Hurst 2009; von Hurst 2010a; von Hurst 2010b; Weisman 1986; Wicherts 2010; Yusupov 2010; Zittermann 2009b; Zubillaga 2006). We contacted the authors, and the authors of 62 trials confirmed that mortality was indeed zero. For 32 trials, we did not obtain such confirmation. Nine trials reported on deaths (n 50), but they did not report the trial intervention group in which the deaths occurred (Cashman 2009; Chapuy 1987; Doetsch 2004; Fedirko 2010; Gallagher 1989; Keane 1998; Moreira-Pfrimer 2009; Orwoll 1990; Peacock 2000). The study authors did not reply to our request for additional information.

Figure 1. Study flow diagram.



In total, 56 trials described in 154 publications, with 95,286 participants, provided data for our analyses of mortality. A further 62 trials with zero mortality in both experimental and control groups were included in our sensitivity analyses.

We contacted 139 study authors to ask for the missing information and received answers from authors of 91 randomised clinical trials (65%).

We identified an additional 11 ongoing randomised clinical trials by 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 tables Characteristics of included studies; Table 1; Table 2; Table 3; Table 4; Appendix 2; Appendix 3; Appendix 4; Appendix 5; and Appendix 6.

Trial characteristics

Of the 56 trials reporting mortality, 54 trials randomly assigned participants individually and two trials as clusters (Larsen 2004; Law 2006). Forty-eight trials used a parallel-group design, and eight trials (Avenell 2004; Avenell 2012; Bolton-Smith 2007; Campbell 2005; Gallagher 2001; Komulainen 1999; Larsen 2004; Latham 2003) used the 2 × 2 factorial design (Pocock 2004). The 56 trials were published from 1973 to 2012.

The trials were conducted in Europe (n = 34), North America (n = 9), Oceania (n = 9) and Asia (n = 4). All 56 trials came from high-income countries.

In 38 trials (69%), vitamin D was provided free of charge by pharmaceutical companies. In the other 18 trials, funding was not reported.

The 62 trials reporting no mortality included a total of 10,723 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 95,286 participants were randomly assigned in the 56 trials reporting mortality (Table 4). The number of participants in each trial ranged from 46 to 36,282 participants (median 226). The age range of participants was from 18 to 107 years. The mean proportion of women was 77% (Table 1).

Forty-eight trials were primary prevention trials that included 94,491 apparently healthy participants. Of these 48 trials, four trials included healthy volunteers, nine trials postmenopausal women and 35 trials older people living independently or in institutional care.

Eight trials with 795 participants were secondary prevention trials that included participants with neurological (Sato 1997; Sato 1999a; Sato 1999b; Sato 2005a), cardiovascular (Schleithoff 2006; Witham 2010), respiratory (Lehouck 2012) or rheumatoid disease (Brohult 1973) (Table 2).

Of the 56 trials reporting mortality, 45 trials (80%) reported the baseline vitamin D status of participants based on serum 25-hydroxyvitamin D levels. Participants in 19 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; Glendenning 2012; 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 26 trials had baseline 25-hydroxyvitamin D levels within a range of vitamin D insufficiency (less than 20 ng/mL). Eleven trials did not report the baseline vitamin D status of participants (Avenell 2004; Baeksgaard 1998; Brohult 1973; Campbell 2005; Komulainen 1999; Lappe 2007; Larsen 2004; Law 2006; Lyons 2007; Porthouse 2005; Sato 1997).

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

Experimental interventions

Vitamin D_3 (cholecalciferol)

Vitamin D was administered as vitamin D_3 (cholecalciferol) in 38 trials (75,927 participants; 76.8% women; age range 51 to 85 years). Vitamin D_3 was tested singly in 11 trials and combined with calcium in 25 trials. An additional two trials tested vitamin D_3 both singly and combined with calcium (Avenell 2004; Avenell 2012). Vitamin D_3 was tested orally in all trials. Vitamin D_3 was administered daily in 30 trials and intermittently in eight trials (daily, weekly or monthly (Chel 2008); twice weekly (Grimnes 2011); weekly (Lips 2010); monthly (Campbell 2005; Lehouck 2012); three-monthly (Glendenning 2012); four-monthly (Trivedi 2003); or yearly (Sanders 2010)). The dose of vitamin D_3 was 300 IU to 500,000 IU (mean daily dose 3650 IU; median daily dose 800 IU). The duration of supplementation in trials using vitamin D_3 was one day to seven years (weighted mean 4.9 years), and the length of the follow-up period was one month to seven years (weighted mean 5.2 years) (Table 3).

Vitamin D_2 (ergocalciferol)

Vitamin D was administered as vitamin D_2 (ergocalciferol) in 12 trials (18,349 participants; 82% women; age range 56 to 89 years). Vitamin D_2 was tested singly in seven trials and combined with calcium in four trials. An additional one trial tested vitamin D_2 both singly and combined with calcium (Harwood 2004). Vitamin D_2 was administered orally in 10 trials. One trial administered vitamin D_2 orally and parenterally (single intramuscular injection) (Harwood 2004), and one trial administered vitamin D_2 parenterally (single intramuscular injection yearly) (Smith 2007). The dosing schedule for vitamin D_2 was daily in five trials (Broe 2007; Corless 1985; Prince 2008; Sato 2005a; Zhu 2008) and intermittently in five trials (weekly (Cooper 2003), 10-weekly (Witham 2010), three-monthly (Law 2006), four-monthly (Lyons 2007) or 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 (weighted mean 2.4 years) (Table 3).

Alfacalcidol (1α-hydroxyvitamin D)

Vitamin D was administered as alfacalcidol in four trials (617 participants; 57% women; age range 68 to 71 years). Alfacalcidol was tested singly in three trials and combined with calcium in one trial (Sato 1997). Alfacalcidol was administered 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 (weighted mean 0.9 years) (Table 3).

Calcitriol (1,25-dihydroxyvitamin D)

Vitamin D was administered as calcitriol in three trials (430 participants; 85% women; age range 67 to 79 years). Calcitriol was tested singly in two trials and combined with calcium in one trial (Ott 1989). Calcitriol was administered orally and daily in all trials. The dose of calcitriol was 0.5 μg in two trials (Gallagher 2001; Grady 1991), and 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 (weighted mean 2.2 years)

and the follow-up period lasted two to five years (weighted mean four years) (Table 3).

Control interventions

A total of 44 trials used placebo vitamin D and 12 trials used no intervention in the control group (Table 1).

Co-interventions

Thirty-four trials used vitamin D in combination with calcium in the experimental intervention groups. Calcium was administered orally and daily in all 34 trials. The dose of calcium was 300 mg to 1600 mg (mean 920 mg; median 1000 mg) (Table 3).
Thirteen trials used calcium combined with vitamin D placebo in the control group. The dose of calcium was 300 mg to 1500 mg (mean 835 mg; median 1000 mg). These trials used an equal dose of calcium in the experimental intervention groups (Table 3).
One trial with a 2 × 2 factorial design tested a combination of vitamin D_3, vitamin K_1 and calcium in one of the intervention groups (Bolton-Smith 2007). The factorial design of this trial allowed us to compare only the vitamin D_3 plus calcium group versus the placebo group of this trial. Another two trials with parallel-group designs and three intervention groups tested in one of the groups the combination of calcium and multivitamins (Baeksgaard 1998) or ipriflavone (Sato 1999b). The parallel-group design of these trials allowed us to compare the vitamin D group versus the placebo group. Two trials with a 2 × 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

Thirty trials reporting mortality (54% of the trials; 71% of the participants) were considered as having low risk of bias. The remaining 26 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 w7, http://ctu.dk/publications/supplementary-material.aspx). The adjusted-rank correlation test (P = 0.44) and the regression asymmetry test (P = 0.08) found no statistically significant evidence of bias.

Figure 2. Risk of bias according to bias domains in the 56 randomised clinical trials on vitamin D and mortality.

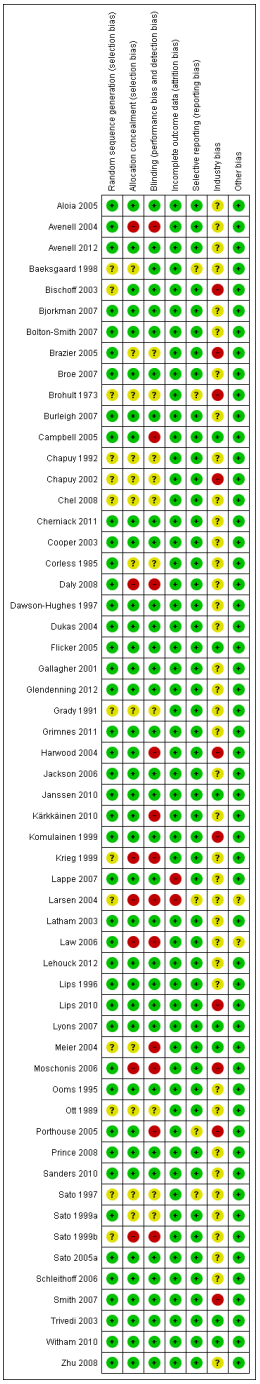
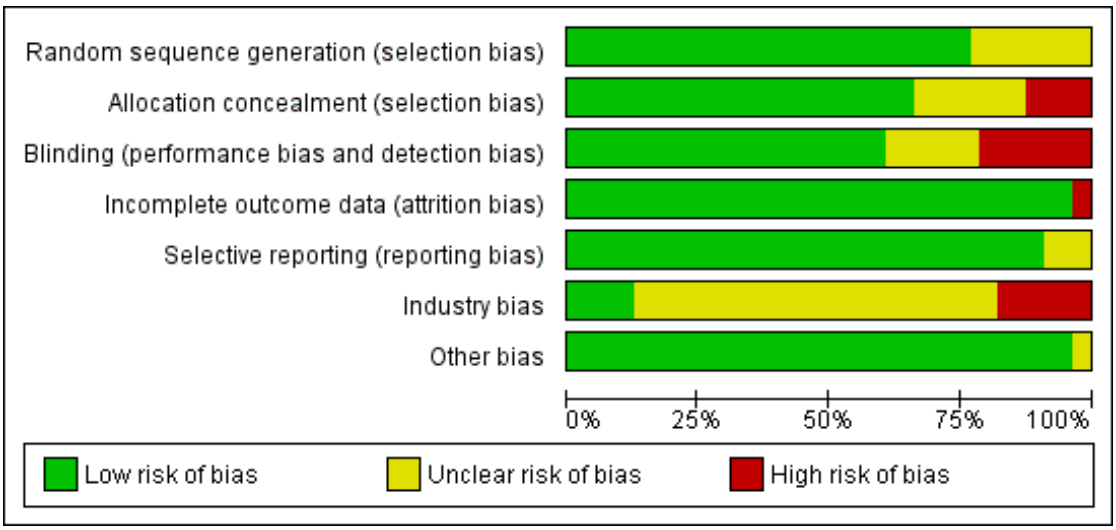


Figure 3. Risk of bias in the included 56 randomised clinical trials on vitamin D and mortality.



Allocation

The generation of the allocation sequence was adequately described in 43 trials. The remaining 13 trials were described as randomised, but the method used for sequence generation was not described (Baeksgaard 1998; Bischoff 2003; Brohult 1973; Chapuy 1992; Chapuy 2002; Chel 2008; Grady 1991; Krieg 1999; Larsen 2004; Meier 2004; Ott 1989; Sato 1997; Sato 1999b).

The method used to conceal allocation was adequately described in 37 trials. The method used for allocation concealment was judged as unclear in 12 trials (Baeksgaard 1998; Bischoff 2003; Brohult 1973; Chapuy 1992; Chapuy 2002; Chel 2008; Corless 1985; Grady 1991; Meier 2004; Ott 1989; Sato 1997; Sato 1999a) and inadequate in seven trials (Avenell 2004; Daly 2008; Krieg 1999; Moschonis 2006; Larsen 2004; Law 2006; Sato 1999b).

Blinding

The method of blinding was adequately described in 34 trials. The method of blinding was unclear in 10 trials (Brazier 2005; Brohult 1973; Chapuy 1992; Chapuy 2002; Chel 2008; Corless 1985; Grady 1991; Ott 1989; Sato 1997; Sato 1999a). Twelve trials were not blinded (Avenell 2004; Campbell 2005; Daly 2008; Harwood 2004; Krieg 1999; Kärkkäinen 2010; Larsen 2004; Law 2006; Meier 2004; Moschonis 2006; Porthouse 2005; Sato 1999b).

Incomplete outcome data

Incomplete data were addressed adequately in 54 trials. In two trials, information is insufficient to allow assessment of whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias on the estimate of effect (Lappe 2007; Larsen 2004).

Selective reporting

Predefined primary and secondary outcomes were reported in 51 trials. Five trials did not report all predefined or clinically relevant and reasonably expected outcomes (Baeksgaard 1998; Brohult 1973; Larsen 2004; Porthouse 2005; Sato 1997). The 103 randomised clinical trials that could not provide data for mortality analyses represent an unknown reservoir of outcome reporting bias.

Industry bias

Seven trials were not funded by industry (Campbell 2005; Flicker 2005; Janssen 2010; Lyons 2007; Meier 2004; Trivedi 2003; Witham 2010). Ten trials were funded by industry (Bischoff 2003; Brazier 2005; Brohult 1973; Chapuy 2002; Harwood 2004; Komulainen 1999; Lips 2010; Moschonis 2006; Porthouse 2005; Smith 2007) and 32 trials reported that trial medications

were funded by industry (Aloia 2005; Avenell 2004; Avenell 2012; Baeksgaard 1998; Bjorkman 2007; Bolton-Smith 2007; Broe 2007; Burleigh 2007; Chapuy 1992; Chel 2008; Cherniack 2011; Cooper 2003; Daly 2008; Dawson-Hughes 1997; Dukas 2004; Gallagher 2001; Grady 1991; Grimnes 2011; Jackson 2006; Kärkkäinen 2010; Krieg 1999; Lappe 2007; Larsen 2004; Latham 2003; Lehouck 2012; Lips 1996; Ooms 1995; Ott 1989; Prince 2008; Sanders 2010; Schleithoff 2006; Zhu 2008). The source of funding is not clear for seven trials (Corless 1985; Glendenning 2012; Law 2006; Sato 1997; Sato 1999a; Sato 1999b; Sato 2005a).

Other potential sources of bias

Two trials had other factors that could put the trials at risk of bias, such as recruitment bias (Larsen 2004; Law 2006). The remaining 54 trials appeared to be free of other components that could put them at 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 0.99); P = 0.02; I^2 = 0%; 95,286 participants; 56 trials; Analysis 1.1). A total of 5920 of 47,472 participants (12.5%) randomly assigned to the vitamin D group versus 6077 of 47,814 participants (12.7%) randomly assigned to the placebo or no intervention group died. A sensitivity analysis excluding the cluster-randomised trials had no noticeable effect on the result (RR 0.96 (95% CI 0.93 to 0.99); P = 0.01; I^2 = 0%; 81,964 participants; 54 trials; Analysis 1.2). The difference between the estimate of the effect of vitamin D on mortality in individually randomised and cluster-randomised trials was not statistically significant by the test of interaction (Chi^2 = 0.48; P = 0.49; Analysis 1.2).

Intervention effects according to bias risk of trials

In the trials with low risk of bias, mortality was significantly decreased in the vitamin D group (RR 0.96 (95% CI 0.92 to 0.99); P = 0.02; I^2 = 0%; 67,516 participants; 30 trials; Analysis 1.1). In the trials with high risk of bias, vitamin D did not significantly affect all-cause mortality (RR 0.99 (95% CI 0.92 to 1.06); P = 0.71; I^2 = 10%; 27,770 participants; 26 trials; Analysis 1.1). The difference between the estimate of the effect of vitamin D on mortality in low- and high-bias risk trials was not statistically significant by the test of interaction (Chi^2 = 0.56; P = 0.46; Analysis 1.1).

Placebo-controlled trials compared with trials with no intervention in the control group

Vitamin D significantly decreased mortality in the placebo-controlled trials (RR 0.96 (95% CI 0.93 to 0.99); P = 0.009; I^2 = 0%; 73,892 participants; 44 trials; Analysis 1.3). Vitamin D had no statistically significant effect on mortality in the trials with no intervention in the control group (RR 1.05 (95% CI 0.91 to 1.21); P = 0.51; I^2 = 29%; 21,394 participants; 12 trials; Analysis 1.3.2). The difference between the estimate of the effect of vitamin D on mortality in the placebo-controlled trials and in trials with no intervention in the control group was not statistically significant by the test of interaction (Chi^2 = 1.50; P = 0.22; Analysis 1.3).

Trials without risk of industry bias compared to trials with risk of industry bias

Vitamin D had no significant effect on mortality in the trials without risk of industry bias (RR 0.97, 95% CI 0.92 to 1.03; P = 0.32; I^2 = 0%; 7,372 participants; 7 trials; Analysis 1.4). Vitamin D significantly decreased mortality in the trials with risk of industry bias (RR 0.96 (95% CI 0.93 to 1.00); P = 0.003; I^2 = 0%; 87,914 participants; 49 trials; Analysis 1.4). The difference between the estimate of the effect of vitamin D on mortality in the trials without risk of industry bias and the trials with risk of industry bias was not statistically significant by the test of interaction (Chi^2 = 0.07; P = 0.80; Analysis 1.4).

Primary prevention compared with secondary prevention

Vitamin D significantly decreased mortality in the primary prevention trials (RR 0.97 (95% CI 0.94 to 0.99); P = 0.02; I^2 = 0%; 94,491 participants; 48 trials; Analysis 1.5). Vitamin D had no statistically significant effect on mortality in the secondary prevention trials (RR 1.31 (95% CI 0.73 to 2.35); P = 0.37; I^2 = 0%; 795 participants; 8 trials; Analysis 1.5). The difference between the estimates of the effect of vitamin D on mortality in the primary prevention and the secondary prevention trials was not statistically significant by the test of interaction (Chi^2 = 1.04; P = 0.31; Analysis 1.5).

Intervention effects according to vitamin D status at entry

Vitamin D significantly decreased mortality in participants with vitamin D insufficiency at entry (RR 0.95 (95% CI 0.91 to 0.99); P = 0.01; I^2 = 0%; 56,697 participants; 26 trials; Analysis 1.6). Vitamin D had no statistically significant effect on mortality in the trials including participants with vitamin D adequacy (RR 0.95 (95% CI 0.87 to 1.05); P = 0.30; I^2 = 0%; 16,283 participants; 19 trials; Analysis 1.6). A similar finding was obtained in the trials including participants with unknown vitamin D status (Analysis 1.6). The difference between the estimates of the effect of vitamin D on mortality in the trials including participants with vitamin D

insufficiency and the trials including participants with vitamin D adequacy was not statistically significant by the test of interaction (Chi^2 = 1.59; P = 0.45; Analysis 1.6).

Trials including participants living independently compared with trials including participants living in care institutions

Vitamin D significantly decreased mortality in ambulatory participants (RR 0.95 (95% CI 0.92 to 0.98); P = 0.0003; I^2 = 0%; 86,071 participants; 45 trials; Analysis 1.7). Vitamin D had no statistically significant effect on mortality in the trials including institutionalised participants (RR 1.02 (95% CI 0.92 to 1.13); P = 0.74; I^2 = 21%; 9215 participants; 11 trials; Analysis 1.7). The difference between the estimates of the effect of vitamin D on mortality in the trials including ambulatory participants and the trials including institutionalised participants was not statistically significant by the test of interaction (Chi^2 = 1.60; P = 0.21; Analysis 1.7).

Sensitivity analyses taking attrition into consideration

Of the 56 trials reporting mortality, 53 trials reported the exact numbers of participants with missing outcomes in the intervention and 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 the intervention groups separately (Lappe 2007). A total of 3634 of 42,024 participants (8.6%) had missing outcomes in the vitamin D group versus 3523 of 42,394 participants (8.3%) in the control group.

'Best-worst case' scenario

If we assume that all participants lost to follow-up in the experimental intervention group survived and all those with missing outcomes in the control intervention group died, vitamin D significantly decreased mortality (RR 0.40 (95% CI 0.32 to 0.51); P < 0.00001; I^2 = 96%; 84,418 participants; 53 trials; Analysis 1.8).

'Worst-best case' scenario

If we assume that all participants lost to follow-up in the experimental intervention group died and all those lost to follow-up in the control intervention group survived, vitamin D significantly increased mortality (RR 2.78 (95% CI 2.13 to 3.63); P < 0.00001; I^2 = 97%; 84,418 participants; 53 trials; Analysis 1.8).

Sensitivity analyses taking zero event trials into account

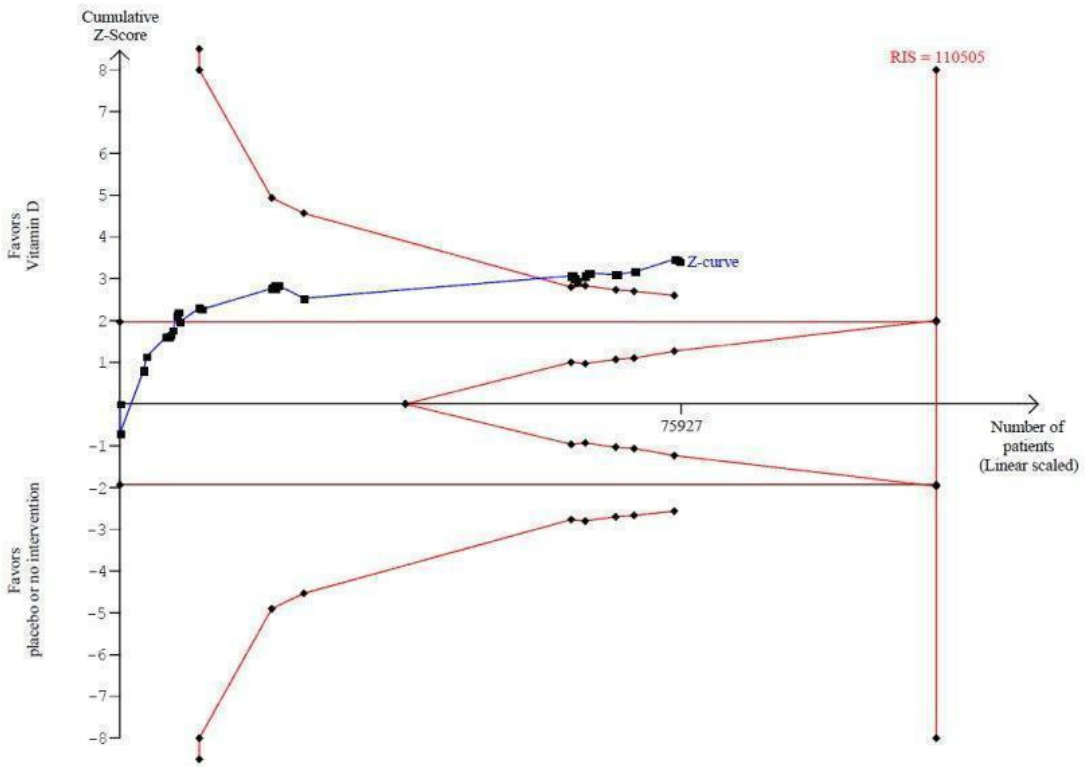
In addition to the 56 trials reporting mortality, 62 trials with 10,804 participants had zero mortality in both experimental and control groups. We assessed the influence of these trials by recalculating the RR with 0.5, 0.01 and 0.001 as empirical continuity corrections. The random-effects model RR for the three continuity corrections was not noticeably influenced (RR 0.97 (95% CI 0.94 to 0.99); P = 0.020; RR 0.97 (95% CI 0.94 to 1.00); P = 0.022; RR 0.97 (95% CI 0.94 to 1.00); P = 0.023; respectively). We also tested the influence of zero event trials using risk difference as the measure of association. Vitamin D significantly decreased all-cause mortality using the fixed-effect model meta-analysis (RD -0.004 (95% CI -0.016 to -0.008); P = 0.015). Heterogeneity was substantial (I^2 = 64%). The random-effects model revealed no statistically significant effect of vitamin D on all-cause mortality (RD -0.002 (95% CI -0.005 to 0.002); P = 0.30).

Vitamin D_3 (cholecalciferol)

Vitamin D_3 was tested in 38 trials (75,927 participants). Inspection of the funnel plot did not suggest potential bias (asymmetry) (Figure w8, http://ctu.dk/publications/supplementary-material.aspx). The adjusted-rank correlation test (P = 0.79) and the regression asymmetry test (P = 0.97) found no statistically significant evidence of bias. Overall, vitamin D_3 significantly decreased mortality (RR 0.94 (95% CI 0.91 to 0.98); P = 0.002; I^2 = 0; 75,927 participants; 38 trials; Analysis 1.9). Vitamin D_3 significantly decreased mortality in the trials with low risk of bias (RR 0.93 (95% CI 0.89 to 0.98); P = 0.009; I^2 = 0%; 52,645 participants; 20 trials; Analysis 1.9). Vitamin D_3 had no statistically significant effect on mortality in the trials with high risk of bias (RR 0.95 (95% CI 0.91 to 1.00); P = 0.06; I^2 = 0%; 23,282 participants; 18 trials; Analysis 1.7.2). The difference between estimates of the effect of vitamin D_3 on mortality in the trials with low risk of bias and the trials with high risk of bias was not statistically significant by the test of interaction (Chi^2 = 0.39; P = 0.53; Analysis 1.9).

Trial sequential analysis of all 38 vitamin D_3 trials was constructed on the basis of diversity-adjusted required information size calculated using 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). No diversity was noted. The trial sequential analysis showed that the required information size had not yet been reached and that the cumulative Z-curve crossed the trial sequential monitoring boundary for benefit in 2006 during the 22nd trial. The trial sequential analysis excludes risk of random errors (Figure 4). The intervention effect corresponds to the number needed to treat for an additional beneficial outcome (NNTB) of 150 participants treated over five years to save one additional life.

Figure 4. Trial sequential analysis on mortality in 38 vitamin D3 trialsThe diversity-adjusted required information size (RIS) was calculated based on mortality in the control group of 10%; relative risk reduction of 5% in the experimental group; type I error of 5%; and type II error of 20% (80% power). No diversity was noted. The required information size was 110,505 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundaries for benefit (red inward sloping line) after the 22nd trial. Accordingly, the risk of random error in the finding seems acceptable according to the O'Brien Fleming stopping rule for an individual trial interim analysis. Subsequently, 16 trials have been published.



Vitamin D_3 and calcium

Vitamin D_3 administered singly versus placebo or no intervention had no statistically significant effect on mortality (RR 0.92 (95% CI 0.85 to 1.00); P = 0.06; I^2 = 5%; 12,609 participants; 13 trials; Analysis 1.10). Vitamin D_3 combined with calcium versus placebo or no intervention significantly decreased mortality (RR 0.96 (95% CI 0.92 to 0.99); P = 0.03; I^2 = 0%; 63,051 participants; 27 trials; Analysis 1.10). The difference between the estimate of the effect of vitamin D_3 on mortality in the trials using vitamin D_3 singly and the trials using vitamin D_3 combined with calcium was not statistically significant by the test of interaction (Chi^2 = 0.49; P = 0.49; Analysis 1.10).

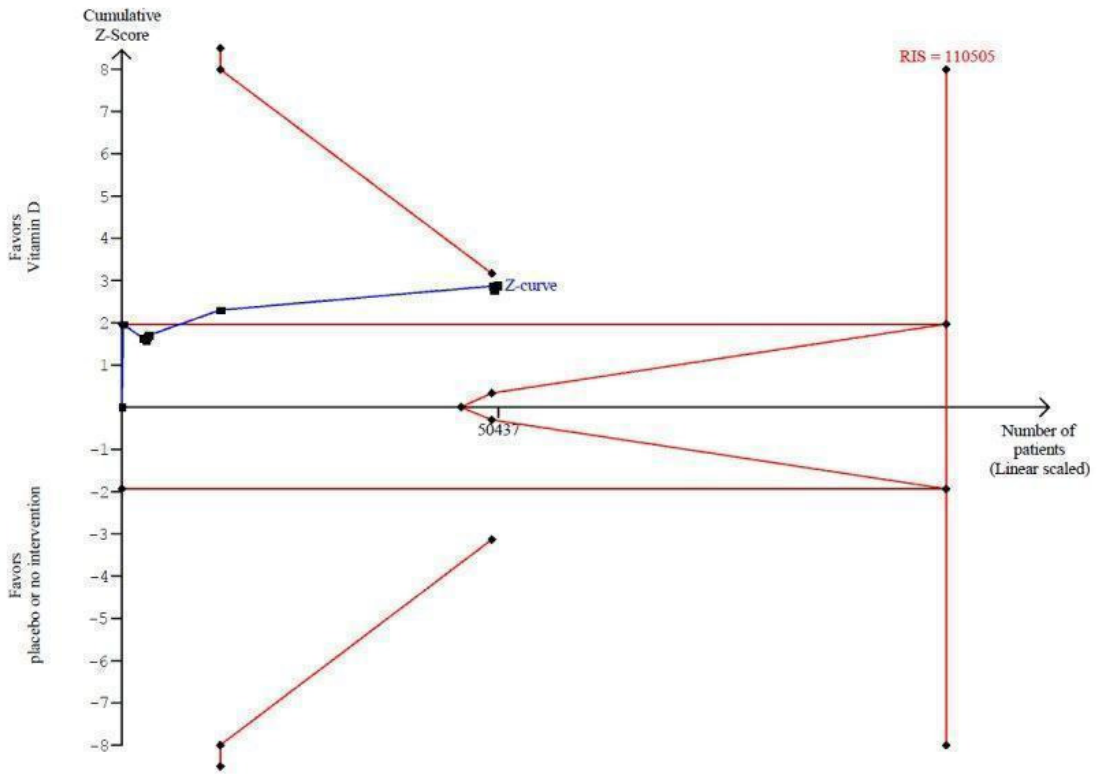
The trial sequential analysis on mortality in the 27 trials that administered vitamin D_3 combined with calcium showed that the cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit (Figure w9, http://ctu.dk/publications/supplementary-material.aspx).

Dose of vitamin D_3

A dose of vitamin D_3 less than 800 IU a day significantly decreased mortality (RR 0.92 (95% CI 0.87 to 0.97); P = 0.005; I^2 = 0%; 50,437 participants; 13 trials; Analysis 1.11). A dose of vitamin D_3 equal to or greater than 800 IU a day had no statistically significant effect on mortality (RR 0.96 (95% CI 0.92 to 1.00); P = 0.07; I^2 = 0%; 25,558 participants; 26 trials; Analysis 1.11). The difference between the estimate of the effect of vitamin D_3 on mortality in the trials using a low dose of vitamin D_3 and the trials using a high dose of vitamin D_3 was not statistically significant by the test of interaction (Chi^2 = 1.37; P = 0.24; Analysis 1.11).

The trial sequential analysis on mortality in the 13 trials that administered a low dose of vitamin D_3 showed that the cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit (Figure 5).

Figure 5. Trial sequential analysis on mortality in the 13 trials that administered low dose of vitamin D3 (i.e. a dose less than 800 IU per day) The diversity-adjusted required information size (RIS) was calculated based on mortality in the control group of 10%; relative risk reduction of 5% in the experimental group; type I error of 5%; and type II error of 20% (80% power). No diversity was noted. The required information size was 110,505 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for benefit (red line) at any time. Accordingly, the crossing of the conventional statistical 5% boundary (the horizontal brown line) may be due to random errors.



Dosing schedule of vitamin D_3

Vitamin D_3 administered daily significantly decreased mortality (RR 0.95 (95% CI 0.91 to 0.98); P = 0.004; I^2 = 0%; 69,168 participants; 31 trials; Analysis 1.12). Vitamin D_3 administered intermittently had no statistically significant effect on mortality (RR 0.89 (95% CI 0.77 to 1.03); P = 0.11; I^2 = 0%; 6871 participants; 8 trials; Analysis 1.12). The difference between the estimate of the effect of vitamin D_3 on mortality in the trials that administered vitamin D_3 daily and the trials that administered vitamin D_3 intermittently was not statistically significant by the test of interaction (Chi^2 = 0.66; P = 0.41; Analysis 1.12).

Intervention effect of vitamin D_3 according to vitamin D

status at entry

Vitamin D_3 significantly decreased mortality in the trials including participants with vitamin D insufficiency (RR 0.95 (95% CI 0.91 to 0.99); P = 0.009; I^2 = 0%; 55,883 participants; 20 trials; Analysis 1.13). Vitamin D_3 had no statistically significant effect on mortality in the trials including participants with vitamin D adequacy (RR 0.92 (95% CI 0.80 to 1.07); P = 0.29; I^2 = 0%; 4979 participants; 10 trials; Analysis 1.13). The difference between the estimate of the effect of vitamin D_3 on mortality in the trials including participants with vitamin D insufficiency and the trials including participants with vitamin D adequacy was not statistically significant by the test of interaction (Chi^2= 0.1; P = 0.75; Analysis 1.13).

Intervention effect of vitamin D_3 according to the sex of the trial participants

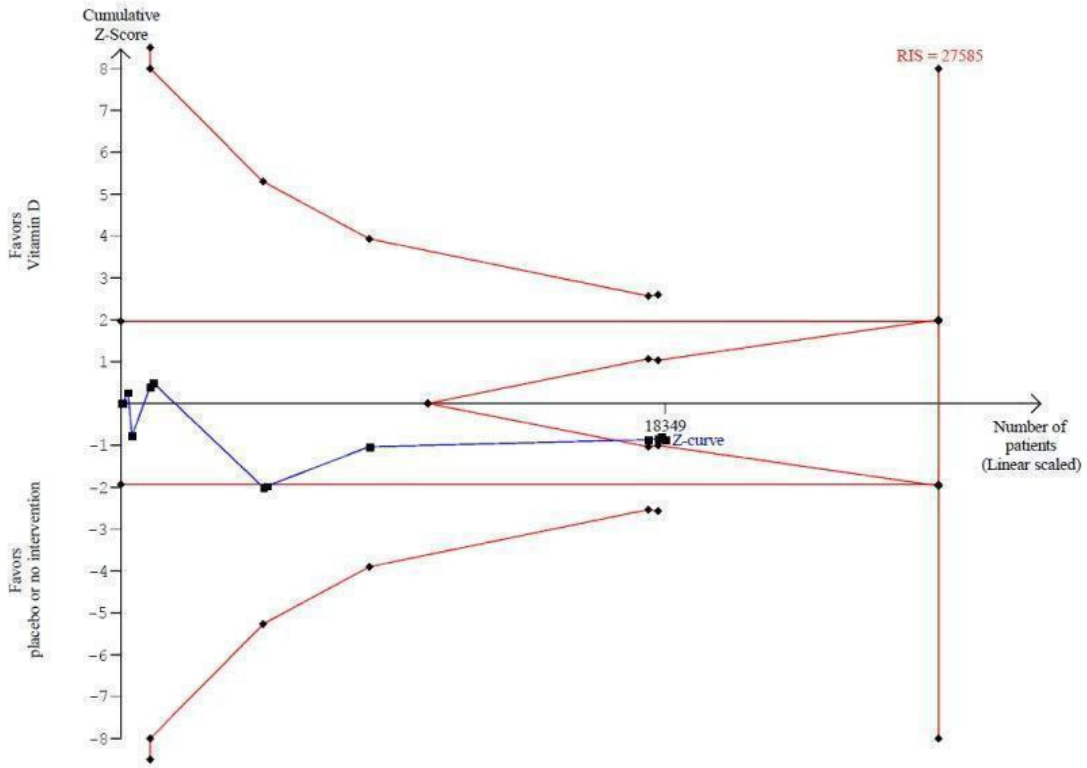
Vitamin D_3 had no statistically significant effect on mortality in the trials that exclusively included women (RR 0.93 (95% CI 0.84 to 1.03); P = 0.16; I^2 = 22%; 53,062 participants; 19 trials; Analysis 1.14). Vitamin D_3 significantly decreased mortality in the trials including both men and women, or including only men (one trial by Daly 2008) (RR 0.94 (95% CI 0.89 to 0.99); P = 0.01; I^2 = 0%; 22,865 participants; 19 trials; Analysis 1.14). The difference between the estimate of the effect of vitamin D_3 on mortality in the trials including only women and the trials including both men and women or only men was not statistically significant by the test of interaction (Chi^2 = 0.03; P = 0.87; Analysis 1.14).

Vitamin D_2 (ergocalciferol)

Vitamin D_2 was tested in 12 trials (18,349 participants). Inspection of the funnel plot did not suggest potential bias (asymmetry) (Figure w10, http://ctu.dk/publications/supplementary-material.aspx). The adjusted-rank correlation test (P = 0.60) and the regression asymmetry test (P = 0.55) found no statistically significant evidence of bias. Overall, vitamin D_2 had no statistically significant effect on mortality (RR 1.02 (95% CI 0.96 to 1.08); P = 0.54; I^2 = 4%; Analysis 1.15). Vitamin D_2 had no statistically significant effect on mortality in the trials with low risk of bias (RR 0.98 (95% CI 0.93 to 1.04); P = 0.57; I^2 = 0%; 14,439 participants; 9 trials; Analysis 1.15). Vitamin D_2 significantly increased mortality in the trials with high risk of bias (RR 1.20 (95% CI 1.05 to 1.37); P = 0.007; I^2 = 0%; 3910 participants; 3 trials; Analysis 1.15). The difference between the estimate of effect of vitamin D_2 on mortality in the trials with low risk of bias and the trials with high risk of bias was statistically significant by the test of interaction (Chi^2 = 7.28; P = 0.007; Analysis 1.15).

The trial sequential analysis of all vitamin D_2 trials suggests that we reached the futility area after the eighth trial, allowing us to conclude that any possible intervention effect, if present, is lower than a 5% relative risk reduction, or that the number needed to treat for an additional beneficial outcome (NNTB) is greater than 150 (Figure 6).

Figure 6. Trial sequential analysis of mortality in 12 vitamin D2 trialsThe diversity-adjusted required information size (RIS) was conducted based on 10% mortality in the control group; relative risk reduction of 10% in the experimental group; type I error of 5%; and type II error of 20% (80% power). No diversity was noted. The required information size was 27,585 participants. The cumulative Z-curve (blue line) crossed the trial sequential monitoring boundaries for futility (red outward sloping line) after the eighth trial.



Vitamin D_2 and calcium

Vitamin D_2 administered singly had no statistically significant effect on mortality (RR 1.03 (95% CI 0.96 to 1.12); P = 0.37; I^2 = 14%; 17,079 participants; 8 trials; Analysis 1.16). Vitamin D_2 combined with calcium had no statistically significant effect on mortality (RR 1.00 (95% CI 0.64 to 1.57); P = 1.00; I^2 = 11%; 1307 participants; 5 trials; Analysis 1.16). The difference between the estimates of effect of vitamin D_2 on mortality in the trials using vitamin D_2 singly and the trials using vitamin D_2 combined with calcium was not statistically significant by the test of interaction (Chi^2 = 0.02; P = 0.88; Analysis 1.16).

Dose of vitamin D_2

A dose of vitamin D_2 less than 800 IU a day, tested in one trial, had no statistically significant effect on mortality (RR 0.82 (95% CI 0.17 to 3.98); P = 0.81; 101 participants; Analysis 1.17). A dose of vitamin D_2 equal to or greater than 800 IU a day had no statistically significant effect on mortality (RR 1.02 (95% CI 0.95 to 1.10); P = 0.51; I^2 = 9%; 18,273 participants; 12 trials; Analysis 1.17). The difference between the estimate of effect of vitamin D_2 on mortality in the trials using a high dose of vitamin D_2 and the trial using low-dose vitamin D_2 was not statistically significant by the test of interaction (Chi^2 = 0.07; P = 0.79; Analysis 1.17).

Dosing schedule of vitamin D_2

Vitamin D_2 administered daily had no statistically significant effect on mortality (RR 0.88 (95% CI 0.68 to 1.12); P = 0.30; I^2 = 0%; 1349 participants; 6 trials; Analysis 1.18). Vitamin D_2 administered intermittently had no statistically significant effect on mortality (RR 1.06 (95% CI 0.95 to 1.18); P = 0.33; I^2 = 46%; 17,000 participants; 6 trials; Analysis 1.18). The difference between the estimates of effect of vitamin D_2 on mortality in the trials that administered vitamin D_2 daily and the trials that admin-

istered vitamin D_2 intermittently was not statistically significant by the test of interaction (Chi^2 = 1.81; P = 0.18; Analysis 1.18).

Intervention effect of vitamin D_2 according to vitamin D status

Vitamin D_2 significantly increased mortality in the trials including participants with vitamin D insufficiency (RR 1.20 (95% CI 1.05 to 1.37); P = 0.008; I^2 = 0%; 4413 participants; 6 trials; Analysis 1.19). Vitamin D_2 had no statistically significant effect on mortality in the trials including participants with vitamin D adequacy (RR 0.97 (95% CI 0.86 to 1.10); P = 0.62; I^2 = 0%; 10,496 participants; 5 trials; Analysis 1.19). The difference between the estimates of effect of vitamin D_2 on mortality in the trials including participants with vitamin D insufficiency and the trials including participants with vitamin D adequacy was statistically significant by the test of interaction (Chi^2 = 5.23; P = 0.02; Analysis 1.19).

Alfacalcidol (1α-hydroxyvitamin D)

Alfacalcidol was tested in four trials (617 participants). Inspection of the funnel plot did not suggest potential bias (asymmetry) (Figure w11, http://ctu.dk/publications/supplementary-material.aspx). The adjusted-rank correlation test (P = 1.00) found no significant evidence of bias. Alfacalcidol had no statistically significant effect on mortality (RR 0.96 (95% CI 0.22 to 4.15); P = 0.95; I^2 = 0%; Analysis 1.20). The effect of alfacalcidol on mortality was not dependent on vitamin D status (Analysis 1.21).

Calcitriol (1,25-dihydroxyvitamin D)

Calcitriol was tested in three trials (430 participants). Inspection of the funnel plot did not suggest potential bias (asymmetry) (Figure w12, http://ctu.dk/publications/supplementary-material.aspx). Calcitriol had no statistically significant effect on mortality (RR 1.37 (95% CI 0.27 to 7.03); P = 0.71; I^2 = 0%; Analysis 1.22). The effect of calcitriol on mortality was not dependent on vitamin D status (Analysis 1.23).

Cause-specific mortality

Vitamin D_3 statistically significantly decreased cancer mortality (RR 0.88 (95% CI 0.78 to 0.98); P = 0.02; I^2 = 0%; 44,492 participants; 4 trials; Analysis 1.24).

Trial sequential analysis on cancer mortality in the four trials that administered vitamin D_3 was performed on the basis of mortality in the control group of 2.85%; relative risk reduction (based on trials with low risk of bias) of 12.28% in the experimental group; type I error of 5%; and type II error of 20% (80% power). No diversity was noted. The required information size was 66,724 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundary for benefit (red line) (Figure w13, http://ctu.dk/publications/supplementary-material.aspx).

Vitamin D_3 had no significant effect on cardiovascular mortality (RR 0.98 (95% CI 0.90 to 1.07); P = 0.68; I^2 = 0%; 47,267 participants; 10 trials; Analysis 1.25).

The trial sequential analysis on cardiovascular mortality in the 10 trials that administered vitamin D_3 was performed on the basis of mortality in the control group of 4.17%; relative risk reduction (based on trials with low risk of bias) of 1.68% in the experimental group; type I error of 5%; and type II error of 20% (80% power). No diversity was noted. The required information size was 2,539,845 participants. The cumulative Z-curve (blue line) did not cross the conventional monitoring boundary for benefit (red line) (Figure w14, http://ctu.dk/publications/supplementary-material.aspx).

We were not able to extract from the included trials relevant data on fracture-related mortality and other causes of mortality.

Adverse events

Several adverse events were reported (e.g. 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 statistically significant effect on the risk of hypercalcaemia (RR 1.36 (95% CI 0.85 to 2.18); P = 0.21; I^2 = 0%; 11,323 participants; 15 trials; Analysis 1.26).

The active forms of vitamin D (alfacalcidol and calcitriol) statistically significantly increased the risk of hypercalcaemia (RR 3.18 (95% CI 1.17 to 8.68); P = 0.02; I^2 = 17%; 710 participants; 3 trials; Analysis 1.26). The difference between the estimate of effect of vitamin D on hypercalcaemia in the trials that administered supplemental forms of vitamin D (D_3 and D_2) and the trials that administered active forms of vitamin D (alfacalcidol or calcitriol) was not statistically significant by the test of interaction (Chi^2 = 2.27; P = 0.13; Analysis 1.26).

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%; 42,876 participants; 4 trials; Analysis 1.26).

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%; 695 participants; 3 trials; Analysis 1.26 renal insufficiency: RR 1.70 (95% CI 0.27 to 10.70); P = 0.57; I^2 = 53%; 5495 participants; 3 trials; Analysis 1.26; cardiovascular disorders: RR 0.95 (95% CI 0.86 to 1.05); P = 0.29; I^2 = 0%; 4495 participants; 8 trials; Analysis 1.26; gastrointestinal disorders: RR 1.36 (95% CI 0.87 to 2.13); P = 0.17; I^2 = 57%; 9702 participants; 16 trials; Analysis 1.26; psychiatric disorders: RR 1.44 (95% CI 0.56 to 3.73); P = 0.45; I^2 = 0%; 580 participants; 3 trials; Analysis 1.26; skin disorders: RR 3.27 (95% CI 0.17 to 62.47); P = 0.43; I^2 = 77%; 3810 participants; 2 trials; Analysis 1.26; cancer: RR 0.99

(95% CI 0.94 to 1.06); P = 0.85; I^2 = 0%; 49,707 participants; 14 trials; Analysis 1.26).

Health-related quality of life

Only one trial published data on health-related quality of life (Witham 2010). Authors reported significant worsening in disease-specific quality of life (MLWHF, Minnesota Living With Heart Failure score) in the vitamin D_2 group compared with the placebo group (Witham 2010). The between-group difference at 20 weeks was 5.3 (0.5 to 10.2), and the minimally important difference (MID) was estimated to be 5 points in either direction.

Health economics

We found only one randomised clinical 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 with calcium supplementation is cost-effective (Lilliu 2003). Mortality was not addressed.

DISCUSSION

Summary of main results

Our systematic review contains a number of important findings. We found evidence suggesting that vitamin D_3 may significantly benefit survival of elderly ambulatory participants living in institutional care who were likely to be vitamin D deficient with significant risk of falls and fractures, when we disregard the risks of attrition bias and outcome reporting bias. However, if these bias risks are considered, we do not yet know whether vitamin D_3 affects mortality. Vitamin D_2, alfacalcidol and calcitriol had no statistically significant effect on mortality, but these estimates are at risk of type II errors because of the fact that much smaller groups of participants were examined compared with the trials assessing vitamin D_3.

A subgroup analysis of trials with high risk of bias suggests that vitamin D_2 may increase mortality, but a 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.

Compared with our previous version of this systematic review (Bjelakovic 2011), the number of included trials in the present review has increased, with six new trials (12%) adding another 1,138 participants (1.2%). In addition, we have obtained updated results of a longer follow-up from one large-scale randomised trial (Avenell 2012). In spite of these additional amounts of information, our results remain largely the same, but our assessment of the robustness of our findings has weakened.

Overall completeness and applicability of evidence

Our published protocol described our plan to analyse the effect of vitamin D on mortality in primary and secondary prevention randomised clinical trials in adults. All eligible randomised clinical trials up to February 2012 were included. All trials were conducted in high-income countries. Both sexes were included. Most of the participants were elderly persons, They were living alone or were living in institutions. A vast majority of the participants came from primary prevention trials, and we assume that they were apparently healthy when included in the trials. Few trials with very few participants were included in the secondary prevention trials, so our ability to say anything about such patients is week to absent. We included randomised trials with both vitamin D-deficient participants and persons who seemed to have adequate vitamin D levels at entry. We were unable to detect significant differences regarding these variables on the estimated intervention effect on mortality. Surprisingly little heterogeneity was found in all of our analyses. Most trials assessed vitamin D_3, and our major conclusions are related to this intervention. Although more than half of the trials were considered of low risk of bias, our analyses revealed that outcome reporting on more than 8% of participants was lacking. This number is too high when mortality is about 12% to 13% in the placebo or no intervention group. Accordingly, our 'best-worst case' and 'worst-best case' analyses revealed that our results were compatible with both a very large beneficial effect and a very large detrimental effect of vitamin D_3 on mortality. Although these extreme sensitivity analyses are unlikely, they reveal how few unaccounted for patients should have died to substantially change our findings of modest benefit into nil effect or maybe even harm. Therefore, we warn against uncritical application of our findings.

Quality of the evidence

Our review follows the overall plan of a published, peer-reviewed Cochrane protocol (Bjelakovic 2008a). It represents a comprehensive review of the topic, including 159 randomised trials with more than 105,000 participants. A total of 56 trials including more than 94,000 participants reported on mortality. This increases the precision and power of our analyses (Higgins 2011). 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 in accordance with The Cochrane Collaboration methodology (Higgins 2011) while implementing findings of methodological studies (Kjaergard 2001; Lundh 2012; Moher 1998; Savovic 2012; Schulz 1995; Wood 2008). Between-

trial heterogeneity is almost absent in our meta-analyses. This may emphasise the consistency of our findings but should also raise concern (Ioannidis 2006). Furthermore, all-cause mortality should generally be connected with unbiased estimates (Savovic 2012; Wood 2008). We also performed trial sequential analyses to control the risk of random errors in a 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; Thorlund 2011a; Thorlund 2011b; Wetterslev 2008; Wetterslev 2009).

A major drawback in most of the included trials is the relatively large proportion of more than 8% of participants who dropped out. This opens up for attrition bias, and our 'best-worst' and 'worst-best' intention-to-treat analyses demonstrate that the intervention effect of vitamin D may be either beneficial or harmful. Although both of the two extreme scenarios are unlikely, they demonstrate that we cannot depend fully on the estimates we arrive at. The percentage of participants lost to follow-up in both experimental and control groups was about 8.5%. Our 'best-worst case' and 'worst-best case' scenario analyses revealed much more extreme confidence limits (95% CI 0.32 to 3.63) compared with our 'complete-case' scenario analysis (95% CI 0.93 to 0.99), and they convey a message of a noticeable degree of uncertainty regarding our results. This observation calls for more comprehensive meta-analyses of individual participant data plus further large randomised clinical trials. We have abstained from conducting 'uncertainty' analyses (Gamble 2005). The latter analyses accept the point estimate from the complete-participant analysis, assuming that the distribution of deaths among the participants lost to follow-up is equal to the distribution of deaths among all participants. 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' analyses themselves uncertain.

We conducted a number of subgroup analyses. We observed no statistically significant different effects of the intervention effect of vitamin D on mortality in subgroup analyses of trials with low risk of bias compared with trials with high risk of bias; of trials using placebo compared with trials using no intervention in the control group; of trials with no risk of industry bias compared with trials with risk of industry bias; of trials assessing primary prevention compared with trials assessing secondary prevention; of trials including participants with vitamin D level below 20 mg/mL at entry compared with trials including participants with normal vitamin D levels at entry; of trials including ambulatory participants compared with trials including institutionalised participants; of vitamin D_3 trials using concomitant calcium supplementation compared with vitamin D_3 trials without calcium; of trials using a dose of vitamin D_3 less than 800 IU per day compared with trials using doses greater than 800 IU per day; of vitamin D_3 trials including only women compared with vitamin D_3 trials including both sexes or only men.

In addition to the 56 trials reporting mortality, 62 trials with 10,804 participants had zero mortality in both the experimental and control groups. These trials were mostly phase I and phase II randomised clinical trials assessing the effects of short-term vitamin D administration on surrogate outcomes. These trials were excluded from the meta-analyses by using RR as the association measure. We assessed the influence of these trials by recalculating the RR with 0.5, 0.01 and 0.001 as empirical continuity corrections. The random-effects model RR for the three continuity corrections was not noticeably influenced. We also tested the influence of zero event trials using a risk difference as the measure of association. Vitamin D significantly decreased all-cause mortality using the fixed-effect model meta-analysis. Heterogeneity was substantial. The random-effects model revealed no statistically significant effect of vitamin D on all-cause mortality. Accordingly, the decreased mortality could be an artefact created by exclusion of trials with zero events in both intervention groups (Bradburn 2007; Sweeting 2004).

Two trials had other factors that could put them at risk of bias (i.e. recruitment bias) (Larsen 2004; Law 2006). These trials were cluster-randomised. We explored the association between intervention effects of vitamin D and the subgrouping of individually randomised and cluster-randomised trials. The influence of cluster-randomised trials on our results was also explored in sensitivity analyses, which included or excluded them. The difference between the estimate of the effect of vitamin D on mortality in individually randomised compared with cluster-randomised trials was not statistically significant. Our sensitivity analyses by including or excluding cluster-randomised trials revealed no noticeable effect on our results.

We conducted trial sequential analyses to control the risk of random errors and to prevent premature statements of superiority of the experimental or control intervention or probably false declarations of absence of effect in the cases for which we had too few data (Thorlund 2011a; Thorlund 2011b; Wetterslev 2008). The finding of significantly decreased mortality with vitamin D_3 (cholecalciferol) did not seem to be due to a random error. The cumulative Z-curve crossed the trial sequential monitoring boundary for benefit after the 22nd trial. However, such an analysis cannot remove risks of bias-detected or undetected. The trial sequential analysis for vitamin D_2 (ergocalciferol) suggests that we reached the futility area after the eighth trial, allowing us to conclude that any possible intervention effect, if present, is lower than a 5% relative risk reduction. One should discuss, however, how much evidence one would require when dealing with potential benefit or harm. On the one hand, beneficial or harmful effects can occur as the result of random errors; therefore, sufficient information needs to be assessed to demonstrate benefit or harm beyond reasonable doubt.

Potential biases in the review process

We repeatedly searched several databases and contacted authors of trials and industry producing vitamin D supplements. Therefore, we believe that we have not overlooked important randomised clinical trials. On the other hand, only about every second trial is reported (Gluud 2008), so we cannot exclude reporting biases, although our funnel plots did not suggest publication bias. On the positive side, we managed to obtain much more information on a number of trials from this update. However, this does not detract from the fact that we did not have access to individual participant data. Accordingly, we have no chance of analysing the effect of vitamin D in only women or in only men. When we separate trials with only women from trials with men and women combined, we see no significant difference in the intervention effect of vitamin D.

We selected all trials and extracted all data in duplicate, and we reached a high level of agreement. We did not conduct the quality assessments or data extractions blinded for authors and bias risks. In this review update, we have now presented a more conservative and, we believe, a more correct interpretation of our findings compared with interpretations in the first version of this review.

Agreements and disagreements with other studies or reviews

In our present systematic review, we found no significant effects of bias on our estimates of intervention of vitamin D in general or of vitamin D_3 specifically.

On the other hand, most of the trials were conducted with some type of support from the industry, and in general, the risk of potential industry bias was poorly described or accounted for. However, the difference in the estimates of vitamin D effect on mortality in the trials sponsored by industry compared with trials that were not sponsored by industry was not statistically significant. Accordingly, we could not confirm results from a recently published Cochrane review (Lundh 2012), which found that sponsorship of a trial by the manufacturing company leads to more favourable results and conclusions compared with trials having no sponsors.

No difference in the estimates of vitamin D effect on mortality was evident in the primary and secondary prevention trials. The number of trials with secondary prevention was low, and these trials included very few participants. Our findings may seem to contrast with earlier claims in the literature that vitamin D might be beneficial for patients with cardiovascular, malignant, infectious or autoimmune diseases (Holick 2007a; Rosen 2011; Souberbielle 2010). Assessment of vitamin D supplementation for participant groups with active disease was outside the scope of the present systematic review.

We found no statistically significant difference regarding the effect of vitamin D on mortality in trials including participants with vitamin D insufficiency (25-hydroxyvitamin D level less than 20 ng/mL) compared with trials including participants with optimal vitamin D status. 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 in the blood also depends much on the laboratory methods used for assessment of vitamin D concentration (Binkley 2009; Holick 2009; Lips 1999). Many external factors (latitude, season, time of the day, air pollution) and internal factors (skin colour, age, clothing, use of sunscreen) influence the cutaneous synthesis of vitamin D, and consequently the 25-hydroxyvitamin D levels (Webb 2006). According to a recent report of the Institute of Medicine (IOM 2011), a serum 25-hydroxyvitamin D level of 20 ng/mL (50 nmol/L) meets the vitamin D requirements of at least 97.5% of the population. Our results do not support earlier claims that participants with insufficient vitamin D status may benefit from vitamin D supplementation (Bischoff-Ferrari 2009c; Holick 2008a; Zittermann 2009a).

No difference was noted in the estimates of vitamin D effect on mortality in trials including ambulatory participants compared with trials including institutionalised participants. This could be due to random error associated with the fact that a much smaller number of institutionalised participants were analysed.

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 seemed to significantly decrease mortality, while the effect of vitamin D_2 may be neutral or even detrimental. The World Health Organization officially regards 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). Evidence on biological differences between the two vitamins in humans has been sparse and contradictory. 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; Heaney 2011; Leventis 2009; Romagnoli 2008; Trang 1998). However, a randomised clinical trial found that vitamin D_3 and vitamin D_2 were comparable in maintaining serum 25-hydroxyvitamin D levels (Holick 2008b). A recently published systematic review and meta-analysis indicated that vitamin D_3 is more efficacious than vitamin D_2 in raising serum 25-hydroxyvitamin D concentrations (Tripkovic 2012). 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 be obtained only through the diet (Norman 2008). Vitamin D_2 seems to upregulate several enzymes that degrade administered vitamin D_2 and endogenous D_3 (Heaney 2008). Our result could be of

interest to 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 2008a), although in some European countries, like France and Great Britain, vitamin D_2 is also available on the market.

Furthermore, we found no statistically significant difference between the intervention effects of vitamin D_3 on mortality in trials using vitamin D_3 singly and trials using vitamin D_3 combined with calcium. Vitamin D_3 was tested in combination with calcium in 27 trials and alone in 13 trials. Because of the small number of included trials assessing vitamin D_3 alone, the findings could be due to a type II error. Our finding seems consistent with the result obtained by Autier et al, who found that calcium supplements did not affect mortality (Autier 2007), but opposite to the results of recent meta-analyses examining the influence of vitamin D on mortality (Rejnmark 2012) or bone health (DIPART 2010). These meta-analyses concluded that vitamin D is effective in preventing mortality (Rejnmark 2012) and hip fractures (DIPART 2010) only when combined with calcium. The complex interactions between vitamin D and calcium make it difficult to separate their effects. More research seems needed.

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 2,000 mg (IOM 2011). The dosages used in the trials included in our meta-analysis are in accordance with recommended intakes. In most 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 results concur 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 found no statistically significant effect of vitamin D on mortality (Avenell 2009), although the review authors assessed a much more limited number of trials. A number of meta-analyses of randomised trials found that vitamin D combined with calcium could prevent falls and fractures (Bischoff-Ferrari 2005; Bischoff-Ferrari 2009a; Bischoff-Ferrari 2009b; Tang 2007). A recent meta-analysis observed that calcium supplementation (with or without co-administration of vitamin D) is associated with increased risk of cardiovascular events, especially myocardial infarction (Bolland 2010; Bolland 2011). Another review of prospective studies and randomised clinical trials found neutral effects of calcium (Patel 2012). A US Preventive Services Task Force recently recommended against daily supplementation with 400 IU or less of vitamin D_3 and 1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalised postmenopausal women (Moyer 2013).

A further important outcome of our review is that we found no significant differences in the effect of vitamin D_3 on mortality in trials assessing doses less than 800 IU a day compared with trials assessing doses equal to or greater 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 if we are to obtain the required information size. Controversy persists about the optimal dosage of vitamin D. 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 70 years of age and older (IOM 2011). Recent randomised trials and meta-analyses of randomised trials that have falls and fractures as the primary outcome have concluded that the reduction in risk for falls and hip and non-vertebral fractures is dose dependent (Bischoff-Ferrari 2009a; Bischoff-Ferrari 2009b; Bischoff-Ferrari 2009c; Bischoff-Ferrari 2012). Conversely, two recent randomised clinical trials (Sanders 2010; Smith 2007) identified a potential harm associated with high doses of vitamin D. Furthermore, recent studies undertaken to examine how vitamin D status in the blood relates to all-cause mortality found a U- or J-shaped association between vitamin D status and all-cause mortality (Durup 2012; Michaëlsson 2010), as well as cancer mortality (Michaëlsson 2010). Both high and low concentrations of plasma 25-hydroxyvitamin D were associated with elevated risks of mortality (Durup 2012; Michaëlsson 2010). Amer et al evaluated the association of 25-hydroxyvitamin D with all-cause and cardiovascular mortality using National Health and Nutrition Examination Survey data (2001 to 2004) (Amer 2013). They found an inverse association between 25-hydroxyvitamin D and all-cause mortality in healthy adults with serum 25-hydroxyvitamin D levels equal to or less than 21 ng/mL (Amer 2013). These results should warn us to be very cautious about the changes in recommended daily intakes of vitamin D (Bischoff-Ferrari 2010b; Holick 2011; Sanders 2013).

It still is not known which dosing schedules are optimal for vitamin D_3 supplementation. We found no significant differences in the effects of vitamin D_3 on mortality in trials that administered vitamin D_3 orally and daily compared with trials that applied vitamin D_3 orally and intermittently. This could be due to type II errors. The randomised trial by Chel et al comparing daily, weekly and monthly dosing of vitamin D_3 found that daily dosing was more effective than weekly and monthly dosing for preventing fractures (Chel 2008). A recently completed randomised clinical trial that assessed annual high-dose vitamin D_3 reported an increase in the primary outcome of fractures compared with placebo (Sanders 2010).

Most of the trial participants were women. However, when we compared the effect of vitamin D_3 on all-cause mortality in trials including participants of both sexes or only men versus the effect of vitamin D_3 on all-cause mortality in trials including only women,

no statistically significant difference was noted. Therefore, our results are compatible with vitamin D_3 having similar effects in men and women. Obviously, further randomised trials stratifying for sex and reporting effects according to the sex of the participants are needed.

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

We lack evidence for drawing any firm conclusions about the influence of the active forms of vitamin D (alfacalcidol and calcitriol) on mortality. Available evidence suggests that alfacalcidol and calcitriol have no statistically significant effect on mortality risk. However, only a few trials were conducted, and the risk of type II errors is high. 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 and increased risk of hypercalcaemia (O'Donnell 2008). Occurrences of hypercalcaemia due to the active forms of vitamin D were increased significantly in our review.

Vitamin D had no significant effect on cardiovascular mortality. Much debate in the literature has surrounded the possible beneficial effect of vitamin D on cardiovascular disease (Holick 2004; Scragg 2010; Zittermann 2006; Zittermann 2010). Results of recently published population-based cohort studies are inconsistent (Schottker 2013; Skaaby 2012). Four recently published systematic reviews summarised the role of vitamin D in cardiovascular disease (Elamin 2011; Myung 2013; Pittas 2010; Wang 2010). These review authors found no evidence to support the use of vitamin D for prevention or treatment of cardiovascular disease (Elamin 2011; Myung 2013; Pittas 2010; Wang 2010).

Vitamin D seems to decrease cancer mortality. However, data were sparse, and selective outcome reporting bias is likely. Furthermore, the cumulative Z-curve did not cross the trial sequential monitoring boundary in our analysis of cancer mortality, and additional evidence seems needed. Pilz and coworkers recently reviewed the evidence on vitamin D status and cancer mortality (Pilz 2009b). They concluded that epidemiological data were inconsistent in favour of the hypothesis that optimal vitamin D status was related to decreased cancer mortality. However, they lacked evidence from randomised clinical trials on intervention with vitamin D to strengthen their conclusion (Pilz 2009b). Although our present data are encouraging, we need more trials to exclude risks of systematic errors and risks of random errors.

We found that vitamin D had no significant effect on cancer occurrence (Bjelakovic 2008b). 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 ecological studies that found an inverse relationship between exposure to sunlight and cancer risk (Apperly 1941; Garland 1980). 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). 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 stating that vitamin D status is not correlated with cancer occurrence (IARC 2008; IOM 2011). Recently, an updated meta-analysis prepared for the US Preventive Services Task Force found inconclusive evidence regarding vitamin D supplementation for the prevention of cancer (Chung 2011). We still lack evidence; therefore, we need additional randomised clinical trials if we are to better understand the potential 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 such as elevated urinary calcium excretion, renal insufficiency, cancer and cardiovascular, gastrointestinal, psychiatric or skin disorders were not statistically significantly influenced by vitamin D supplementation.

We lack sufficient evidence on the effect of vitamin D supplementation on health-related quality of life and on the cost-effectiveness of vitamin D supplementation. However, vitamin D_3 products and calcium are relatively cheap, so these interventions are likely to be cost-effective if they work sufficiently well.

In conclusion, we see a potentially positive effect of vitamin D_3 on mortality, but we caution against thinking that now we know what to do in clinical practice because of the following. Our collection of trials showed a large dropout rate, which could seriously influence our results. The 'worst-best case' scenario analysis does not exclude a risk of increased mortality associated with vitamin D. We found no significant difference in mortality between vitamin D_3 given singly compared with combined with calcium, or vitamin D_3 given in doses greater than compared with less than 800 IU/d. Vitamin D_3 in doses less than 800 IU did not cross the trial sequential monitoring boundary for benefit, so random errors cannot be excluded. The effect of vitamin D_3 on participants with adequate vitamin D status is unknown. Furthermore, we do not know the harm-to-benefit ratio when the intervention is used over a longer time. Moreover, we lack information on the effect in men and in younger persons of both sexes. All these reservations lead us to conclude that more research is urgently needed.

A great debate has been documented 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 its effects 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; Pilz 2012; Zittermann 2009a). 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). Most 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). However, the evidence was considered insufficient and inconclusive for extraskeletal outcomes, including mortality (IOM 2011). A recent meta-analysis on the effects of vitamin D supplements on bone mineral density concluded that vitamin D supplementation for osteoporosis prevention in community-dwelling adults without specific risk factors for vitamin D deficiency seems inappropriate (Reid 2013; Rosen 2013).

AUTHORS' CONCLUSIONS

Implications for practice

We found some evidence that vitamin D_3 may decrease all-cause mortality and cancer mortality in predominantly elderly participants living independently or in institutional care. Vitamin D_3 combined with calcium increased nephrolithiasis. Vitamin D_2, alfacalcidol and calcitriol had no statistically significant effect on mortality. Alfacalcidol and calcitriol increased hypercalcaemia. Elevated urinary calcium excretion, renal insufficiency, cancer and cardiovascular, gastrointestinal, psychiatric or skin disorders were not statistically significantly influenced by vitamin D supplementation. However, because of risks of attrition bias, of outcome reporting bias and other biases, we cannot yet recommend or refute the use of vitamin D for preventing all-cause mortality or cancer mortality.

Implications for research

More randomised clinical trials are needed on the effects of vitamin D_3 on mortality in younger, healthy persons and in elderly community-dwelling and institutionalised persons without apparent vitamin D deficiency. Before drawing conclusions, we need more evidence on the effect of vitamin D on cancer and cardiovascular disease, especially when we consider the different forms of vitamin D used for supplementation. More randomised clinical trials are needed to test the efficacy of vitamin D_3 applied singly or in combination with calcium and to compare different doses of vitamin D_3. The effects of vitamin D on health-related quality of life and cost-effectiveness deserve further investigation. A number of issues are still insufficiently addressed. We do not know the importance of daily doses of vitamin D_3, the influence of vitamin D insufficiency, the influence of dietary habits, the influence of sun exposure, the influence of latitude on the globe, the influence of sex of the participants and the influence of age. Future randomised clinical trials ought to be conducted without influence of industry on the design and reporting and ought to stratify participants for age and sex. Future trials ought to be designed according to the SPIRIT guidelines (Chan 2013) and reported according to the CONSORT guidelines (www.consort-statement.org). Future trials ought to report individual participant data, so that proper individual participant data meta-analyses of the effects of vitamin D in subgroups can be conducted.

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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
Stated aim of study	"To examine the effect of vitamin D_3 supplementation on bone loss in African American women."
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."

Aloia 2005 (*Continued*)

	Additional information on the risk of bias domains was received through personal communication with Dr John F Aloia (30.01.2009; 03.02.2009)

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
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
Industry bias	Unclear risk	Vitamin D_3 capsules and matched placebo capsules were custom manufactured for the trial (Tishcon Corp, Westbury, NY)
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. The calcium supplements were provided as calcium carbonate.
Outcomes	Primary outcomes were recruitment, compliance, and retention within a randomised trial
Stated aim of study	"To assess the effects of an open trial design (without placebo and participants knowing what tablets they were given) when compared with a blinded, placebo-controlled design on recruitment, compliance, and retention within a randomised trial of secondary osteoporotic fracture prevention."
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

Industry bias	Unclear risk	"Shire Pharmaceuticals funded the capsules, which were co-funded and manufactured by Nycomed."
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

Avenell 2012

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 6.2 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
Stated aim of study	"To assess whether vitamin D_3 and calcium, either alone or in combination, were effective in prevention of secondary fractures."
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 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
Industry bias	Unclear risk	Shire Pharmaceuticals co-funded the drugs, with Nycomed, who also manufactured the drugs
Other bias	Low risk	The trial appears to be free of other components 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 (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 oestrogen 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; cyanocobalamin 1 μg; folic acid 100 μg; niacin 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
Stated aim of study	"To evaluate the effect of vitamin D supplement and a calcium supplement plus or minus multivitamins on bone loss at the hip, spine, and forearm."
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	

Baeksgaard 1998 (*Continued*)

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	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)	Unclear risk	Not all pre-defined or clinically relevant and reasonably expected outcomes are reported on
Industry bias	Unclear risk	All placebo and active treatment tablets were provided by Lube Ltd
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

Bischoff 2003 (*Continued*)

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
Stated aim of study	"To evaluate hypothesis that higher vitamin D serum levels may increase muscle strength and reduce the number of falls."
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

Bischoff 2003 (*Continued*)

Industry bias	High risk	The trial was supported by Strathmann AG, Germany.
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

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
Stated aim of study	"To evaluate the effects of vitamin D supplementation on parathyroid function and bone turnover in aged, chronically immobile patients."

Bjorkman 2007 (*Continued*)

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
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
Industry bias	Unclear risk	Treatment agents were produced by Vigantol, Merck KGaA, Darmstadt, Germany
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, non-osteoporotic 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
Stated aim of study	"The putative beneficial role of high dietary vitamin K_1 (phylloquinone) on bone mineral density and the possibility of interactive benefits with vitamin D were studied."
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

Bolton-Smith 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
Industry bias	Unclear risk	Hoffmann-La Roche (Basel, Switzerland) provided the supplementation tablets
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, oestrogen, 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
Stated aim of study	"An evaluation of the clinical and laboratory safety of a one-year course of treatment with a combination vitamin D and calcium tablets in ambulatory women aged > 65 years with vitamin D insufficiency."
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)

Brazier 2005 (*Continued*)

	"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
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
Industry bias	High risk	This trial was supported by Innothera Laboratories, Arcueil, France
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

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 medica-

	tion, 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
Stated aim of study	"To determine the effect of four vitamin D supplement doses on the risk of falls in elderly nursing home residents."
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
Industry bias	Unclear risk	The vitamin D_2 tablets were purchased from Tishcon Corporation (Westbury, NY)
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

Brohult 1973

Methods	Randomised, double-blind, controlled trial using parallel group design (two intervention groups)
Participants	Country: Sweden. Number of participants randomised: 100 (68 % women), aged 18 to 69 years (mean age 52) Inclusion criteria: ambulatory patients with rheumatoid arthritis of at least two years duration Exclusion criteria: patients with steroid, gold, or antimalaria therapy
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (100,000 IU) daily (n = 25); Intervention group 2 (Control group): placebo daily (n = 25); for a one year period.
Outcomes	The primary outcomes were subjective an objective improvement
Stated aim of study	To determine the effect of vitamin D supplementation on objective and subjective improvement of patients with rheumatoid arthritis

Brohult 1973 (*Continued*)

Notes	The trial was supported financially by a grant from Ekhagastiftelsen

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	There is insufficient information to assess whether the type of blinding used is likely to induce bias on the estimate of effect
Incomplete outcome data (attrition bias) All outcomes	Low risk	The underlying reasons for missing data are unlikely to make treatment effects depart from plausible values
Selective reporting (reporting bias)	Unclear risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on
Industry bias	High risk	The trial was supported financially by a grant from Ekhagastiftelsen
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'

Burleigh 2007 (*Continued*)

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.
Stated aim of study	"To determine whether routine supplementation with vitamin D plus calcium reduces numbers of fallers and falls in a cohort of hospital admissions while they are inpatients."
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."
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

Burleigh 2007 (*Continued*)

Industry bias	Unclear risk	Strakan Pharmaceuticals supplied all trial drugs free of charge
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
Stated aim of study	"To assess the efficacy and cost effectiveness of a home safety programme and a home exercise programme to reduce falls and injuries in older people with poor vision."

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
Industry bias	Low risk	The trial is not funded by a manufacturer of vitamin D.
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)
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
Stated aim of study	"To evaluate if vitamin D and calcium supplements reduce the risk 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

Chapuy 1992 (*Continued*)

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
Industry bias	Unclear risk	Duphar and Company Laboratories provided the vitamin D_3 (Devaron), and Merck-Clevenot Laboratories provided the tricalcium phosphate (Ostram)
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)."
Outcomes	The primary outcomes were biochemical variables of calcium homeostasis, femoral neck bone mineral density, and hip fracture risk
Stated aim of study	"To confirm the effects of combined vitamin D supplementation and calcium on 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

Chapuy 2002 (*Continued*)

Industry bias	High risk	The trial was sponsored by MERCK KGaA, Darmstadt, Germany.
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

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 4 months. 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
Stated aim of study	"To investigate, in a Dutch nursing home population, whether there is a difference in efficacy of different doses and intervals of oral vitamin D_3 supplementation with the same total dose compared with placebo. A second aim 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**
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
Industry bias	Unclear risk	Solvay Pharmaceuticals supplied the research medication.
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

Cherniack 2011

Methods	Randomised, double-blind, controlled trial using parallel group design (two intervention groups)
Participants	Country: United States. Number of participants randomised: 46 (2% women), aged 70 years an older (mean age 80) Inclusion criteria: community-dwelling elderly veterans living in south Florida who were aged 70 and older Exclusion criteria: current users of vitamin D or corticosteroids; or had hypo- or hypercalcaemia, hypercalciuria, hyperparathyroidism, chronic serum creatinine greater than 2.0 mg/dL, or cholestatic liver disease; or were unable to take medication daily
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (2000 IU) daily (n = 23); Intervention group 2 (Control group): placebo daily (n = 23); for a one year period. The 41 participants found to have inadequate calcium intake (< 1200 mg/d) according to dietary questionnaire were also dispensed a calcium supplement to provide adequate daily intake
Outcomes	The primary outcomes were serum calcium, 25-hydroxyvitamin D, parathyroid hormone, and 24-hour urinary calcium
Stated aim of study	"To determine the prevalence of hypovitaminosis D (serum 25-hydroxyvitamin D < 32 ng/mL; HVD) in a population of elderly veterans and conduct a preliminary assessment of the efficacy of supplementation with cholecalciferol in correcting HVD"
Notes	Carlson Laboratories donated the cholecalciferol and placebo capsules

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 outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	There is insufficient information to assess whether the missing data mechanism in combination with the method used to han-

Cherniack 2011 (*Continued*)

		dle missing data are likely to induce bias on the estimate of effect
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on
Industry bias	Unclear risk	Carlson Laboratories donated the cholecalciferol and placebo capsules
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 ± two 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.
Stated aim of study	"To examine the effects of vitamin D_2 supplementation on changes in bone mineral density in younger (age: 56 years) postmenopausal women who were also given 1000 mg calcium daily and to compare those changes with the changes in bone mineral density in women given 1000 mg calcium daily only."
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."

Cooper 2003 (*Continued*)

	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
Industry bias	Unclear risk	Vitamin D_2 was provided by Ostelin; Boots Healthcare Pharmaceuticals, Sydney, Australia. Calcium carbonate was provided by Cal-Sup; 3M Pharmaceutical, Sydney, Australia
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: 82, 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
Stated aim of study	"To evaluate the effect of oral vitamin D supplements on the ability of elderly hospital patients with low or low normal plasma 25(OH)D to perform basic activities of daily living."
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

Corless 1985 (*Continued*)

Industry bias	Unclear risk	The source of funding is not clear.
Other bias	Low risk	The trial appears to 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.
Stated aim of study	"To assess the effects of calcium and vitamin D_3 fortified milk on bone mineral density in community living men > 50 years of age."
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**

Daly 2008 (*Continued*)

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. 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
Industry bias	Unclear risk	The vitamin D (Vitamin D_3) used to fortify the milk was obtained from DSM Nutritional Products Pty (NSW, Australia)
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, oestrogen, 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

Dawson-Hughes 1997 (*Continued*)

Outcomes	The primary outcome measures were bone mineral density, biochemical measures of bone metabolism, and the incidence of nonvertebral fractures
Stated aim of study	"To examine the effects of combined vitamin D supplementation and calcium on bone loss, biochemical measures of bone metabolism, and the incidence of nonvertebral fractures in men and women 65 years of age or older who were living in the community."
Notes	Procter & Gamble, Cincinnati manufactured calcium tablets. Additional information on mortality was received through personal communication with Professor Bess Dawson-Hughes (04.02.2009)

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
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
Industry bias	Unclear risk	Procter & Gamble, Cincinnati manufactured calcium tablets.
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
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
Stated aim of study	"To evaluate whether treatment with alfacalcidol, a precursor of the D hormone calcitriol, reduces the number of fallers and falls in community-dwelling men and women."
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."

Dukas 2004 (*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
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
Industry bias	Unclear risk	Trial medication was provided by TEVA Pharmaceuticals Industries Ltd, Israel
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.

Stated aim of study	"To test whether administration of vitamin D could reduce the incidence of falls and fractures in nursing home residents."
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 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
Industry bias	Low risk	The trial is not funded by a manufacturer of vitamin D.
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
Stated aim of study	"To examine the effect of oestrogen and 1,25-dihydroxyvitamin D therapy given individually or in combination on bone loss in elderly women."
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 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

Gallagher 2001 (*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. 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
Industry bias	Unclear risk	The active trial drug and placebo were supplied by Wyeth-Ayerst Laboratories, Inc Pharm, Hoffman-LaRoche Inc and Pharmacia & Upjohn, Inc
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

Glendenning 2012

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups)
Participants	Country: Australia. Number of participants randomised: 686 community-dwelling ambulant women aged over 70 years (mean 76.7) Inclusion criteria: age over 70 years, registration with a general practitioner, and likelihood, in the investigators' opinion, of attending four study visits over 9 months Exclusion criteria: consumption of vitamin D supplementation either in isolation or as part of a combination treatment; e.g., Actonel combi +D or Fosamax plus, cognitive impairment (Mini Mental State Score < 24), and individuals who in the investigators' opinion would not be suitable for the study.
Interventions	Participants were randomly assigned to receive: Intervention group 1: cholecalciferol 150,000 three-monthly (n = 353); Intervention group 2 (Control group): placebo vitamin D three-monthly (n = 333); for a nine-month period.

Outcomes	The primary outcome measures were falls, muscle strength, and mobility. Secondary outcome measures were serum 25-hidrohyvitamin D levels, and adverse events
Stated aim of study	"to evaluate the effects of cholecalciferol treatment and lifestyle advice compared to lifestyle advice alone on falls, serum 25OHD levels, physical function, and adverse events in 686 women aged over 70 years"
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)	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 outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The underlying reasons for missing data are unlikely to make treatment effects depart from plausible values
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on
Industry bias	Unclear risk	The source of funding is not clear.
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, placebo-controlled trial using parallel group design (two intervention groups)
Participants	Country: United States. Number of participants randomised: 98 elderly ambulatory men and women (54%) women, aged 70 to 97 (mean 79.1) years of age

Grady 1991 (*Continued*)

	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.
Stated aim of study	"To test the hypothesis that the weakness associated with aging is in part due to inadequate serum concentrations of 1,25-$(OH_2)D_3$."
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*)

Industry bias	Unclear risk	Calcitriol and placebo capsules were provided by Hoffman-LaRoche (Nutley, NJ)
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

Grimnes 2011

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups)
Participants	Country: Norway. Number of participants randomised: 104 (45% women), mean age 51.5 years Inclusion criteria: participants with low serum 25-hydroxyvitamin D levels Exclusion criteria: diabetes, acute myocardial infarction or stroke during the past 12 months, cancer during the past 5 years, steroid use, serum creatinine $\geq$130 μmol/L (males) $\geq$ 110 μmol/L (females), possible primary hyperparathyroidism (plasma parathyroid hormone [PTH] > 5.0 pmol/L combined with serum calcium > 2.50 mmol/L), sarcoidosis, systolic blood pressure > 175 mmHg or diastolic blood pressure > 105 mmHg, and specifically for women, pregnancy, lactation, or fertile age and no contraception use
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (20,000 IU) twice weekly (n = 51); Intervention group 2 (Control group): placebo twice weekly (n = 53); for a six months period.
Outcomes	The primary outcomes were insulin sensitivity and secretion. Secondary outcome measure was blood lipid level
Stated aim of study	"to compare insulin sensitivity (the primary end point) and secretion and lipids in subjects with low and high serum 25(OH)D (25-hydroxyvitamin D) levels and to assess the effect of vitamin D supplementation on the same outcomes among the participants with low serum 25(OH)D levels."
Notes	Vitamin D_3 was manufactured by Dekristol; Mibe, Brehna, Germany.

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

Grimnes 2011 (*Continued*)

		foreseen in advance of, or during, enrolment
Blinding (performance bias and detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The underlying reasons for missing data are unlikely to make treatment effects depart from plausible values
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on
Industry bias	Unclear risk	Vitamin D_3 was manufactured by Dekristol; Mibe, Brehna, Germany.
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 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
Stated aim of study	"To compare the effects of different calcium and vitamin D supplementation regimens on bone biochemical markers, bone mineral density, and rate of falls in elderly women post-hip fracture."

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
Industry bias	High risk	The trial was supported by Provalis Healthcare Ltd.
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

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 oestrogen (with or without a progestin) was according to randomisation among women in the Hormone Therapy trial. Independent use of hormone therapy or selective oestrogen-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
Stated aim of study	"To test the primary hypothesis that postmenopausal women randomly assigned to vitamin D supplementation plus calcium would have a lower risk of hip fracture, and, secondarily, of all fractures than women assigned to placebo. Another secondary hypothesis was that women receiving calcium with vitamin D supplementation would have a lower rate of colorectal cancer than those receiving placebo."
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) We extracted data about cancer occurrence and cancer mortality from the article: Brunner RL, Wactawski-Wende J, Caan BJ, Cochrane BB, Chlebowski RT, Gass ML, et al. The effect of calcium plus vitamin D on risk for invasive cancer: results of the Women's Health Initiative (WHI) calcium plus vitamin D randomised clinical trial. Nutrition an Cancer 2011;63(6):827-41

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

Jackson 2006 (*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
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
Industry bias	Unclear risk	The active trial drug and placebo were supplied by GlaxoSmithKline Consumer Healthcare (Pittsburgh)
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

Janssen 2010

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups)
Participants	Country: Netherlands. Number of participants randomised: 70 female geriatric patients older than 65 years with serum 25 hydroxyvitamin D concentrations between 20 and 50 nmol/L Inclusion criteria: vitamin D insufficient geriatric patients able to walk and follow simple instructions Exclusion criteria: treatment with vitamin D or steroids in the previous six months, a history of hypercalcaemia or renal stones, liver cirrhosis, serum creatinine > 200 μmol/L, malabsorptive bowel syndrome, primary hyperparathyroidism, uncontrolled thyroid disease, anticonvulsant drug therapy, and/or presence of any other condition that would probably interfere with the patients compliance (i.e., surgery planned)
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (400 IU) plus calcium (500 mg) daily (n = 36); Intervention group 2 (Control group): placebo vitamin D_3 plus calcium (500 mg) daily (n = 34); for a six months period.

Janssen 2010 (*Continued*)

Outcomes	The primary outcomes were muscle strength, power and functional mobility
Stated aim of study	"To test the hypothesis that vitamin D plus calcium supplementation improves muscle strength and mobility, compared with calcium monotherapy in vitamin D insufficient female geriatric patients."
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)	Low risk	Allocation was controlled by a central and independent randomisation unit
Blinding (performance bias and detection bias) All outcomes	Low risk	The outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The underlying reasons for missing data are unlikely to make treatment effects depart from plausible values
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on
Industry bias	Low risk	The trial is not funded by a manufacturer of vitamin D.
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.
Stated aim of study	"To examine the long term effects of a sequential oestrogen-progestin combination therapy (estradiol valerate and cyproterone acetate) and low dose vitamin D_3 supplementation on bone mineral density in nonosteoporotic, early postmenopausal women and to determine whether vitamin D_3 supplementation can give additional benefit to hormone replacement therapy."
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

Komulainen 1999 (*Continued*)

		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
Industry bias	High risk	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
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
Stated aim of study	"To assess the effect of supplementation with vitamin D and calcium on quantitative ultrasound parameters and metabolic disturbances in elderly institutionalised women."
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**

Krieg 1999 (*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)	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
Industry bias	Unclear risk	Trial agents were provided by Novartis Pharma, Basle, Switzerland
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.
Stated aim of study	"To test the hypothesis that the calcium and vitamin D supplementation prevents falls at the population level."

Kärkkäinen 2010 (*Continued*)

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
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on
Industry bias	Unclear risk	The trial was supported by Leiras-Nycomed Ltd with calcium and vitamin D supplementation
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 occurrence
Stated aim of study	"To determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types."
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**
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

Lappe 2007 (*Continued*)

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
Industry bias	Unclear risk	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).
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
Stated aim of study	"To evaluate the effect of two programmes for the prevention of fractures leading to acute hospital admission in a population of elderly community-dwelling Danish residents. One programme included the provision of vitamin D and calcium, whereas the other programme offered an evaluation of and suggestions for the improvement of the domestic environment. Both programmes included revision of the resident's current pharmaceutical treatment."
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
Industry bias	Unclear risk	The trial was supported by Nycomed DAK. Nycomed DAK supplied the free vitamin D tablets and calcium (Calcichew)
Other bias	Unclear risk	There are other factors in the trial that could put it at risk of bias. 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
Stated aim of study	"To determine whether a simple home-based programme of resistance exercise to the quadriceps muscles or a single high dose of vitamin D could improve self-reported physical health and reduce the risk of falls in frail older people who had recently been discharged from hospital."
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)

Latham 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
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
Industry bias	Unclear risk	The trial is supported by grants from the Health Research Council of New Zealand, the Auckland University of Technology Research Fund, and a bequest from the Lenore Wilson Estate
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

Law 2006 (*Continued*)

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.
Stated aim of study	"To determine whether vitamin D supplementation reduces the risk of fracture or falls in elderly people in care home accommodation."
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
Industry bias	Unclear risk	The source of funding is not clear.
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

Lehouck 2012

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (two intervention groups)
Participants	Country: Belgium. Number of participants randomised: 182 patients with chronic obstructive pulmonary disease (COPD), (20% women), mean age 68 years Inclusion criteria: current or former smokers, older than 50 years, diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease definition (postbronchodilator FEV_1 - FVC ratio < 0.7), and had an FEV_1 less than 80% predicted. Exclusion criteria: a history of hypercalcaemia, sarcoidosis, or active cancer
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 100,000 IU monthly (n = 91); Intervention group 2 (Control group): matched placebo monthly (n = 91); for one year.
Outcomes	The primary outcome was time to first exacerbation. Secondary outcomes were exacerbation rate, time to first hospitalisation, time to second exacerbation, FEV_1, quality of life, and death.
Stated aim of study	"To explore the effect of adequate vitamin D supplementation on exacerbations in patients with moderate to very severe COPD."
Notes	Laboratoires SMB Brussels, Belgium, provided the study medication free of charge

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 outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	The underlying reasons for missing data are unlikely to make treatment effects depart from plausible values
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on

Lehouck 2012 (*Continued*)

Industry bias	Unclear risk	Laboratoires SMB Brussels, Belgium, provided the study medication free of charge
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

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.
Outcomes	The primary outcomes were hip fractures and other peripheral bone fractures
Stated aim of study	"To determine whether vitamin D supplementation decreases the incidence of 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

Lips 1996 (*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
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
Industry bias	Unclear risk	Vitamin D and placebo tablets were provided by Solvay-Duphar, Inc, Weesp, the Netherlands
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 multicenter trial using parallel group design (two intervention groups)
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

Lips 2010 (*Continued*)

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
Stated aim of study	"To assess whether a once-weekly treatment with 8400 IU vitamin D_3 would improve body postural stability and lower-extremity function in elderly people with low vitamin D status (serum 25-hydroxyvitamin D concentrations $\leq$ 20 ng/mL)."
Notes	"All patients who completed the trial were adherent to treatment, which was defined as taking $\geq$ 13 of the 16 total doses prescribed." Supported by Merck & Co Inc.

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
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

Lips 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on
Industry bias	High risk	The trial is funded by a manufacturer of vitamin D.
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
Stated aim of study	"To examine the effect of vitamin D supplementation on fracture rate in people living in sheltered accommodation."
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)."

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

Lyons 2007 (*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
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
Industry bias	Low risk	The trial is not funded by a manufacturer of vitamin D.
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 six-month period 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 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

Meier 2004 (*Continued*)

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
Stated aim of study	"To evaluate the circannual changes in bone turnover, and bone mineral density and to determine the effect of oral calcium and vitamin D_3 supplementation on 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
Industry bias	Low risk	The trial is not funded by a manufacturer of vitamin D.
Other bias	Low risk	The trial appears to 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.
Stated aim of study	"To examine whether the use of calcium supplementation could prevent bone loss in healthy postmenopausal women or more favourable outcomes could be obtained using a holistic approach combining dietary intervention and consumption of dairy products fortified with calcium and vitamin D_3."
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
Industry bias	High risk	The trial was supported by a research grant from Friesland Foods Hellas
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

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
Stated aim of study	"To determine the effect of vitamin D supplementation on bone turnover and bone loss in elderly women."
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
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
Industry bias	Unclear risk	The trial medication was provided by Duphar Nederland BV, Amsterdam, the Netherlands
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
Stated aim of study	"To determine if calcitriol is an effective treatment in postmenopausal osteoporosis."
Notes	Hoffman-La Roche (Nutley, New Jersey) supplied the vitamin D supplements

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

Ott 1989 (*Continued*)

Industry bias	Unclear risk	Hoffman-La Roche (Nutley, New Jersey) supplied the vitamin D supplements
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); 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
Stated aim of study	"To assess whether supplementation with calcium and vitamin D_3 reduces the risk of fracture in women with one or more risk factors for fracture of the hip."
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

Porthouse 2005 (*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
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
Industry bias	High risk	The trial was supported by Shire and Nycomed. Shire supplied the vitamin D supplements and calcium
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias

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); Intervention 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
Stated aim of study	"To evaluate the effect of vitamin D_2 and calcium supplementation compared with calcium alone on the 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) 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. 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

Prince 2008 (*Continued*)

Industry bias	Unclear risk	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
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); Intervention 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."
Outcomes	The primary outcome measures were falls and fractures. Secondary outcome measures were serum 25-hydroxycholecalciferol and intact parathyroid hormone levels
Stated aim of study	"To determine whether a single annual dose of 500 000 IU of cholecalciferol administered orally to older women in autumn or winter would improve adherence and reduce the risk of falls and fracture."
Notes	"Study staff confirmed by telephone the ingestion of study medication." Study medication was supplied by PSM Healthcare, Auckland, New Zealand
Risk of bias	

Sanders 2010 (*Continued*)

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
Industry bias	Unclear risk	Study medication was supplied by PSM Healthcare, Auckland, New Zealand
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 oestrogen, 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
Stated aim of study	"To evaluate the efficacy of 1(OH)D_3 and supplemental elemental calcium in reducing the severity of osteopenia in the second metacarpals and decreasing the risk of hip fractures in chronically ill stroke patients with hemiplegia."
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
Industry bias	Unclear risk	The source of funding is not clear.
Other bias	Low risk	The trial appears to 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
Stated aim of study	"To evaluate the efficacy of 1-α hydroxyvitamin D_3 (alfacalcidol) in reducing progression of osteopenia in the second metacarpal and in decreasing non-vertebral fractures in elderly patients with Parkinson's disease with low serum 1,25-dihydroxyvitamin D concentrations."
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

Sato 1999a (*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
Industry bias	Unclear risk	The source of funding is not clear.
Other bias	Low risk	The trial appears to 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.
Stated aim of study	"To evaluate the effect of ipriflavone and 1 alpha-hydroxyvitamin D_3 administration on bone mineral density preservation."
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

Sato 1999b (*Continued*)

		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
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
Industry bias	Unclear risk	The source of funding is not clear.
Other bias	Low risk	The trial appears to 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
Stated aim of study	"To evaluate the efficacy of vitamin D_2 therapy in reducing the risk of falls in elderly women with stroke. Histochemical examination of skeletal muscles was performed to assess the effect of the therapy."

Sato 2005a (*Continued*)

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 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
Industry bias	Unclear risk	The source of funding is not clear.
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.
Stated aim of study	"To evaluate the effect of vitamin D supplementation on the survival rate and different biochemical variables in patients with congestive heart failure."
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 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

Schleithoff 2006 (*Continued*)

Industry bias	Unclear risk	Vitamin D_3 was provided by Vigantol Oel; Merck, Darmstadt, Germany, and placebo by Migliol-Oel; Merck, Darmstadt, Germany
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
Stated aim of study	"To evaluate if vitamin D_2 is effective in preventing non-vertebral fractures among elderly men and women resident in the general population."
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

Smith 2007 (*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. 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
Industry bias	High risk	The trial was supported by Celltech UK plc.
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 74.7) 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
Stated aim of study	"To determine the effect of four monthly vitamin D supplementation on the rate of fractures in men and women aged 65 years and over living in the community."
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 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. 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

Trivedi 2003 (*Continued*)

Industry bias	Low risk	The trial is not funded by a manufacturer of vitamin D.
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
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
Stated aim of study	"To examine whether vitamin D supplementation could improve parameters that are directly relevant to older people with heart failure - i.e., exercise capacity, physical function and quality of life."
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	

Witham 2010 (*Continued*)

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
Industry bias	Low risk	The trial is not funded by a manufacturer of vitamin D.
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
Stated aim of study	"To evaluate the relative benefits of 5 year of calcium supplementation of 1200 mg with or without 1000 IU vitamin D_2, compared with placebo, on hip BMD and bone-related biochemistry in ambulant elderly women aged 70 to 80 year living in a sunny climate."
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
Industry bias	Unclear risk	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
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: oestrogen replacement therapy; FEV: Forced expiratory volume; FEV: forced vital capacity

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
Bernstein 1996	Randomised controlled trial. This trial included patients receiving corticosteroids (diagnosed with inflammatory bowel disease)

(*Continued*)

Berry 2010	This is not a randomised controlled trial.
Binkley 2011	Randomised controlled trial. All participants received vitamin D
Bischoff-Ferrari 2010a	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
Giusti 2010	Randomised controlled trial. All participants received vitamin D
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.
Heaney 2011	Randomised controlled trial. All participants received vitamin D

(*Continued*)

Hedström 2002	Randomised controlled trial. Vitamin D group also received anabolic steroids
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
Javanbakht 2011	Randomised controlled trial. This trial included participants younger than 18 years
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.

(*Continued*)

Nuti 2006	Randomised controlled trial. All participants received vitamin D
Orwoll 1989	Randomised controlled trial. Participants received 25-hydroxyvitamin D_3.
Pekkarinen 2010	Randomised controlled trial. All participants received vitamin D
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
Rosenblum 2012	Randomised controlled trial. Participants received a combination of vitamin D, vitamin C, vitamin B_1, vitamin B_{12}, and folate.
Russo 2011	This is not a randomised controlled trial.
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 menatrenone, 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.
Slatkovska 2011	Randomised controlled trial. All participants received vitamin D
Smith 2009	Randomised controlled trial. All participants received vitamin D

(*Continued*)

Stein 2011	Randomised controlled trial. All 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
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 × 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 longer) 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/m^2) , history of anaemia, leukaemia or other hematological abnormalities, lupus, rheumatoid arthritis, or other rheumatological 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 to 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, long-term 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 before 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

Aloia 2008b (*Continued*)

	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; or Intervention group 4 (control group): placebo daily for a period of six months
Outcomes	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
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 × 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 measures at least 2 mm 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 participant'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 infection (tuberculosis, histoplasmosis, coccidioidomycosis, blasto-

Baron 2004 (*Continued*)

	mycosis), 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 five 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 three or four in the past five 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 long-term oral corticosteroid therapy in the past five years; use of lithium in the past five years; use of phenytoin 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; or Intervention group 4 (control group): placebo daily for a period of five years. Women who decline to forego calcium supplementation will be randomly assigned only to calcium alone or to calcium plus vitamin D intervention
Outcomes	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	

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/m^2; 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

Gallagher 2007 (*Continued*)

	Exclusion criteria: cancer (exceptions: basal cell carcinoma or cancer that 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 (longer than three months), parathyroid hormone (PTH) or PTH derivatives (e.g. teriparatide or fluoride) in the past six months; previous treatment within the past six months with calcitonin or oestrogen (except birth control pills); long-term high-dose corticosteroid therapy (> 10 mg/day) for over six months and not within the past 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; or Intervention group 5 (control group): placebo daily for a period of one year
Outcomes	Primary outcome measures will be serum 25-hydroxyvitamin D and parathyroid hormone. Secondary outcome measures will be serum and urine calcium levels
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 with 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 travelling 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

Giovannucci 2007 (*Continued*)

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; or Intervention group 4 (control group): placebo daily for a period of three months. Participants will be followed six months
Outcomes	Primary outcome measures will include to identify among blacks 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 occurrence. Secondary outcome measures will be to determine the influence of oral vitamin D supplementation on inflammatory markers and to 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	

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 past year; intent to become pregnant; menopause onset within one 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 three months; oestrogen or testosterone); prescription vitamin D, lithium; oral corticosteroids; antiseizure 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 < 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

Harris 2008 (*Continued*)

Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (4000 IU) daily; or Intervention group 2 (control group): placebo daily for a period of 12 weeks
Outcomes	Primary outcome measure will be insulin secretion, insulin sensitivity and glucose control
Starting date	July 2008; Expected completion: February 2011
Contact information	Nancy Palermo, BS; tel: 617-556-3073; nancy.palermo@tufts.edu
Notes	

Manson 2009

Trial name or title	Vitamin D and omega-3 trial (VITAL)
Methods	Randomised, double-blind, placebo-controlled trial using 2 × 2 factorial design
Participants	Country: United States Estimated number of participants: 20,000 Inclusion criteria: men aged 50 or older or women aged 55 or older who have at least a high school education Exclusion criteria: history of cancer (except non-melanoma skin cancer), heart attack, stroke, transient ischaemic attack, angina pectoris, coronary artery bypass graft or percutaneous coronary intervention; history of renal failure or dialysis, hypercalcaemia, hypoparathyroidism or hyperparathyroidism, severe liver disease (cirrhosis) or sarcoidosis or other granulomatous diseases such as active chronic tuberculosis or Wegener's granulomatosis; allergy to fish or soy; other serious illness that would preclude participation; consuming no more than 800 IU of vitamin D from all supplemental sources combined (individual vitamin D supplements, calcium + vitamin D supplements, medications with vitamin D [e.g. Fosamax Plus D] and multivitamins), or, if taking, willing to decrease or forego such use during the trial; consuming no more than 1200 mg/d of calcium from all supplemental sources combined, or, if taking, willing to decrease or forego such use during the trial; taking fish oil supplements, or, if taking, willing to forego their use during the trial
Interventions	Intervention group 1: vitamin D_3 and omega-3; Intervention group 2: vitamin D_3 and omega-3 placebo; Intervention group 3: vitamin D placebo and omega-3; or Intervention group 4 (control group): vitamin D placebo and omega-3 placebo orally, daily for a two-year period
Outcomes	Cancer and cardiovascular disease
Starting date	July 2010
Contact information	Project manager; 1-800-388-3963; vitalstudy@rics.bwh.harvard.edu www.vitalstudy.org
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 antihypertensive medication; receiving Vitamin D or calcium supplementation; chronic disease renal/hepatic/malignancy/gastrointestinal; on any medication within the last month that 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; or Intervention group 2 (control group): placebo weekly for a period of six weeks
Outcomes	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
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; or Intervention group 3 (control group): placebo daily for a period of 12 weeks

Schwartz 2008 (*Continued*)

Outcomes	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
Notes	

Scragg 2011

Trial name or title	ViDA (vitamin D assessment) trial
Methods	Randomised, double-blind, placebo-controlled trial using parallel-group design (two intervention groups)
Participants	Country: New Zealand Estimated number of participants: 5100 Inclusion criteria: age 50 to 84 years; ability to give informed consent; resident in Auckland at recruitment; anticipated residence in New Zealand for the four-year study period Exclusion criteria: current use of vitamin D supplements (> 600 IU per day if aged 50 to 70 years; > 800 IU per day if aged 71 to 84 years); diagnosis of psychiatric disorders that would limit ability to comply with study protocol (i.e. history of regular exacerbation of major psychosis (schizophrenia, bipolar disorder) in past two years); history of hypercalcaemia, nephrolithiasis, sarcoidosis, parathyroid disease or gastric bypass surgery; enrolled in another study, which could affect participation in the vitamin D study; serum calcium from baseline blood sample > 2.50 mmol/L
Interventions	Intervention group 1: vitamin D_3 200,000 IU oral capsule at baseline, then 100,000 IU oral capsule monthly (aside from 200,000 IU oral capsule in each June); or Intervention group 2 (control group): placebo (sunflower lecithin) for four years
Outcomes	Incidence rate of fatal and non-fatal cardiovascular disease, as assessed by mortality, hospital discharges and family doctors
Starting date	7/04/2011
Contact information	
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 two years since last menses; obese or overweight; living in the geographic vicinity of Rutgers University Exclusion criteria: currently taking 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 six 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 before 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; or Intervention group 4 (control group): vitamin D_3 (1200 IU) daily plus weight maintenance for a period of five weeks
Outcomes	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	

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 three months on maximally tolerated medical therapy with no recent change in medication; able to give informed written consent Exclusion criteria: currently taking (or have taken in the previous three months) calcium or other vitamin supplements; currently prescribed amlodipine or other calcium channel antagonists (intake of spironolactone

Witte 2009 (*Continued*)

	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; or Intervention group 2 (control group): placebo daily for a period of one year
Outcomes	Primary outcome measures will be left ventricular function assessed at baseline and 12 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, 12 months; exercise tolerance, measured at baseline and 12 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, 12 months; flow-mediated dilatation, measured at baseline and 12 months; immune status, measured at baseline and 12 months; insulin resistance, measured at baseline and 12 months; autonomic activation (measured by heart rate variability), measured at baseline and 12 months; renal function, measured at baseline and 1, 4, 8 and 12 months; B-type natriuretic peptide, measured at baseline and 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	

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

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 low or high risk of bias	56	95286	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
1.1 Trials with low risk of bias	30	67516	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 0.99]
1.2 Trials with high risk of bias	26	27770	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
2 All-cause mortality in individually randomised and cluster-randomised trials	56	95286	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
2.1 Individually randomised trials	54	81964	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.93, 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	56	95286	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
3.1 Placebo in the control group	44	73892	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.93, 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 and risk of industry bias	56	95286	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
4.1 Trials without risk of industry bias	7	7372	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.92, 1.03]
4.2 Trials with risk of industry bias	49	87914	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.93, 1.00]
5 All-cause mortality in primary and secondary prevention trials	56	95286	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
5.1 Primary prevention trials	48	94491	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
5.2 Secondary prevention trials	8	795	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.73, 2.35]
6 All-cause mortality and vitamin D status	56	95286	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
6.1 Vitamin D insufficiency	26	56697	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.99]
6.2 Vitamin D adequacy	19	16283	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.05]
6.3 Unknown vitamin D status	11	22306	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.92, 1.13]
7 All-cause mortality in ambulatory and institutionalised participants	56	95286	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.94, 0.99]
7.1 Ambulatory participants	45	86071	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.92, 0.98]
7.2 Institutionalised participants	11	9215	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.92, 1.13]

8 All-cause mortality ('best-worst case' and 'worst-best case' scenario)	53		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 'Best-worst' case scenario	53	84418	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.32, 0.51]
8.2 'Worst-best' case scenario	53	84418	Risk Ratio (M-H, Random, 95% CI)	2.78 [2.13, 3.63]
9 All-cause mortality in trials using vitamin D_3 (cholecalciferol)	38	75927	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.91, 0.98]
9.1 Vitamin D_3 trials with low risk of bias	20	52645	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.89, 0.98]
9.2 Vitamin D_3 trials with high risk of bias	18	23282	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 1.00]
10 All-cause mortality in trials using vitamin D_3 singly or combined with calcium	38		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Vitamin D_3 singly	13	12609	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 1.00]
10.2 Vitamin D_3 combined with calcium	27	63051	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 0.99]
11 All-cause mortality in trials using low or high dose of vitamin D_3	38		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Low dose of vitamin D_3 (< 800 IU a day)	13	50437	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.87, 0.97]
11.2 High dose of vitamin D_3 (≥ 800 IU a day)	26	25558	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.00]
12 All-cause mortality in trials applying vitamin D_3 daily or intermittently	38		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Vitamin D_3 daily	31	69168	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.98]
12.2 Vitamin D_3 intermittently	8	6871	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.77, 1.03]
13 All-cause mortality in trials using vitamin D_3 and vitamin D status	38	75927	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.91, 0.98]
13.1 Vitamin D insufficiency	20	55883	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 0.99]
13.2 Vitamin D adequacy	10	4979	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.07]
13.3 Unknown vitamin D status	8	15065	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
14 All-cause mortality in trials using vitamin D_3 according to the participant's sex	38	75927	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.91, 0.98]
14.1 Vitamin D_3 trialsincluding only women	19	53062	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
14.2 Vitamin D_3 trials including men and women	19	22865	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.89, 0.98]
15 All-cause mortality in trials using vitamin D_2 (ergocalciferol)	12	18349	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]
15.1 Vitamin D_2 trials with low risk of bias	9	14439	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.04]
15.2 Vitamin D_2 trials with high risk of bias	3	3910	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.05, 1.37]

16 All-cause mortality in trials using vitamin D_2 singly or combined with calcium	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 Vitamin D_2 singly	8	17079	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.12]
16.2 Vitamin D_2 combined with calcium	5	1307	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.64, 1.57]
17 All-cause mortality in trials using low or high dose of vitamin D_2	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 Low dose of vitamin D_2	1	101	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.17, 3.98]
17.2 High dose of vitamin D_2	12	18273	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.95, 1.10]
18 All-cause mortality in trials applying vitamin D_2 daily or intermittently	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 Vitamin D_2 daily	6	1349	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.68, 1.12]
18.2 Vitamin D_2 intermittently	6	17000	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.95, 1.18]
19 All-cause mortality in trials using vitamin D_2 and vitamin D status	12	18349	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]
19.1 Vitamin D insufficiency	6	4413	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.05, 1.37]
19.2 Vitamin D adequacy	5	10496	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.10]
19.3 Unknown vitamin D status	1	3440	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
20 All-cause mortality in trials using alfacalcidol (1α-hydroxyvitamin D)	4	617	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.22, 4.15]
21 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]
21.1 Vitamin D insufficiency	2	155	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.11, 9.52]
21.2 Vitamin D adequacy	1	378	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.37]
21.3 Unknown vitamin D status	1	84	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.06, 13.40]
22 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]
23 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]
23.1 Vitamin D insufficiency	1	86	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.96]
23.2 Vitamin D adequacy	2	344	Risk Ratio (M-H, Random, 95% CI)	2.28 [0.34, 15.39]
24 Cancer mortality	4	44492	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.98]
25 Cardiovascular mortality	10	47267	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.07]
26 Adverse events	35		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 Hypercalcemia in trials using supplemental forms of vitamin D	15	11323	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.85, 2.18]
26.2 Hypercalcemia in trials using active forms of vitamin D	3	710	Risk Ratio (M-H, Random, 95% CI)	3.18 [1.17, 8.68]

26.3 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]
26.4 Nephrolithiasis in trials using calcitriol	1	246	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.10]
26.5 Hypercalciuria	3	695	Risk Ratio (M-H, Random, 95% CI)	4.64 [0.99, 21.76]
26.6 Renal insufficiency	3	5495	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.27, 10.70]
26.7 Cardiovascular disorders	8	4495	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.05]
26.8 Gastrointestinal disorders	16	9702	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.87, 2.13]
26.9 Psychiatric disorders	3	580	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.56, 3.73]
26.10 Skin disorders	2	3810	Risk Ratio (M-H, Random, 95% CI)	3.27 [0.17, 62.47]
26.11 Cancer	14	49707	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.06]

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

Study or subgroup	Favours vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Trials with low risk of bias					
Aloia 2005	1/104	2/104		0.0 %	0.50 [0.05, 5.43]
Avenell 2012	836/2649	881/2643		13.8 %	0.95 [0.88, 1.02]
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]
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		1.2 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Jackson 2006	744/18176	807/18106		8.8 %	0.92 [0.83, 1.01]

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Study or subgroup	Favours vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
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]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		4.1 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Lyons 2007	947/1725	953/1715		23.1 %	0.99 [0.93, 1.05]
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		0.5 %	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		4.2 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.1 %	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)	**33879**	**33637**		**59.7 %**	**0.96 [0.92, 0.99]**
Total events: 3604 (Favours vitamin D), 3758 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 20.29$, df = 29 (P = 0.88); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.29 (P = 0.022)					
2 Trials with high risk of bias					
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]
Brazier 2005	3/95	1/97		0.0 %	3.06 [0.32, 28.93]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		22.0 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.8 %	0.76 [0.55, 1.06]
Chel 2008	25/166	33/172		0.4 %	0.78 [0.49, 1.26]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
Corless 1985	8/41	8/41		0.1 %	1.00 [0.42, 2.41]

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Study or subgroup	Favours 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]
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		0.3 %	0.81 [0.48, 1.36]
Kärkkäinen 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		11.0 %	0.93 [0.85, 1.01]
Law 2006	347/1762	322/1955		4.4 %	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		0.7 %	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)	**13593**	**14177**		**40.3 %**	**0.99 [0.92, 1.06]**
Total events: 2316 (Favours vitamin D), 2319 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 27.75, df = 25 (P = 0.32); I^2 =10%					
Test for overall effect: Z = 0.38 (P = 0.71)					
Total (95% CI)	**47472**	**47814**		**100.0 %**	**0.97 [0.94, 0.99]**
Total events: 5920 (Favours vitamin D), 6077 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 48.60, df = 55 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: Chi^2 = 0.56, df = 1 (P = 0.46), I^2 =0.0%					

Analysis 1.2. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 2 All-cause mortality in individually randomised 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 randomised 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]
Avenell 2012	836/2649	881/2643		13.8 %	0.95 [0.88, 1.02]
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]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
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		22.0 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.8 %	0.76 [0.55, 1.06]
Chel 2008	25/166	33/172		0.4 %	0.78 [0.49, 1.26]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
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		1.2 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]

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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
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	807/18106		8.8 %	0.92 [0.83, 1.01]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Krieg 1999	21/124	26/124		0.3 %	0.81 [0.48, 1.36]
Kärkkäinen 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]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		4.1 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Lyons 2007	947/1725	953/1715		23.1 %	0.99 [0.93, 1.05]
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		0.7 %	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		0.5 %	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]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Smith 2007	355/4727	354/4713		4.2 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.1 %	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]

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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
Subtotal (95% CI)	**40753**	**41211**		**84.6 %**	**0.96 [0.93, 0.99]**
Total events: 4741 (Vitamin D), 4916 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 38.57$, df = 53 (P = 0.93); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.52 (P = 0.012)					
2 Cluster-randomised trials					
Larsen 2004	832/4957	839/4648		11.0 %	0.93 [0.85, 1.01]
Law 2006	347/1762	322/1955		4.4 %	1.20 [1.04, 1.37]
Subtotal (95% CI)	**6719**	**6603**		**15.4 %**	**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)	**47472**	**47814**		**100.0 %**	**0.97 [0.94, 0.99]**
Total events: 5920 (Vitamin D), 6077 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 48.60$, df = 55 (P = 0.72); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: $Chi^2 = 0.48$, df = 1 (P = 0.49), $I^2 = 0.0\%$					

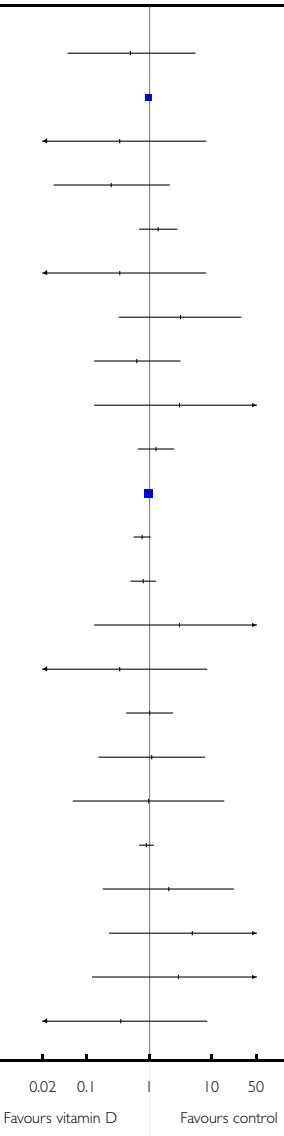
Analysis 1.3. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 3 All-cause mortality in placebo-controlled and no intervention trials.

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]
Avenell 2012	836/2649	881/2643		13.8 %	0.95 [0.88, 1.02]
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]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
Burleigh 2007	16/101	13/104		0.2 %	1.27 [0.64, 2.50]
Chapuy 1992	893/1634	917/1636		22.0 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.8 %	0.76 [0.55, 1.06]
Chel 2008	25/166	33/172		0.4 %	0.78 [0.49, 1.26]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
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		1.2 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]



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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	807/18106		8.8 %	0.92 [0.83, 1.01]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
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]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		4.1 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Lyons 2007	947/1725	953/1715		23.1 %	0.99 [0.93, 1.05]
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]
Prince 2008	0/151	1/151		0.0 %	0.33 [0.01, 8.12]
Sanders 2010	40/1131	47/1127		0.5 %	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 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		4.2 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.1 %	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)	**37021**	**36871**		**83.1 %**	**0.96 [0.93, 0.99]**
Total events: 4613 (Vitamin D), 4788 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 31.83$, df = 43 (P = 0.90); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.63 (P = 0.0086)					
2 No intervention in the control group					
Avenell 2004	4/70	3/64		0.0 %	1.22 [0.28, 5.24]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Krieg 1999	21/124	26/124		0.3 %	0.81 [0.48, 1.36]
Kärkkäinen 2010	15/1718	13/1714		0.2 %	1.15 [0.55, 2.41]

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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
Larsen 2004	832/4957	839/4648		11.0 %	0.93 [0.85, 1.01]
Law 2006	347/1762	322/1955		4.4 %	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]
Porthouse 2005	57/1321	68/1993		0.7 %	1.26 [0.90, 1.79]
Sato 1999b	0/34	1/35		0.0 %	0.34 [0.01, 8.13]
Subtotal (95% CI)	**10451**	**10943**		**16.9 %**	**1.05 [0.91, 1.21]**
Total events: 1307 (Vitamin D), 1289 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 15.41, df = 11 (P = 0.16); I^2 =29%					
Test for overall effect: Z = 0.67 (P = 0.51)					
Total (95% CI)	**47472**	**47814**		**100.0 %**	**0.97 [0.94, 0.99]**
Total events: 5920 (Vitamin D), 6077 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 48.60, df = 55 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: Chi^2 = 1.50, df = 1 (P = 0.22), I^2 =33%					

Analysis 1.4. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 4 All-cause mortality and risk of industry bias.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 4 All-cause mortality and risk of industry bias

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 Trials without risk of industry bias					
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Flicker 2005	76/313	85/312		1.2 %	0.89 [0.68, 1.16]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
Lyons 2007	947/1725	953/1715		23.1 %	0.99 [0.93, 1.05]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Trivedi 2003	224/1345	247/1341		3.1 %	0.90 [0.77, 1.07]
Witham 2010	4/53	2/52		0.0 %	1.96 [0.38, 10.26]
Subtotal (95% CI)	**3697**	**3675**		**27.5 %**	**0.97 [0.92, 1.03]**
Total events: 1257 (Vitamin D), 1299 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.23$, df = 6 (P = 0.65); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.00 (P = 0.32)					
2 Trials with risk of industry bias					
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]
Avenell 2012	836/2649	881/2643		13.8 %	0.95 [0.88, 1.02]
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]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
Burleigh 2007	16/101	13/104		0.2 %	1.27 [0.64, 2.50]
Chapuy 1992	893/1634	917/1636		22.0 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.8 %	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		0.4 %	0.78 [0.49, 1.26]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
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]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	807/18106		8.8 %	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		0.3 %	0.81 [0.48, 1.36]
Kärkkäinen 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		11.0 %	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		4.4 %	1.20 [1.04, 1.37]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		4.1 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
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		0.7 %	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		0.5 %	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]

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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 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]
Smith 2007	355/4727	354/4713		4.2 %	1.00 [0.87, 1.15]
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**43775**	**44139**		**72.5 %**	**0.96 [0.93, 1.00]**
Total events: 4663 (Vitamin D), 4778 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 44.38$, df = 48 (P = 0.62); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.11 (P = 0.035)					
Total (95% CI)	**47472**	**47814**		**100.0 %**	**0.97 [0.94, 0.99]**
Total events: 5920 (Vitamin D), 6077 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 48.60$, df = 55 (P = 0.72); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: $Chi^2 = 0.07$, df = 1 (P = 0.80), $I^2 = 0.0\%$					

Analysis 1.5. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 5 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: 5 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]
Avenell 2012	836/2649	881/2643		13.8 %	0.95 [0.88, 1.02]
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		22.0 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.8 %	0.76 [0.55, 1.06]
Chel 2008	25/166	33/172		0.4 %	0.78 [0.49, 1.26]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
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		1.2 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]

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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
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	807/18106		8.8 %	0.92 [0.83, 1.01]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Krieg 1999	21/124	26/124		0.3 %	0.81 [0.48, 1.36]
Kärkkäinen 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		11.0 %	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		4.4 %	1.20 [1.04, 1.37]
Lips 1996	282/1291	306/1287		4.1 %	0.92 [0.80, 1.06]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Lyons 2007	947/1725	953/1715		23.1 %	0.99 [0.93, 1.05]
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		0.7 %	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		0.5 %	0.85 [0.56, 1.28]
Smith 2007	355/4727	354/4713		4.2 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.1 %	0.90 [0.77, 1.07]
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**47072**	**47419**		**99.8 %**	**0.97 [0.94, 0.99]**
Total events: 5896 (Vitamin D), 6059 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 45.30$, df = 47 (P = 0.54); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.37 (P = 0.018)					
2 Secondary prevention trials					
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]

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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
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)	**400**	**395**		**0.2 %**	**1.31 [0.73, 2.35]**
Total events: 24 (Vitamin D), 18 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.28, df = 7 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 0.90 (P = 0.37)					
Total (95% CI)	**47472**	**47814**		**100.0 %**	**0.97 [0.94, 0.99]**
Total events: 5920 (Vitamin D), 6077 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 48.60, df = 55 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: Chi^2 = 1.04, df = 1 (P = 0.31), I^2 =4%					

Analysis 1.6. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 6 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: 6 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]
Avenell 2012	836/2649	881/2643		13.8 %	0.95 [0.88, 1.02]
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		22.0 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.8 %	0.76 [0.55, 1.06]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
Corless 1985	8/41	8/41		0.1 %	1.00 [0.42, 2.41]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	807/18106		8.8 %	0.92 [0.83, 1.01]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
Krieg 1999	21/124	26/124		0.3 %	0.81 [0.48, 1.36]
Kärkkäinen 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]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		4.1 %	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		0.5 %	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]

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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]
Witham 2010	4/53	2/52		0.0 %	1.96 [0.38, 10.26]
Subtotal (95% CI)	**28530**	**28167**		**51.2 %**	**0.95 [0.91, 0.99]**
Total events: 2984 (Vitamin D), 3107 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 21.11$, df = 25 (P = 0.69); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.57 (P = 0.010)					
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		0.4 %	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		1.2 %	0.89 [0.68, 1.16]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
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		4.2 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.1 %	0.90 [0.77, 1.07]
Zhu 2008	0/39	2/81		0.0 %	0.41 [0.02, 8.34]
Subtotal (95% CI)	**8200**	**8083**		**9.3 %**	**0.95 [0.87, 1.05]**
Total events: 737 (Vitamin D), 754 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.31$, df = 18 (P = 0.97); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.03 (P = 0.30)					
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]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]

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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
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		11.0 %	0.93 [0.85, 1.01]
Law 2006	347/1762	322/1955		4.4 %	1.20 [1.04, 1.37]
Lyons 2007	947/1725	953/1715		23.1 %	0.99 [0.93, 1.05]
Porthouse 2005	57/1321	68/1993		0.7 %	1.26 [0.90, 1.79]
Sato 1997	1/45	1/39		0.0 %	0.87 [0.06, 13.40]
Subtotal (95% CI)	**10742**	**11564**		**39.4 %**	**1.02 [0.92, 1.13]**
Total events: 2199 (Vitamin D), 2216 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 16.87, df = 10 (P = 0.08); I^2 =41%					
Test for overall effect: Z = 0.33 (P = 0.74)					
Total (95% CI)	**47472**	**47814**		**100.0 %**	**0.97 [0.94, 0.99]**
Total events: 5920 (Vitamin D), 6077 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 48.60, df = 55 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: Chi^2 = 1.59, df = 2 (P = 0.45), I^2 =0.0%					

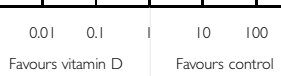
Analysis 1.7. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 7 All-cause mortality in ambulatory and institutionalised participants.

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 ambulatory and institutionalised participants

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 Ambulatory participants					
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]
Avenell 2012	836/2649	881/2643		13.8 %	0.95 [0.88, 1.02]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
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]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		22.0 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		0.8 %	0.76 [0.55, 1.06]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
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]
Gallagher 2001	2/123	1/123		0.0 %	2.00 [0.18, 21.77]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Harwood 2004	24/113	5/37		0.1 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	807/18106		8.8 %	0.92 [0.83, 1.01]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
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
Kärkkäinen 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		11.0 %	0.93 [0.85, 1.01]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		4.1 %	0.92 [0.80, 1.06]
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]
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		0.7 %	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		0.5 %	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]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Smith 2007	355/4727	354/4713		4.2 %	1.00 [0.87, 1.15]
Trivedi 2003	224/1345	247/1341		3.1 %	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)	**42881**	**43190**		**70.1 %**	**0.95 [0.92, 0.98]**
Total events: 4446 (Vitamin D), 4620 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 32.50$, df = 44 (P = 0.90); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.99 (P = 0.0028)					
2 Institutionalised participants					
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]
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		0.4 %	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
Corless 1985	8/41	8/41		0.1 %	1.00 [0.42, 2.41]
Flicker 2005	76/313	85/312		1.2 %	0.89 [0.68, 1.16]
Krieg 1999	21/124	26/124		0.3 %	0.81 [0.48, 1.36]
Law 2006	347/1762	322/1955		4.4 %	1.20 [1.04, 1.37]
Lyons 2007	947/1725	953/1715		23.1 %	0.99 [0.93, 1.05]
Sato 2005a	1/48	2/48		0.0 %	0.50 [0.05, 5.33]
Subtotal (95% CI)	**4591**	**4624**		**29.9 %**	**1.02 [0.92, 1.13]**
Total events: 1474 (Vitamin D), 1457 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 12.63, df = 10 (P = 0.25); I^2 =21%					
Test for overall effect: Z = 0.33 (P = 0.74)					
Total (95% CI)	**47472**	**47814**		**100.0 %**	**0.97 [0.94, 0.99]**
Total events: 5920 (Vitamin D), 6077 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 48.60, df = 55 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: Chi^2 = 1.60, df = 1 (P = 0.21), I^2 =37%					

Analysis 1.8. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 8 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: 8 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		1.0 %	0.03 [0.00, 0.24]
Avenell 2004	4/70	10/64		2.0 %	0.37 [0.12, 1.11]
Avenell 2012	836/2649	917/2643		3.5 %	0.91 [0.84, 0.98]
Baeksgaard 1998	0/80	16/80		0.6 %	0.03 [0.00, 0.50]
Bischoff 2003	1/62	15/60		1.0 %	0.06 [0.01, 0.47]
Bjorkman 2007	27/150	9/68		2.7 %	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		1.9 %	0.11 [0.03, 0.34]
Broe 2007	5/99	2/25		1.4 %	0.63 [0.13, 3.07]
Brohult 1973	1/25	0/25		0.5 %	3.00 [0.13, 70.30]
Burleigh 2007	16/101	23/104		2.9 %	0.72 [0.40, 1.27]
Campbell 2005	6/195	12/196		2.2 %	0.50 [0.19, 1.31]
Chapuy 1992	258/1634	337/1636		3.4 %	0.77 [0.66, 0.89]
Chapuy 2002	70/389	70/194		3.3 %	0.50 [0.38, 0.66]
Chel 2008	25/166	33/172		3.1 %	0.78 [0.49, 1.26]
Cherniack 2011	1/23	6/23		1.0 %	0.17 [0.02, 1.28]
Cooper 2003	0/93	14/94		0.6 %	0.03 [0.00, 0.58]
Corless 1985	8/41	15/41		2.6 %	0.53 [0.25, 1.12]
Daly 2008	1/85	28/82		1.0 %	0.03 [0.00, 0.25]
Dawson-Hughes 1997	2/187	32/202		1.6 %	0.07 [0.02, 0.28]
Dukas 2004	1/192	31/186		1.0 %	0.03 [0.00, 0.23]
Flicker 2005	76/313	128/312		3.4 %	0.59 [0.47, 0.75]
Gallagher 2001	2/123	11/123		1.5 %	0.18 [0.04, 0.80]

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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
Glendenning 2012	2/353	26/333		1.5 %	0.07 [0.02, 0.30]
Grady 1991	1/50	1/48		0.6 %	0.96 [0.06, 14.92]
Grimnes 2011	0/51	9/53		0.6 %	0.05 [0.00, 0.92]
Harwood 2004	24/113	5/37		2.3 %	1.57 [0.65, 3.82]
Jackson 2006	744/18176	1291/18106		3.5 %	0.57 [0.53, 0.63]
Janssen 2010	0/36	4/34		0.6 %	0.11 [0.01, 1.88]
Komulainen 1999	0/116	4/116		0.6 %	0.11 [0.01, 2.04]
Krieg 1999	21/124	71/124		3.1 %	0.30 [0.19, 0.45]
Kärkkäinen 2010	15/1718	36/1714		2.8 %	0.42 [0.23, 0.76]
Latham 2003	11/121	8/122		2.4 %	1.39 [0.58, 3.33]
Law 2006	347/1762	386/1955		3.4 %	1.00 [0.88, 1.14]
Lehouck 2012	9/91	13/91		2.5 %	0.69 [0.31, 1.54]
Lips 1996	282/1291	315/1287		3.4 %	0.89 [0.78, 1.03]
Lips 2010	1/114	15/112		1.0 %	0.07 [0.01, 0.49]
Lyons 2007	947/1725	1039/1715		3.5 %	0.91 [0.86, 0.96]
Meier 2004	0/30	9/25		0.6 %	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		2.8 %	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		3.3 %	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		3.2 %	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		0.9 %	0.17 [0.02, 1.33]
Schleithoff 2006	7/61	11/62		2.4 %	0.65 [0.27, 1.56]
Smith 2007	355/4727	2423/4713		3.5 %	0.15 [0.13, 0.16]
Trivedi 2003	224/1345	324/1341		3.4 %	0.69 [0.59, 0.80]
Witham 2010	4/53	4/52		1.7 %	0.98 [0.26, 3.72]
Zhu 2008	0/39	7/81		0.6 %	0.14 [0.01, 2.33]
Subtotal (95% CI)	**42024**	**42394**		**100.0 %**	**0.40 [0.32, 0.51]**

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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: 4448 (Vitamin D), 8102 (Control)					
Heterogeneity: Tau² = 0.42; Chi² = 1382.06, df = 52 (P<0.00001); I² =96%					
Test for overall effect: Z = 7.54 (P < 0.00001)					
2 'Worst-best' case scenario					
Aloia 2005	30/104	2/104		1.7 %	15.00 [3.68, 61.15]
Avenell 2004	18/70	3/64		1.9 %	5.49 [1.70, 17.75]
Avenell 2012	867/2649	881/2643		3.1 %	0.98 [0.91, 1.06]
Baeksgaard 1998	15/80	1/80		1.1 %	15.00 [2.03, 110.88]
Bischoff 2003	19/62	4/60		2.1 %	4.60 [1.66, 12.72]
Bjorkman 2007	27/150	9/68		2.6 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	8/62	1/61		1.1 %	7.87 [1.01, 61.05]
Brazier 2005	21/95	1/97		1.1 %	21.44 [2.94, 156.24]
Broe 2007	8/99	2/25		1.6 %	1.01 [0.23, 4.46]
Brohult 1973	1/25	0/25		0.6 %	3.00 [0.13, 70.30]
Burleigh 2007	20/101	13/104		2.6 %	1.58 [0.83, 3.01]
Campbell 2005	45/195	10/196		2.6 %	4.52 [2.35, 8.72]
Chapuy 1992	302/1634	917/1636		3.1 %	0.33 [0.30, 0.37]
Chapuy 2002	109/389	46/194		3.0 %	1.18 [0.88, 1.59]
Chel 2008	25/166	33/172		2.8 %	0.78 [0.49, 1.26]
Cherniack 2011	7/23	0/23		0.7 %	15.00 [0.91, 248.21]
Cooper 2003	20/93	1/94		1.1 %	20.22 [2.77, 147.56]
Corless 1985	25/41	8/41		2.6 %	3.13 [1.60, 6.10]
Daly 2008	30/85	0/82		0.7 %	58.87 [3.66, 947.17]
Dawson-Hughes 1997	39/187	2/202		1.7 %	21.06 [5.16, 86.02]
Dukas 2004	26/192	1/186		1.1 %	25.19 [3.45, 183.73]
Flicker 2005	130/313	85/312		3.0 %	1.52 [1.22, 1.91]
Gallagher 2001	22/123	1/123		1.1 %	22.00 [3.01, 160.68]
Glendenning 2012	24/353	0/333		0.7 %	46.23 [2.82, 757.19]
Grady 1991	1/50	0/48		0.6 %	2.88 [0.12, 69.07]
Grimnes 2011	2/51	1/53		0.9 %	2.08 [0.19, 22.22]
Harwood 2004	42/113	5/37		2.4 %	2.75 [1.18, 6.43]
Jackson 2006	1240/18176	807/18106		3.1 %	1.53 [1.40, 1.67]

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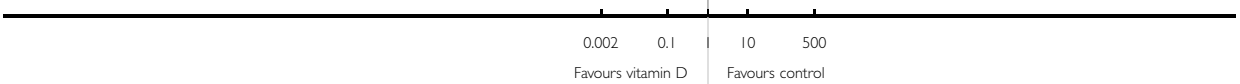
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Janssen 2010	8/36	1/34		1.1 %	7.56 [1.00, 57.26]
Komulainen 1999	3/116	1/116		1.0 %	3.00 [0.32, 28.42]
Krieg 1999	74/124	26/124		2.9 %	2.85 [1.96, 4.12]
Kärkkäinen 2010	20/1718	13/1714		2.6 %	1.53 [0.77, 3.08]
Latham 2003	13/121	3/122		1.9 %	4.37 [1.28, 14.95]
Law 2006	396/1762	322/1955		3.1 %	1.36 [1.20, 1.56]
Lehouck 2012	19/91	6/91		2.3 %	3.17 [1.33, 7.56]
Lips 1996	289/1291	306/1287		3.1 %	0.94 [0.82, 1.08]
Lips 2010	9/114	0/112		0.7 %	18.67 [1.10, 316.98]
Lyons 2007	1039/1725	953/1715		3.1 %	1.08 [1.02, 1.15]
Meier 2004	3/30	1/25		1.0 %	2.50 [0.28, 22.56]
Moschonis 2006	3/42	1/70		1.0 %	5.00 [0.54, 46.53]
Ooms 1995	51/177	21/171		2.8 %	2.35 [1.48, 3.73]
Ott 1989	7/43	1/43		1.1 %	7.00 [0.90, 54.50]
Porthouse 2005	109/1321	68/1993		3.0 %	2.42 [1.80, 3.25]
Prince 2008	7/151	1/151		1.1 %	7.00 [0.87, 56.21]
Sanders 2010	116/1131	47/1127		3.0 %	2.46 [1.77, 3.42]
Sato 1999a	3/43	0/43		0.7 %	7.00 [0.37, 131.56]
Sato 1999b	2/34	1/35		0.9 %	2.06 [0.20, 21.67]
Sato 2005a	5/48	2/48		1.5 %	2.50 [0.51, 12.26]
Schleithoff 2006	19/61	6/62		2.4 %	3.22 [1.38, 7.51]
Smith 2007	2447/4727	354/4713		3.1 %	6.89 [6.21, 7.65]
Trivedi 2003	307/1345	247/1341		3.1 %	1.24 [1.07, 1.44]
Witham 2010	5/53	2/52		1.5 %	2.45 [0.50, 12.08]
Zhu 2008	6/39	2/81		1.5 %	6.23 [1.32, 29.47]
Subtotal (95% CI)	**42024**	**42394**	◆	**100.0 %**	**2.78 [2.13, 3.63]**

Total events: 8083 (Vitamin D), 5219 (Control)

Heterogeneity: $Tau^2 = 0.60$; $Chi^2 = 2048.65$, df = 52 (P<0.00001); $I^2 = 97\%$

Test for overall effect: Z = 7.52 (P < 0.00001)



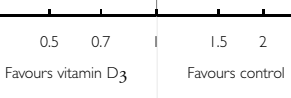
Analysis 1.9. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 9 All-cause mortality in trials using vitamin D3 (cholecalciferol).

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 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]
Avenell 2012	836/2649	881/2643		20.7 %	0.95 [0.88, 1.02]
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]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Jackson 2006	744/18176	807/18106		13.2 %	0.92 [0.83, 1.01]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
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]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		6.2 %	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		0.7 %	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		4.6 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**26411**	**26234**		**46.6 %**	**0.93 [0.89, 0.98]**
Total events: 2216 (Vitamin D), 2355 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 15.81$, df = 19 (P = 0.67); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.62 (P = 0.0089)					
2 Vitamin D_3 trials with high risk of bias					



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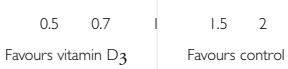
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Avenell 2004	4/70	3/64		0.1 %	1.22 [0.28, 5.24]
Baeksgaard 1998	0/80	1/80		0.0 %	0.33 [0.01, 8.06]
Bischoff 2003	1/62	4/60		0.0 %	0.24 [0.03, 2.10]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		33.0 %	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]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
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]
Kärkkäinen 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		16.5 %	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		1.0 %	1.26 [0.90, 1.79]
Subtotal (95% CI)	**11406**	**11876**		**53.4 %**	**0.95 [0.91, 1.00]**
Total events: 1937 (Vitamin D), 1985 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 14.87$, df = 17 (P = 0.60); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.89 (P = 0.059)					
Total (95% CI)	**37817**	**38110**		**100.0 %**	**0.94 [0.91, 0.98]**
Total events: 4153 (Vitamin D), 4340 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 31.05$, df = 37 (P = 0.74); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.16 (P = 0.0016)					
Test for subgroup differences: $Chi^2 = 0.39$, df = 1 (P = 0.53), $I^2 = 0.0\%$					



Analysis 1.10. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 10 All-cause mortality in trials using vitamin D3 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: 10 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		0.1 %	0.50 [0.05, 5.27]
Avenell 2012	421/1343	434/1332		40.1 %	0.96 [0.86, 1.07]
Brohult 1973	1/25	0/25		0.1 %	3.00 [0.13, 70.30]
Campbell 2005	6/195	10/196		0.7 %	0.60 [0.22, 1.63]
Chel 2008	25/166	33/172		3.0 %	0.78 [0.49, 1.26]
Glendenning 2012	2/353	0/333		0.1 %	4.72 [0.23, 97.90]
Grimnes 2011	0/51	1/53		0.1 %	0.35 [0.01, 8.31]
Latham 2003	11/121	3/122		0.4 %	3.70 [1.06, 12.92]
Lehouck 2012	9/91	6/91		0.7 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		27.5 %	0.92 [0.80, 1.06]
Ooms 1995	11/177	21/171		1.4 %	0.51 [0.25, 1.02]
Sanders 2010	40/1131	47/1127		4.0 %	0.85 [0.56, 1.28]
Trivedi 2003	224/1345	247/1341		21.7 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**6324**	**6285**		**100.0 %**	**0.92 [0.85, 1.00]**
Total events: 1033 (Vitamin D), 1110 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.66$, df = 12 (P = 0.39); $I^2 = 5\%$					
Test for overall effect: Z = 1.85 (P = 0.065)					
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]
Avenell 2012	415/1306	434/1332		13.3 %	0.98 [0.87, 1.09]
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]

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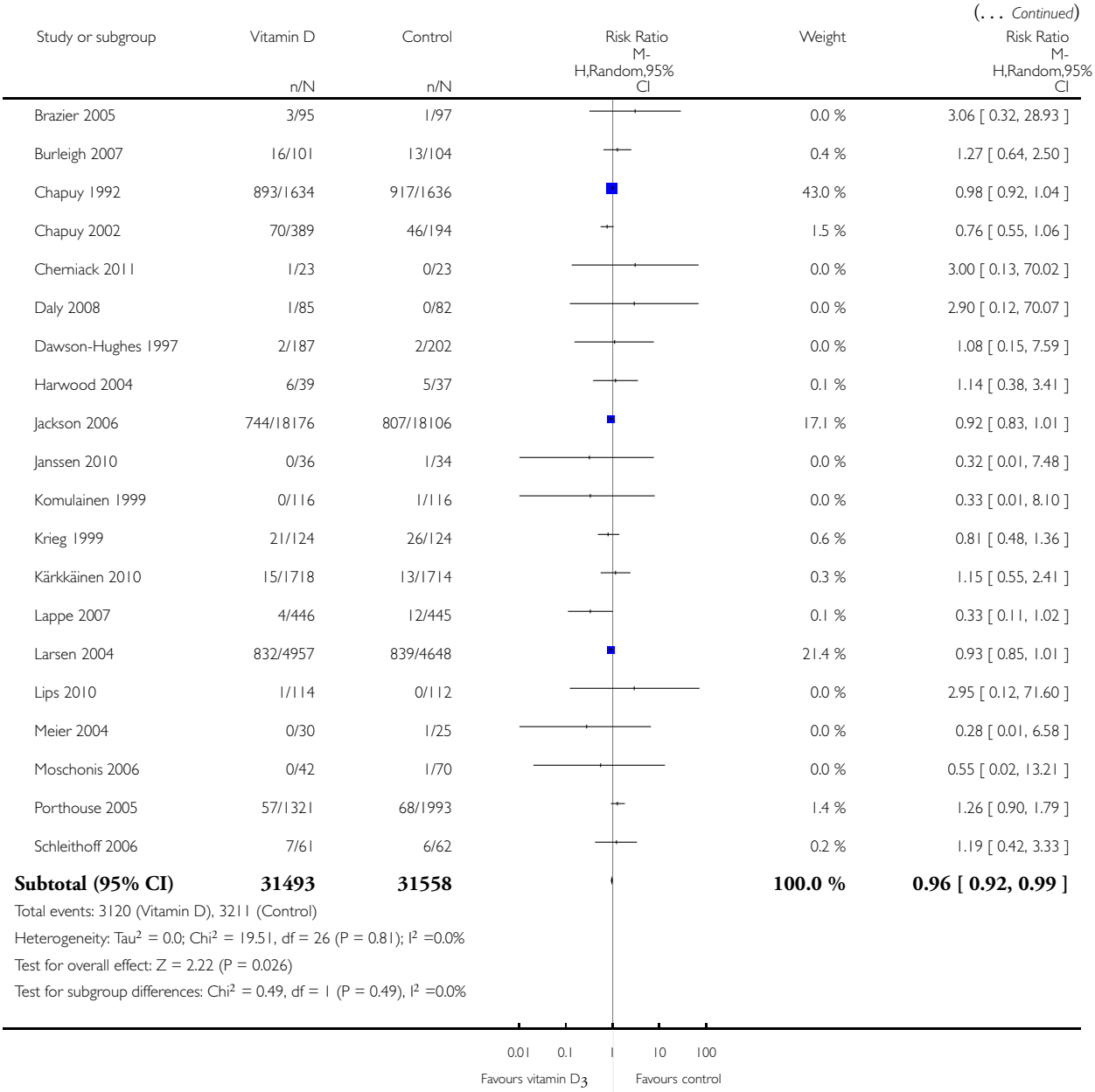


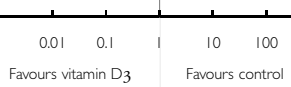
Analysis 1.11. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 11 All-cause mortality in trials using low or high dose of vitamin D3.

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 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]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Larsen 2004	832/4957	839/4648		44.5 %	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)	**25397**	**25040**		**100.0 %**	**0.92 [0.87, 0.97]**
Total events: 1913 (Vitamin D), 2023 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.09$, df = 12 (P = 0.78); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.84 (P = 0.0046)					
2 High dose of vitamin D_3 (≥ 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]
Avenell 2012	836/2649	881/2643		32.7 %	0.95 [0.88, 1.02]
Bischoff 2003	1/62	4/60		0.0 %	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]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]



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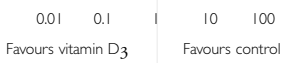
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Burleigh 2007	16/101	13/104		0.4 %	1.27 [0.64, 2.50]
Campbell 2005	6/195	10/196		0.2 %	0.60 [0.22, 1.63]
Chapuy 1992	893/1634	917/1636		52.2 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		1.8 %	0.76 [0.55, 1.06]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
Daly 2008	1/85	0/82		0.0 %	2.90 [0.12, 70.07]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Harwood 2004	6/39	5/37		0.2 %	1.14 [0.38, 3.41]
Krieg 1999	21/124	26/124		0.7 %	0.81 [0.48, 1.36]
Kärkkäinen 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		0.1 %	3.70 [1.06, 12.92]
Lehouck 2012	9/91	6/91		0.2 %	1.50 [0.56, 4.04]
Lips 2010	1/114	0/112		0.0 %	2.95 [0.12, 71.60]
Porthouse 2005	57/1321	68/1993		1.7 %	1.26 [0.90, 1.79]
Sanders 2010	40/1131	47/1127		1.2 %	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		7.3 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**12420**	**13138**		**100.0 %**	**0.96 [0.92, 1.00]**

Total events: 2240 (Vitamin D), 2326 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 22.76$, df = 25 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 1.78 (P = 0.075)

Test for subgroup differences: $Chi^2 = 1.37$, df = 1 (P = 0.24), $I^2 = 27\%$



Analysis 1.12. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 12 All-cause mortality in trials applying vitamin D3 daily or intermittently.

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 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]
Avenell 2012	836/2649	881/2643		22.0 %	0.95 [0.88, 1.02]
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]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
Burleigh 2007	16/101	13/104		0.3 %	1.27 [0.64, 2.50]
Chapuy 1992	893/1634	917/1636		35.1 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		1.2 %	0.76 [0.55, 1.06]
Chel 2008	8/55	12/57		0.2 %	0.69 [0.31, 1.56]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
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]
Harwood 2004	6/39	5/37		0.1 %	1.14 [0.38, 3.41]
Jackson 2006	744/18176	807/18106		14.0 %	0.92 [0.83, 1.01]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Krieg 1999	21/124	26/124		0.5 %	0.81 [0.48, 1.36]
Kärkkäinen 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]

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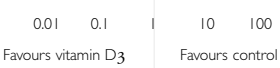
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Larsen 2004	832/4957	839/4648		17.5 %	0.93 [0.85, 1.01]
Latham 2003	11/121	3/122		0.1 %	3.70 [1.06, 12.92]
Lips 1996	282/1291	306/1287		6.6 %	0.92 [0.80, 1.06]
Meier 2004	0/30	1/25		0.0 %	0.28 [0.01, 6.58]
Moschonis 2006	0/42	1/70		0.0 %	0.55 [0.02, 13.21]
Ooms 1995	11/177	21/171		0.3 %	0.51 [0.25, 1.02]
Porthouse 2005	57/1321	68/1993		1.1 %	1.26 [0.90, 1.79]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Subtotal (95% CI)	**34426**	**34742**		**100.0 %**	**0.95 [0.91, 0.98]**
Total events: 3854 (Vitamin D), 4008 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 26.88, df = 30 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 2.90 (P = 0.0038)					
2 Vitamin D_3 intermittently					
Campbell 2005	6/195	10/196		2.0 %	0.60 [0.22, 1.63]
Chel 2008	25/166	33/172		9.0 %	0.78 [0.49, 1.26]
Glendenning 2012	2/353	0/333		0.2 %	4.72 [0.23, 97.90]
Grimnes 2011	0/51	1/53		0.2 %	0.35 [0.01, 8.31]
Lehouck 2012	9/91	6/91		2.0 %	1.50 [0.56, 4.04]
Lips 2010	1/114	0/112		0.2 %	2.95 [0.12, 71.60]
Sanders 2010	40/1131	47/1127		11.8 %	0.85 [0.56, 1.28]
Trivedi 2003	224/1345	247/1341		74.6 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**3446**	**3425**		**100.0 %**	**0.89 [0.77, 1.03]**
Total events: 307 (Vitamin D), 344 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.06, df = 7 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 1.59 (P = 0.11)					
Test for subgroup differences: Chi^2 = 0.66, df = 1 (P = 0.41), I^2 =0.0%					

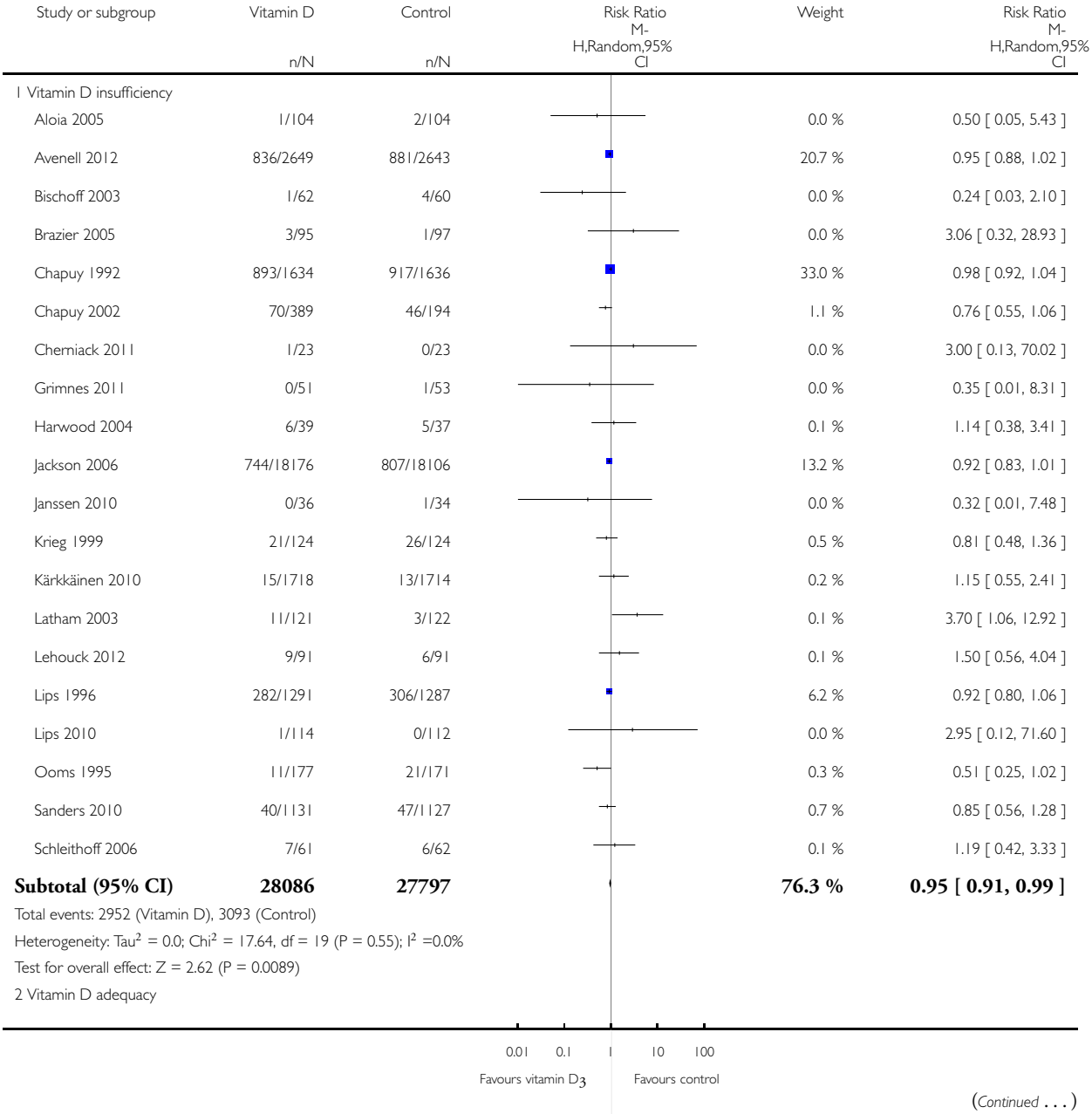


Analysis 1.13. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 13 All-cause mortality in trials using vitamin D3 and vitamin D status.

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 vitamin D_3 and vitamin D status



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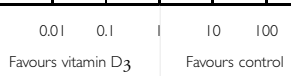
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bjorkman 2007	27/150	9/68		0.3 %	1.36 [0.68, 2.73]
Bolton-Smith 2007	0/62	1/61		0.0 %	0.33 [0.01, 7.90]
Burleigh 2007	16/101	13/104		0.3 %	1.27 [0.64, 2.50]
Chel 2008	25/166	33/172		0.6 %	0.78 [0.49, 1.26]
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]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
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		4.6 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**2521**	**2458**		**5.8 %**	**0.92 [0.80, 1.07]**
Total events: 297 (Vitamin D), 307 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.22$, df = 9 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.05 (P = 0.29)					
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]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
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		16.5 %	0.93 [0.85, 1.01]
Porthouse 2005	57/1321	68/1993		1.0 %	1.26 [0.90, 1.79]
Subtotal (95% CI)	**7210**	**7855**		**17.8 %**	**0.95 [0.78, 1.16]**
Total events: 904 (Vitamin D), 940 (Control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.08$, df = 7 (P = 0.33); $I^2 = 13\%$					
Test for overall effect: Z = 0.46 (P = 0.64)					
Total (95% CI)	**37817**	**38110**		**100.0 %**	**0.94 [0.91, 0.98]**
Total events: 4153 (Vitamin D), 4340 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 31.05$, df = 37 (P = 0.74); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.16 (P = 0.0016)					
Test for subgroup differences: $Chi^2 = 0.11$, df = 2 (P = 0.95), $I^2 = 0.0\%$					



Analysis 1.14. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 14 All-cause mortality in trials using vitamin D3 according to the participant's sex.

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 using vitamin D_3 according to the participant's sex

Study or subgroup	Vitamin D_3 n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vitamin D_3 trialsincluding only women					
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]
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]
Chapuy 1992	893/1634	917/1636		33.0 %	0.98 [0.92, 1.04]
Chapuy 2002	70/389	46/194		1.1 %	0.76 [0.55, 1.06]
Glendenning 2012	2/353	0/333		0.0 %	4.72 [0.23, 97.90]
Jackson 2006	744/18176	807/18106		13.2 %	0.92 [0.83, 1.01]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
Komulainen 1999	0/116	1/116		0.0 %	0.33 [0.01, 8.10]
Krieg 1999	21/124	26/124		0.5 %	0.81 [0.48, 1.36]
Kärkkäinen 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]
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		1.0 %	1.26 [0.90, 1.79]
Sanders 2010	40/1131	47/1127		0.7 %	0.85 [0.56, 1.28]
Subtotal (95% CI)	**26187**	**26875**		**50.3 %**	**0.93 [0.84, 1.03]**
Total events: 1873 (Vitamin D_3), 1978 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 23.13, df = 18 (P = 0.19); I^2 =22%					
Test for overall effect: Z = 1.42 (P = 0.16)					
2 Vitamin D_3 trials including men and women					
Avenell 2004	4/70	3/64		0.1 %	1.22 [0.28, 5.24]

0.01 0.1 1 10 100

Favours vitamin D3 Favours control

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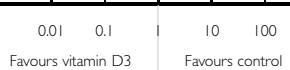
Study or subgroup	Vitamin D_3 n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Avenell 2012	836/2649	881/2643		20.7 %	0.95 [0.88, 1.02]
Bjorkman 2007	27/150	9/68		0.3 %	1.36 [0.68, 2.73]
Brohult 1973	1/25	0/25		0.0 %	3.00 [0.13, 70.30]
Burleigh 2007	16/101	13/104		0.3 %	1.27 [0.64, 2.50]
Campbell 2005	6/195	10/196		0.1 %	0.60 [0.22, 1.63]
Chel 2008	25/166	33/172		0.6 %	0.78 [0.49, 1.26]
Cherniack 2011	1/23	0/23		0.0 %	3.00 [0.13, 70.02]
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]
Grimnes 2011	0/51	1/53		0.0 %	0.35 [0.01, 8.31]
Harwood 2004	6/39	5/37		0.1 %	1.14 [0.38, 3.41]
Larsen 2004	832/4957	839/4648		16.5 %	0.93 [0.85, 1.01]
Lehouck 2012	9/91	6/91		0.1 %	1.50 [0.56, 4.04]
Lips 1996	282/1291	306/1287		6.2 %	0.92 [0.80, 1.06]
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]
Schleithoff 2006	7/61	6/62		0.1 %	1.19 [0.42, 3.33]
Trivedi 2003	224/1345	247/1341		4.6 %	0.90 [0.77, 1.07]
Subtotal (95% CI)	**11630**	**11235**		**49.7 %**	**0.94 [0.89, 0.98]**
Total events: 2280 (Vitamin D_3), 2362 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 7.80, df = 18 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 2.56 (P = 0.011)					
Total (95% CI)	**37817**	**38110**		**100.0 %**	**0.94 [0.91, 0.98]**
Total events: 4153 (Vitamin D_3), 4340 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 31.05, df = 37 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 3.16 (P = 0.0016)					
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.87), I^2 =0.0%					

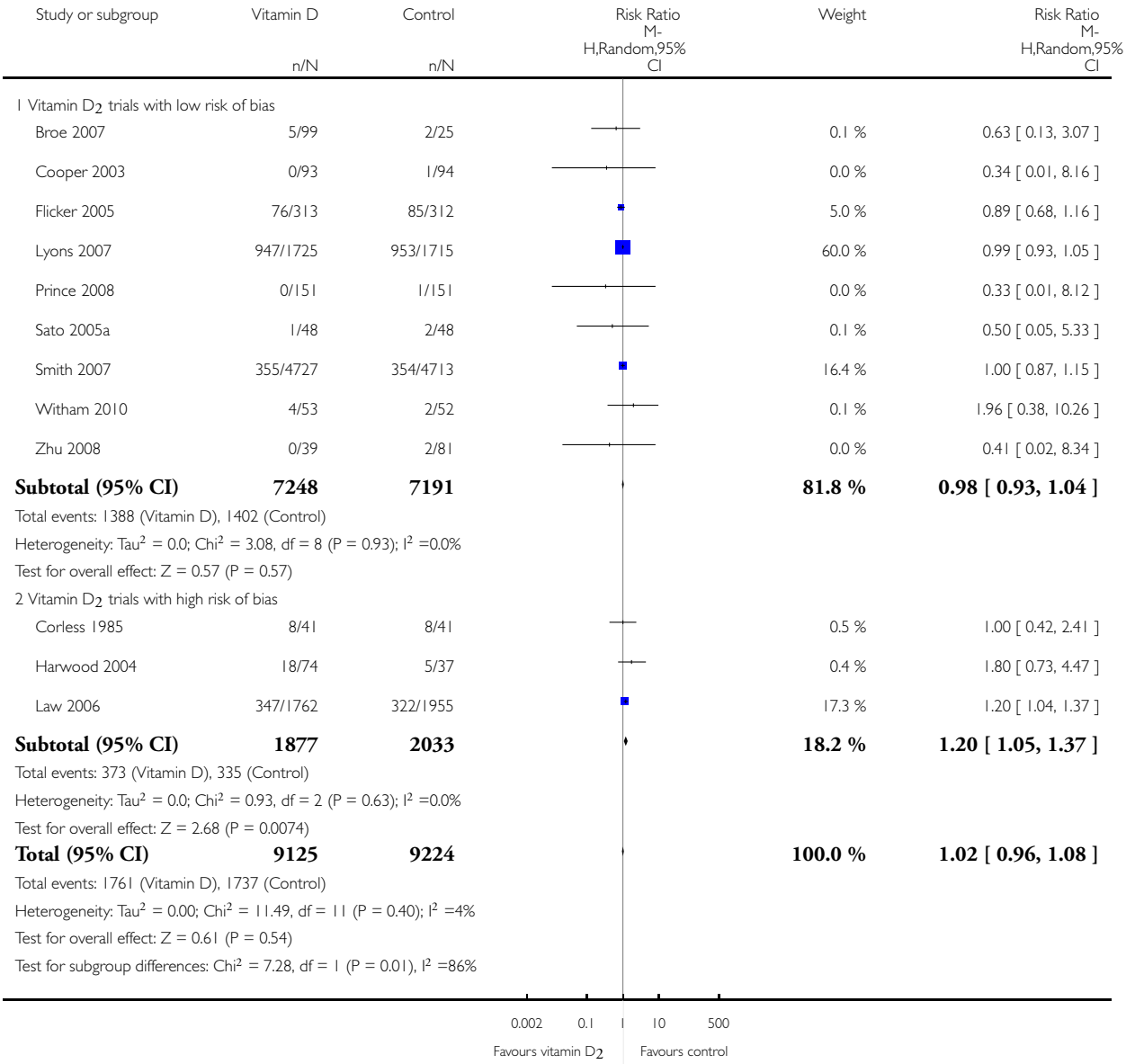


Analysis 1.15. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 15 All-cause mortality in trials using vitamin D2 (ergocalciferol).

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 (ergocalciferol)

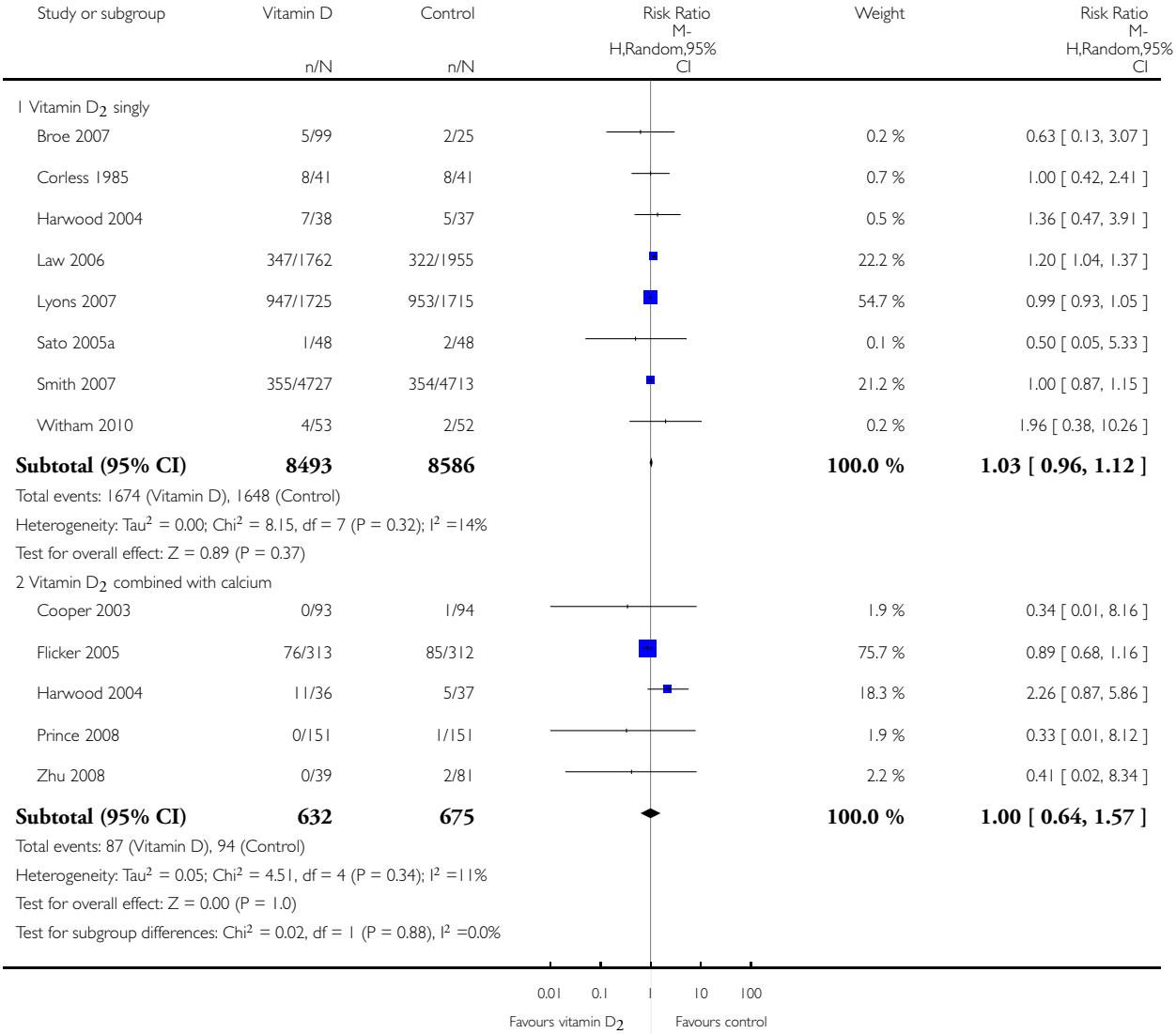


Analysis 1.16. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 16 All-cause mortality in trials using vitamin D2 singly or combined with calcium.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 16 All-cause mortality in trials using vitamin D_2 singly or combined with calcium

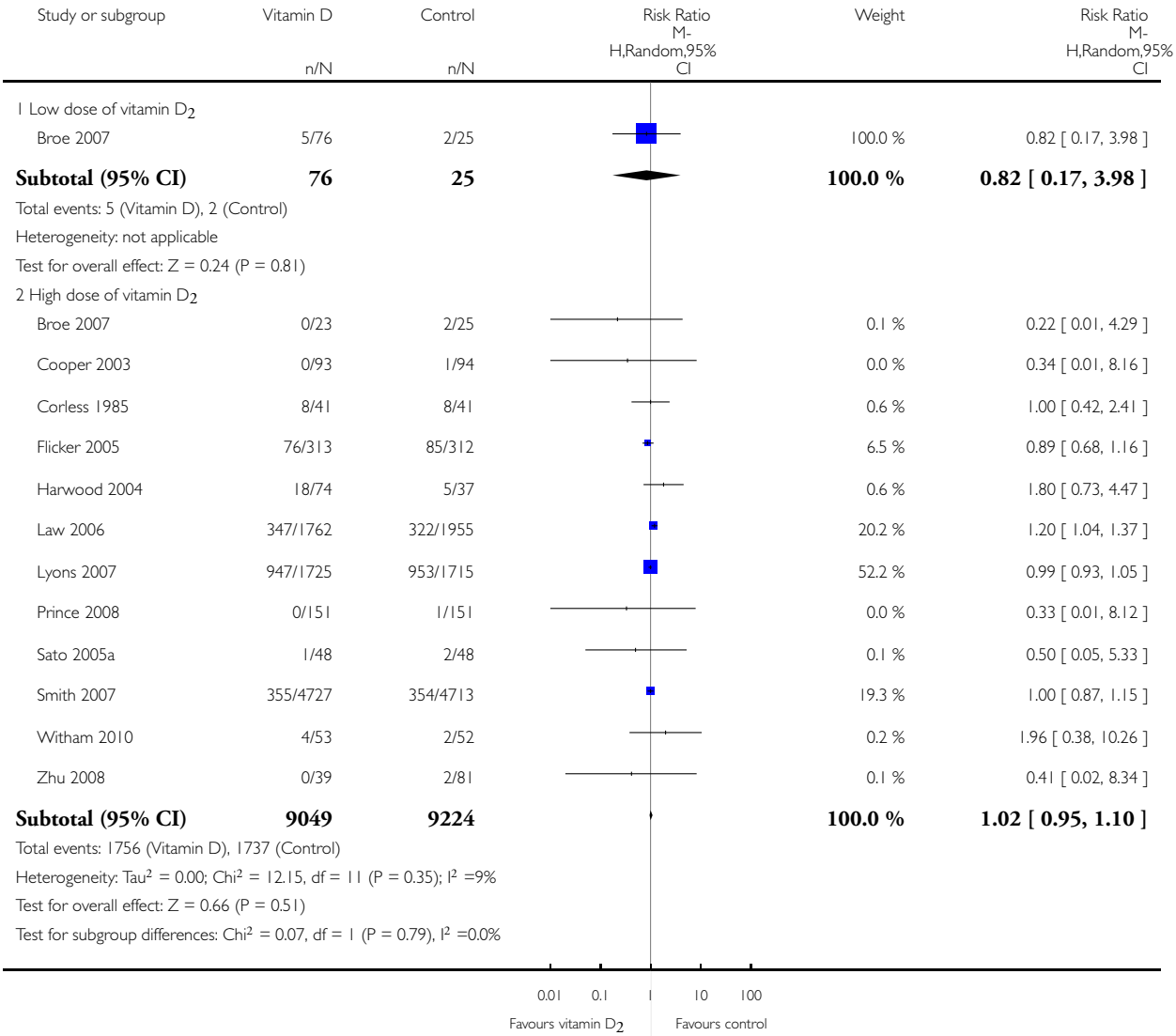


Analysis 1.17. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 17 All-cause mortality in trials using low or high dose of vitamin D2.

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 low or high dose of vitamin D_2



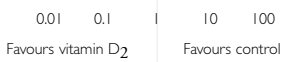
Analysis 1.18. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 18 All-cause mortality in trials applying vitamin D2 daily or intermittently.

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 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		28.0 %	1.20 [1.04, 1.37]
Lyons 2007	947/1725	953/1715		42.8 %	0.99 [0.93, 1.05]
Smith 2007	355/4727	354/4713		27.2 %	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: 1671 (Vitamin D), 1637 (Control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 9.18$, df = 5 (P = 0.10); $I^2 = 46\%$					
Test for overall effect: Z = 0.97 (P = 0.33)					
Test for subgroup differences: $Chi^2 = 1.81$, df = 1 (P = 0.18), $I^2 = 45\%$					



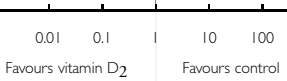
Analysis 1.19. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 19 All-cause mortality in trials using vitamin D2 and vitamin D status.

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 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		17.3 %	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**		**18.4 %**	**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		16.4 %	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**		**21.6 %**	**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	947/1725	953/1715		60.0 %	0.99 [0.93, 1.05]
Subtotal (95% CI)	**1725**	**1715**		**60.0 %**	**0.99 [0.93, 1.05]**
Total events: 947 (Vitamin D), 953 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.40 (P = 0.69)					
Total (95% CI)	**9125**	**9224**		**100.0 %**	**1.02 [0.96, 1.08]**
Total events: 1761 (Vitamin D), 1737 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 11.49, df = 11 (P = 0.40); I^2 =4%					
Test for overall effect: Z = 0.61 (P = 0.54)					
Test for subgroup differences: Chi^2 = 7.29, df = 2 (P = 0.03), I^2 =73%					



Analysis 1.20. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 20 All-cause mortality in trials using alfacalcidol (1α-hydroxyvitamin D).

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 20 All-cause mortality in trials using alfacalcidol (1α -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)

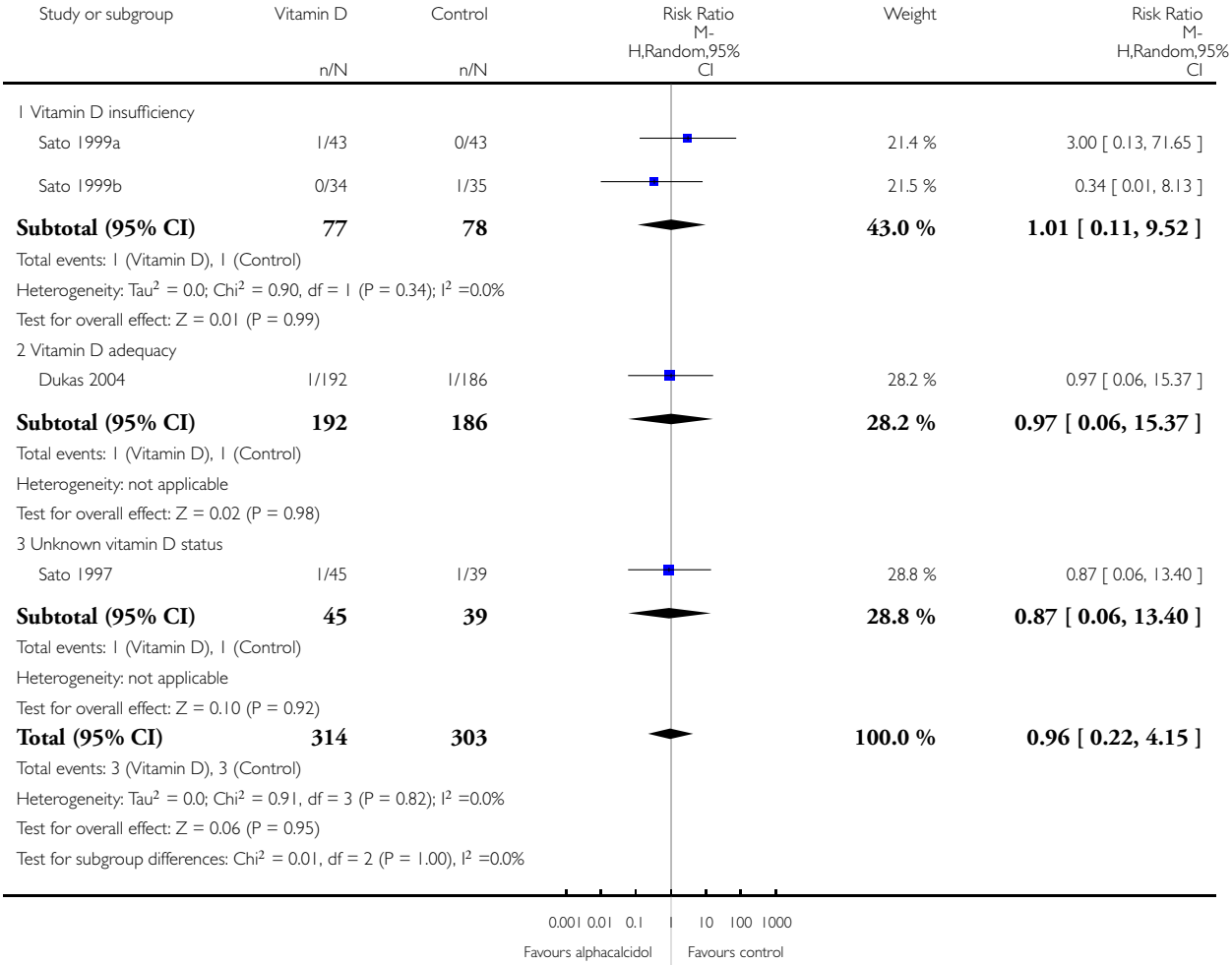
Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 21 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: 21 All-cause mortality in trials using alfacalcidol and vitamin D status



Analysis 1.22. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 22 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: 22 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)

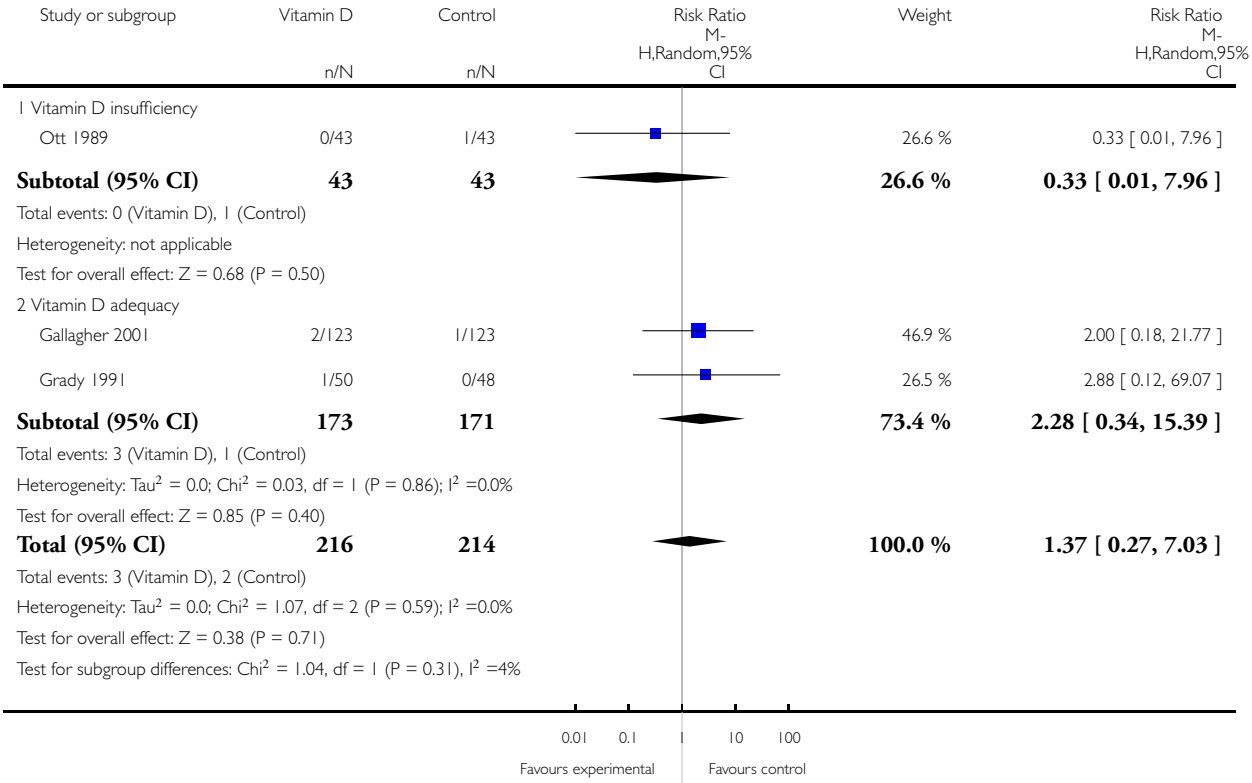
Test for subgroup differences: Not applicable

Analysis 1.23. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 23 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: 23 All-cause mortality in trials using calcitriol and vitamin D status



Analysis 1.24. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 24 Cancer mortality.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 24 Cancer mortality

Study or subgroup	Vitamin D3 n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Avenell 2012	151/2649	178/2643		28.3 %	0.85 [0.69, 1.04]
Jackson 2006	344/18176	383/18106		60.1 %	0.89 [0.77, 1.03]
Komulainen 1999	0/116	1/116		0.1 %	0.33 [0.01, 8.10]
Trivedi 2003	63/1345	72/1341		11.5 %	0.87 [0.63, 1.21]
Total (95% CI)	**22286**	**22206**		**100.0 %**	**0.88 [0.78, 0.98]**

Total events: 558 (Vitamin D3), 634 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.54$, df = 3 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 2.30 (P = 0.021)

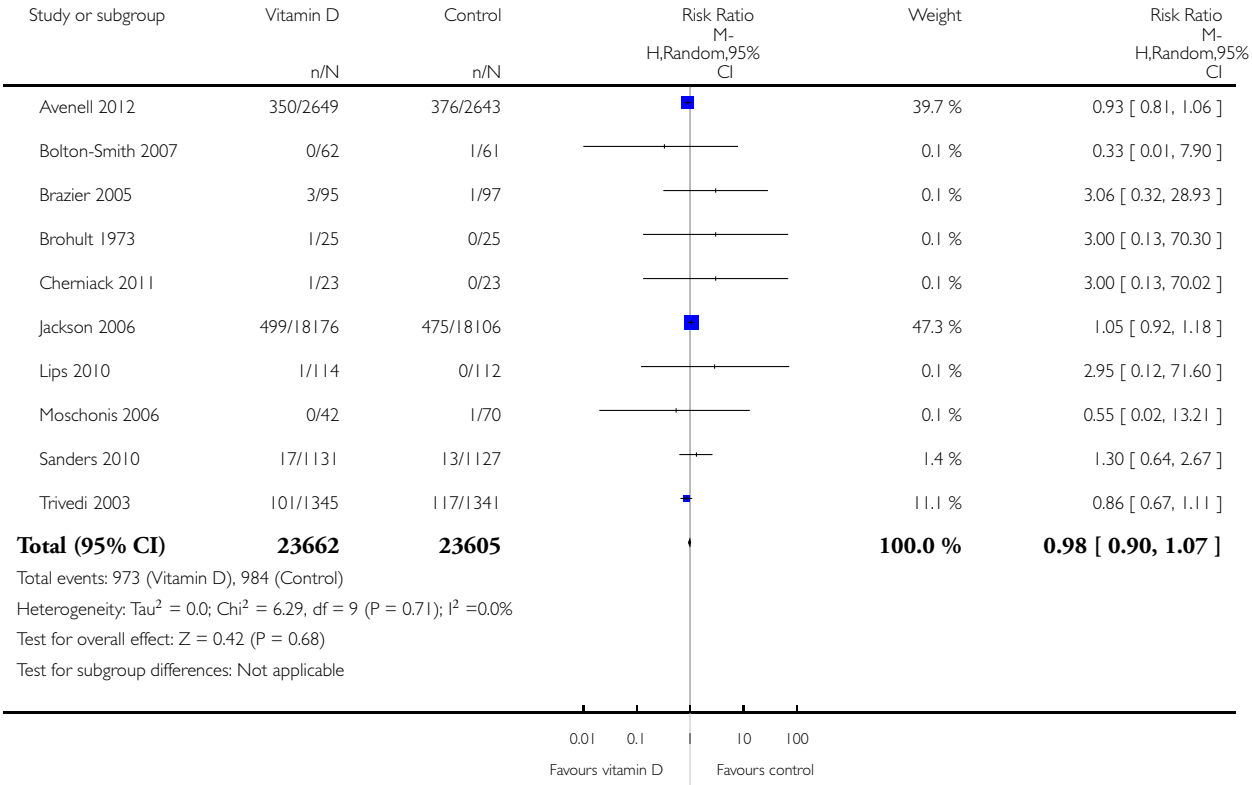
Test for subgroup differences: Not applicable

Analysis 1.25. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 25 Cardiovascular mortality.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 25 Cardiovascular mortality

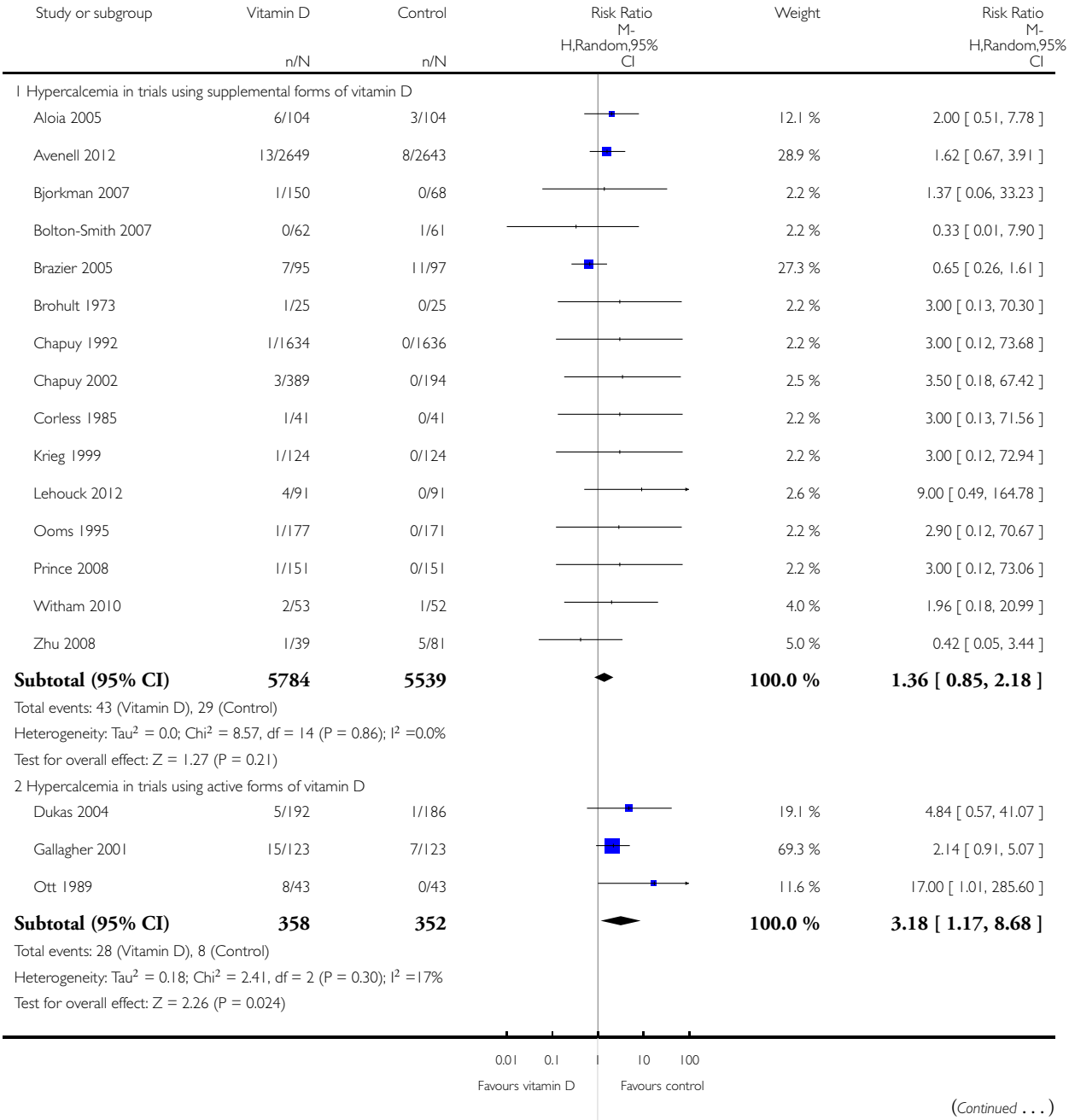


Analysis 1.26. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 26 Adverse events.

Review: Vitamin D supplementation for prevention of mortality in adults

Comparison: 1 Vitamin D versus placebo or no intervention

Outcome: 26 Adverse events



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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
3 Nephrolithiasis in trials using vitamin D_3 combined with calcium					
Avenell 2012	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]**
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					
Avenell 2012	2/2649	5/2643		42.1 %	0.40 [0.08, 2.06]
Grady 1991	2/50	0/48		23.5 %	4.80 [0.24, 97.55]
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]
Cherniack 2011	2/23	2/23		0.3 %	1.00 [0.15, 6.51]
Gallagher 2001	8/123	7/123		1.0 %	1.14 [0.43, 3.05]
Glendenning 2012	5/353	6/333		0.7 %	0.79 [0.24, 2.55]
Komulainen 1999	2/116	0/116		0.1 %	5.00 [0.24, 103.02]

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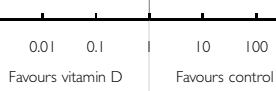
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Prince 2008	5/151	6/151		0.7 %	0.83 [0.26, 2.67]
Trivedi 2003	477/1345	503/1341		95.8 %	0.95 [0.86, 1.04]
Witham 2010	5/53	5/52		0.7 %	0.98 [0.30, 3.19]
Subtotal (95% CI)	**2259**	**2236**		**100.0 %**	**0.95 [0.86, 1.05]**
Total events: 510 (Vitamin D), 534 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 1.65, df = 7 (P = 0.98); I² =0.0%					
Test for overall effect: Z = 1.05 (P = 0.29)					
8 Gastrointestinal disorders					
Baeksgaard 1998	2/80	2/80		4.0 %	1.00 [0.14, 6.93]
Bischoff 2003	2/62	0/60		1.9 %	4.84 [0.24, 98.80]
Bolton-Smith 2007	2/62	0/61		1.9 %	4.92 [0.24, 100.43]
Brazier 2005	22/95	21/97		13.2 %	1.07 [0.63, 1.81]
Burleigh 2007	4/101	3/104		5.9 %	1.37 [0.32, 5.98]
Chapuy 1992	40/1634	28/1636		13.7 %	1.43 [0.89, 2.31]
Chapuy 2002	24/389	16/194		12.5 %	0.75 [0.41, 1.37]
Cherniack 2011	1/23	0/23		1.8 %	3.00 [0.13, 70.02]
Daly 2008	5/85	0/82		2.1 %	10.62 [0.60, 188.99]
Dawson-Hughes 1997	4/187	2/202		4.9 %	2.16 [0.40, 11.66]
Gallagher 2001	23/123	22/123		13.2 %	1.05 [0.62, 1.77]
Krieg 1999	6/124	0/124		2.1 %	13.00 [0.74, 228.31]
Kärkkäinen 2010	64/1718	0/1714		2.2 %	128.70 [7.97, 2078.10]
Moschonis 2006	0/42	4/70		2.1 %	0.18 [0.01, 3.32]
Prince 2008	16/151	18/151		12.2 %	0.89 [0.47, 1.68]
Witham 2010	3/53	4/52		6.0 %	0.74 [0.17, 3.13]
Subtotal (95% CI)	**4929**	**4773**		**100.0 %**	**1.36 [0.87, 2.13]**
Total events: 218 (Vitamin D), 120 (Control)					
Heterogeneity: Tau² = 0.32; Chi² = 34.82, df = 15 (P = 0.003); I² =57%					
Test for overall effect: Z = 1.36 (P = 0.17)					
9 Psychiatric disorders					
Gallagher 2001	7/123	4/123		62.3 %	1.75 [0.53, 5.83]
Krieg 1999	3/124	2/124		28.7 %	1.50 [0.26, 8.82]
Ott 1989	0/43	1/43		9.0 %	0.33 [0.01, 7.96]
Subtotal (95% CI)	**290**	**290**		**100.0 %**	**1.44 [0.56, 3.73]**
Total events: 10 (Vitamin D), 7 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.92, df = 2 (P = 0.63); I² =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 = 0.76 (P = 0.45)					
10 Skin disorders					
Dukas 2004	37/192	34/186		60.8 %	1.05 [0.69, 1.60]
Kärkkäinen 2010	9/1718	0/1714		39.2 %	18.96 [1.10, 325.43]
Subtotal (95% CI)	**1910**	**1900**		**100.0 %**	**3.27 [0.17, 62.47]**
Total events: 46 (Vitamin D), 34 (Control)					
Heterogeneity: Tau^2 = 3.68; Chi^2 = 4.42, df = 1 (P = 0.04); I^2 =77%					
Test for overall effect: Z = 0.79 (P = 0.43)					
11 Cancer					
Avenell 2012	369/2649	354/2643		19.8 %	1.04 [0.91, 1.19]
Bolton-Smith 2007	1/62	0/61		0.0 %	2.95 [0.12, 71.09]
Daly 2008	4/85	3/82		0.2 %	1.29 [0.30, 5.57]
Gallagher 2001	6/123	5/123		0.3 %	1.20 [0.38, 3.83]
Glendenning 2012	19/353	15/333		0.8 %	1.19 [0.62, 2.31]
Grady 1991	1/50	0/48		0.0 %	2.88 [0.12, 69.07]
Jackson 2006	1306/18176	1333/18106		67.4 %	0.98 [0.91, 1.05]
Janssen 2010	0/36	1/34		0.0 %	0.32 [0.01, 7.48]
Komulainen 1999	2/116	3/116		0.1 %	0.67 [0.11, 3.92]
Lappe 2007	13/446	37/733		0.9 %	0.58 [0.31, 1.07]
Ott 1989	1/43	0/43		0.0 %	3.00 [0.13, 71.65]
Prince 2008	1/151	5/151		0.1 %	0.20 [0.02, 1.69]
Sanders 2010	7/1131	10/1127		0.4 %	0.70 [0.27, 1.83]
Trivedi 2003	188/1345	173/1341		9.9 %	1.08 [0.89, 1.31]
Subtotal (95% CI)	**24766**	**24941**		**100.0 %**	**0.99 [0.94, 1.06]**
Total events: 1918 (Vitamin D), 1939 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 9.64, df = 13 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 0.19 (P = 0.85)					

ADDITIONAL TABLES

Table 1. Characteristics of included trials (I)

Characteristic Study ID	Design	Arms	Bias risk	Blinding	Participants [N]	Women [%]	Mean age [years]
Aloia 2005	Parallel	2	Low	PL	208	100	60
Avenell 2004	2 × 2	4	High	NI	134	83	77
Avenell 2012	2 × 2	4	Low	PL	5292	85	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	2 × 2	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
Brohult 1973	Parallel	2	High	PL	50	68	52
Burleigh 2007	Parallel	2	Low	PL	205	59	83
Campbell 2005	2 × 2	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
Cherniack 2011	Parallel	2	High	PL	46	2	80
Cooper 2003	Parallel	2	Low	PL	187	100	56
Corless 1985	Parallel	2	High	PL	65	78	82.4

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

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	2 × 2	4	Low	PL	489	100	71.5
Glendenning 2012	Parallel	2	Low	PL	686	100	76.7
Grady 1991	Parallel	2	High	PL	98	54	79.1
Grimnes 2011	Parallel	2	Low	PL	104	49	52
Harwood 2004	Parallel	4	High	NI	150	100	81.2
Jackson 2006	Parallel	2	Low	PL	36,282	100	62.4
Janssen 2010	Parallel	2	Low	PL	70	100	80.8
Komulainen 1999	2 × 2	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	2 × 2	4	High	NI	9605	60	75
Latham 2003	2 × 2	4	Low	PL	243	53	79.5
Law 2006	Parallel	2	High	NI	3717	76	85
Lehouck 2012	Parallel	2	Low	PL	181	20	68
Lips 1996	Parallel	2	Low	PL	2578	74	80

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

Lips 2010	Parallel	2	Low	PL	226	NR	78
Lyons 2007	Parallel	2	Low	PL	3440	76	84
Meier 2004	Parallel	2	High	NI	55	65	56.5
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; NR: not reported; PL: placebo

Table 2. Characteristics of included trials (II)

Characteristic Study ID	Participants	Outcome Measures	Country	Sponsor
Aloia 2005	Black postmenopausal African-American women	Bone mineral density	USA	No
Avenell 2004	Elderly people with an osteoporotic fracture within the past 10 years	Recruitment, compliance and retention within a randomised trial	UK	Yes
Avenell 2012	Elderly people with low-trauma osteoporotic fracture in the previous 10 years	Fractures	UK	Yes
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 non-osteoporotic women	Bone mineral density	UK	Yes
Brazier 2005	Elderly vitamin D-insufficient women	Bone mineral density	France	Yes
Broe 2007	Nursing home residents	Falls	USA	Yes
Brohult 1973	Patients with rheumatoid arthritis	Objective and subjective improvement	Sweden	Yes
Burleigh 2007	Older geriatric inpatients	Falls	UK	Yes
Campbell 2005	Elderly people with visual impairment	Numbers of falls and injuries resulting from falls	New Zealand	No
Chapuy 1992	Healthy ambulatory women	Fractures	France	Yes
Chapuy 2002	Elderly people living in institutional care	Biochemical variables of calcium homeostasis,	France	Yes

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

		femoral neck bone mineral density and hip fracture risk		
Chel 2008	Nursing home residents	Vitamin D status	Netherlands	Yes
Cherniack 2011	Elderly people	Vitamin D status	USA	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	UK	Yes
Daly 2008	Healthy ambulatory men	Bone mineral density	Australia	Yes
Dawson-Hughes 1997	Healthy ambulatory participants	Bone mineral density	USA	Yes
Dukas 2004	Elderly people	Falls	Switzerland	Yes
Flicker 2005	Elderly people living in institutional care	Falls and fractures	Australia	No
Gallagher 2001	Elderly women	Bone mineral density	USA	No
Glendenning 2012	Elderly community-dwelling ambulatory women	Falls, muscular strength and mobility	Australia	No
Grady 1991	Elderly people	Muscle strength	USA	Yes
Grimnes 2011	Healthy people with a low vitamin D status	Insulin sensitivity and secretion	Norway	No
Harwood 2004	Elderly women following surgery for hip fracture	Bone mineral density, falls and fractures	UK	Yes
Jackson 2006	Postmenopausal women	Fractures	USA	Yes
Janssen 2010	Elderly vitamin D-insufficient women	Muscle strength, power and functional mobility	Netherlands	Yes
Komulainen 1999	Postmenopausal women	Bone mineral density	Finland	Yes
Krieg 1999	Elderly institutionalised women	Bone mineral density	Switzerland	Yes

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

Kärkkäinen 2010	Postmenopausal women	Falls	Finland	Yes
Lappe 2007	Healthy postmenopausal white women	Fractures	USA	Yes
Larsen 2004	Older community-dwelling residents	Falls	Denmark	Yes
Latham 2003	Frail elderly people	Self-rated physical health and falls	New Zealand	No
Law 2006	Nursing home residents	Falls and fractures	UK	No
Lehouck 2012	Patients with chronic obstructive pulmonary disease	Time to first exacerbation	Belgium	Yes
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	UK	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	USA	Yes
Porthouse 2005	Elderly women with one or more risk factors for hip fracture	Fractures	UK	Yes
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

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

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	UK	No
Trivedi 2003	Elderly people	Mortality, fractures	UK	No
Witham 2010	Patients with systolic heart failure	Exercise capacity	UK	No
Zhu 2008	Elderly women	Bone mineral density	Australia	No

Table 3. Characteristics of included trials (III)

Characteristic Study ID	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[a]	Daily	Oral	3	3
Avenell 2004	800				1000[b]	Daily	Oral	1	1
Avenell 2012	800				500[b]	Daily	Oral	3.75	6.2
Baeksgaard 1998	560				1000	Daily	Oral	2	2
Bischoff 2003	800				1200[a]	Daily	Oral	0.25	0.25
Bjorkman 2007	400 1200				500[a]	Daily	Oral	0.5	0.5

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

Bolton-Smith 2007	400				1000	Daily	Oral	2	2
Brazier 2005	800				1000	Daily	Oral	1	1
Broe 2007		200 400 600 800				Daily	Oral	0.42	0.42
Brohult 1973	100,000					Daily	Oral	1	1
Burleigh 2007	800				1200[a]	Daily	Oral	0.08	0.08
Campbell 2005	50,000 100,000					Monthly	Oral	1	1
Chapuy 1992	800				1200	Daily	Oral	1.5	4
Chapuy 2002	800				1200	Daily	Oral	2	2
Chel 2008	600 4200 18.000				800 1600	Daily Weekly Monthly	Oral	0.33	0.33
Cherniack 2011	2000				1200[a]	Daily	Oral	0.5	0.5
Cooper 2003		10,000			1000[a]	Weekly	Oral	2	2
Corless 1985		9000				Daily	Oral	0.75	0.75
Daly 2008	800				1000	Daily	Oral	2	3.5
Dawson-Hughes 1997	700				500	Daily	Oral	3	3
Dukas 2004			1			Daily	Oral	0.75	0.75

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

Flicker 2005		1000 10,000			600[a]	Daily Weekly	Oral	2	2
Gallagher 2001				0.5		Daily	Oral	3	5
Glendenning 2012	150,000					Three-monthly	Oral	0.5	0.75
Grady 1991				0.5		Daily	Oral	0.5	0.5
Grimnes 2011	20,000					Twice weekly	Oral	0.5	0.5
Harwood 2004	800	300,000			1000	Single dose daily	Intramuscular Oral	1	1
Jackson 2006	400				1000	Daily	Oral	7	7
Janssen 2010	400				500[a]	Daily	Oral	0.5	0.5
Komulainen 1999	300				500	Daily	Oral	5	5
Krieg 1999	880				1000	Daily	Oral	2	2
Kärkkäinen 2010	800				1000	Daily	Oral	3	3
Lappe 2007	1000				1400-1500[b]	Daily	Oral	4	4
Larsen 2004	400				1000	Daily	Oral	3.5	3.5
Latham 2003	300,000					Single dose	Oral	0.003	0.5
Law 2006		100,000				Four-monthly	Oral	0.83	0.83

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

Lehouck 2012	100,000					Monthly	Oral	1	1
Lips 1996	400					Daily	Oral	3.5	3.5
Lips 2010	8400				500[a]	weekly	Oral	0.31	0.31
Lyons 2007		100,000				Four-monthly	Oral	3	3
Meier 2004	500				500	Daily	Oral	0.5	1
Mochonis 2006	300				1200[b]	Daily	Oral	1	1
Ooms 1995	400					Daily	Oral	2	2
Ott 1989				0.5 2	1000[a]	Daily	Oral	2	2
Porthouse 2005	800				1000	Daily	Oral	2	2
Prince 2008		1000			1000[a]	Daily	Oral	1	1
Sanders 2010	500,000					Yearly	Oral	2.96	2.96
Sato 1997			1		300[a]	Daily	Oral	0.5	0.5
Sato 1999a			1			Daily	Oral	1.5	1.5
Sato 1999b			1			Daily	Oral	1	1
Sato 2005a		1000				Daily	Oral	2	2
Schleithoff 2006	2000				500[a]	Daily	Oral	0.75	1.25
Smith 2007		300,000				Yearly	Intramuscular	3	3

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

Trivedi 2003	100,000					Four-monthly	Oral	5	5
Witham 2010		100,000				10-weekly	Oral	0.38	0.38
Zhu 2008		1000			1200[b]	Daily	Oral	5	5

[a] Equal dose of calcium was administered to a control group
[b] 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; IU: international units; µg: microgram

Table 4. Overview of study populations

Characteristic Study ID	Intervention(s) and control(s)	[N] screened / eligible	[N] randomised	[N] ITT	[N] finishing study	[%] of randomised participants finishing study
1. Aloia 2005	I: vitamin D_3 plus calcium	322	104	104	74	71
	C: placebo		104	104	74	71
total:			208	208	148	71
2. Avenell 2004	I: vitamin D_3	180	70	70	-	-
	C: no intervention		64	64	-	-
total:			134	134	-	-
3. Avenell 2012	I: vitamin D_3	15,024	2649	2649	1813	68
	C: matched placebo tablets		2643	2643	1762	67
total:			5292	5292	3575	68
4. Baeksgaard 1998	I: vitamin D_3 plus calcium	-	80	80	65	81
	C: matched placebo tablets		80	80	64	80

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

total:			160	160	129	80
5. Bischoff 2003	I: vitamin D_3 plus calcium	130	62	62	-	-
	C: calcium		60	60	-	-
total:			122	122	89	73
6. Bjorkman 2007	I: vitamin D_3 plus calcium	1215	150	150	123	82
	C: calcium		68	68	59	87
total:			218	218	182	83
7. Bolton-Smith 2007	I: vitamin D_3 plus calcium	-	62	62	50	81
	C: matched placebo		61	61	56	92
total:			123	123	106	86
8. Brazier 2005	I: vitamin D_3 plus calcium	360	95	95	74	78
	C: matched placebo tablets		97	97	68	70
total:			192	192	142	74
9. Broe 2007	I: vitamin D_2	126	99	99	96	97
	C: matched placebo tablets		25	25	25	100
total:			124	124	121	98
10. Brohult 1973	I: vitamin D_3	-	25	25	24	96
	C: placebo		25	25	25	100
total:			50	50	49	98
11. Burleigh 2007	I: vitamin D_3 plus calcium	515	101	101	98	97
	C: placebo		104	104	101	97

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

total:			205	205	199	97
12. Campbell 2005	I: home safety assessment and modification programme	391	195	195	177	91
	C: social visits		196	196	184	94
total:			391	391	361	92
13. Chapuy 1992	I: vitamin D_3 plus calcium	-	1634	1634	1590	97
	C: double placebo		1636	1636	1573	96
total:			3270	3270	3163	96
14. Chapuy 2002	I: vitamin D_3 plus calcium	639	393	393	-	-
	C: double placebo		190	190	-	-
total:			583	583	-	-
15. Chel 2008	I: vitamin D_3	1006	166	166	139	84
	C: matched placebo tablets		172	172	137	80
total:			338	338	276	82
16. Cherniack 2011	I: vitamin D_3 plus calcium	52	23	23	17	74
	C: matched placebo plus calcium		23	23	17	74
total:			46	46	34	74
17. Cooper 2003	I: vitamin D_2 plus calcium	-	93	93	73	78
	C: calcium		94	94	80	85
total:			187	187	153	82

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

18. Coreless 1985	I: vitamin D_2	320	32	32	8	25
	C: placebo		33	33	17	51
total:			65	65	25	38
19. Daly 2006	I: calcium-vitamin D_3-fortified milk plus calcium	422	85	85	76	89
	C: no intervention		82	82	73	89
total:			167	167	149	89
20. Dawson-Hughes 1997	I: vitamin D_3 plus calcium	545	187	187	148	79
	C: placebo		202	202	170	84
total:			389	389	318	82
21. Dukas 2004	I: alfacalcidol	410	192	192	-	-
	C: placebo		186	186	-	-
total:			378	378	-	-
22. Flicker 2005	I: vitamin D_3 plus calcium	1767	313	313	269	86
	C: calcium		312	312	271	87
total:			625	625	540	86
23. Gallagher 2001	I: calcitriol	1905	123	123	101	82
	C: matched placebo		123	123	112	91
total:			246	246	213	87
24. Glendenning 2012	I: cholecalciferol 150,000 three-monthly	2110	353	353	331	94
	C: placebo vitamin D		333	333	307	92

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

total:			686	686	638	93
25. Grady 1991	I: calcitriol	98	50	50	49	98
	C: placebo vitamin D		48	48	47	98
total:			98	98	96	98
26. Grimnes 2011	I: vitamin D_3	108	51	51	49	96
	C: placebo		53	53	45	85
total:			104	104	94	90
27. Harwood 004	I: vitamin D plus calcium	208	113	113	-	-
	C: no intervention		37	37	-	-
total:			150	150	-	-
28. Jackson 2006	I: vitamin D_3 plus calcium	68,132	18,176	18,176	16,936	93
	C: matched placebo		18,106	18,106	16,815	93
total:			36,282	36,282	33,751	93
29. Janssen 2010	I: vitamin D_3 plus calcium	91	36	36	18	50
	C: matched placebo vitamin D_3 plus calcium		34	34	31	91
total:			70	70	49	70
30. Komulainen 1999	I: oestradiol valerate and cyproterone acetate	13,100	116	116	-	-
	C: placebo		116	116	-	-
total:			232	232	-	-

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

31. Krieg 1999	I: vitamin D_3 plus calcium	-	124	124	50	40
	C: no treatment		124	124	53	43
total:			248	248	103	41
32. Kärkkäinen 2010	I: vitamin D_3 plus calcium	5407	1718	1718	1566	91
	C: no treatment		1714	1714	1573	92
total:			3432	3432	3139	91
33. Lappe 2007	I: vitamin D_3 plus calcium	1180	446	446	-	-
	C: calcium plus placebo tablets		733	733	-	-
total:			1179	1179	-	-
34. Larsen 2004	I: home safety inspection, vitamin D_3 plus calcium	62,000	4957	4957	-	-
	C: no intervention		4648	4648	-	-
total:			9605	9605	-	-
35. Latham 2003	I: vitamin D_3	3,028	121	121	108	89
	C: matched placebo tablets		122	122	114	93
total:			243	243	222	91
36. Law 2006	I: vitamin D_2	-	1762	1762	1366	77
	C: no intervention		1955	1955	1569	80
total:			3717	3717	2935	79
37. Lehouck 2012	I: vitamin D_3	419	91	91	72	79

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

	C: matched placebo		91	91	78	86
total:			182	182	150	82
38. Lips 1996	I: vitamin D_3	-	1291	1291	1061	82
	C: matched placebo		1287	1287	1029	80
total:			2578	2578	2090	81
39. Lips 2010	I: vitamin D_3	593	114	114	105	92
	C: matched placebo		112	112	97	87
total:			226	226	202	89
40. Lyons 2007	I: vitamin D_2	5745	1725	1725	778	45
	C: matched placebo tablets		1715	1715	762	44
total:			3440	3440	1540	44
41. Meier 2004	I: vitamin D_3	-	30	30	27	90
	C: no intervention		25	25	16	64
total:			55	55	43	78
42. Mochonis 2006	I: vitamin D_3 plus calcium	-	72	72	65	90
	C: no intervention		40	40	36	90
total:			112	112	101	90
43. Ooms 1995	I: vitamin D_3	-	177	177	126	71
	C: matched placebo		171	171	118	69
total:			348	348	244	70

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

44. Ott 1989	I: vitamin D_3 plus calcium	-	43	43	39	91
	C: matched placebo vitamin D plus calcium		43	43	37	86
total:			86	86	76	88
45. Porthouse 2005	I: vitamin D_3 plus calcium	11,022	1321	1321	1212	92
	C: no intervention		1993	1993	1862	93
total:			3454	3454	3074	92
46. Prince 2008	I: vitamin D_2 plus calcium	827	151	151	144	95
	C: matched placebo tablets of vitamin D plus calcium		151	151	145	96
total:			302	302	289	95
47. Sanders 2010	I: vitamin D_3	7204	1131	1131	1015	90
	C: matched placebo tablets		1127	1127	1017	90
total:			2258	2258	1032	90
48. Sato 1997	I: vitamin D (alfacalcidol) plus calcium	-	45	45	30	67
	C: matched placebo tablets of vitamin D and calcium		39	39	34	87
total:			84	84	64	76
49. Sato 1999a	I: vitamin D (alfacalcidol)	-	43	43	40	93

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

	C: matched placebo tablets of vitamin D		43	43	40	93
total:			86	86	80	93
50. Sato 1999b	I: vitamin D (alfacalcidol)	-	34	34	32	94
	C: matched placebo tablet of vitamin D		35	35	32	91
total:			69	69	64	93
51. Sato 2005a	I: vitamin D_2	-	48	48	43	90
	C: matched placebo tablets of vitamin D		48	48	42	87
total:			96	96	85	88
52. Schleithoff 2006	I: vitamin D_3 plus calcium	-	61	61	42	69
	C: matched placebo vitamin D plus calcium		62	62	51	82
total:			103	103	93	90
53. Smith 2007	I: vitamin D_2	13,487	4727	4727	2304	49
	C: matched placebo intramuscular injection		4713	4713	2266	48
total:			9440	9440	4570	48
54. Trivedi 2003	I: vitamin D_3	-	1345	1345	1262	94
	C: matched placebo vitamin D		1341	1341	1264	94

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

total:			2696	2696	2526	94
55. Witham 2010	I: vitamin D_2	173	53	53	48	91
	C: matched placebo tablets		52	52	48	91
total:			105	105	96	91
56. Zhu 2008	I: vitamin D_2 plus calcium	-	39	39	33	85
	C: matched placebo vitamin D and calcium		81	81	74	91
total:			120	120	107	89
Grand total	***All interventions***		***47,472***		***45,351***	
	All controls		***47,814***		***45,278***	
	All interventions and controls		***95,286***		***90,629[a]***	

"-" denotes not reported
[a]Numbers not available for all studies
C: control; I: intervention; ITT: intention-to-treat

APPENDICES

Appendix 1. Search strategies

Search terms for various databases
Unless otherwise stated, search terms are free-text terms. Abbreviations: '$': stands for any character; '?': substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp: exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word

(*Continued*)

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
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 cholecalciferol* 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/

(*Continued*)

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.
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.

(*Continued*)

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. 31. or/24-30 32. (comment or editorial or historical-article).pt. 33. 31 not 32 34. 23 or 33 35. 10 and 13 and 34 36. 10 and 17 and 34 37. 35 or 36 38. limit 37 to human
LILACS
1. Vitamin D 2. Cholecalciferol 3. Ergocalciferol 4. Alfacalcidol 5. Calcitriol
ISI Web of Science
1. TS=(vitamin d2 OR vitamin d 2 OR hydroxyvitamin* OR cholecalciferol* OR calciferol* OR calcitriol* OR calcifediol* OR dihydrotachysterol* OR alfacalcidol* OR alphacalcidol* OR colecalciferol*) 2. TS=(mortalit* OR prevent* OR cancer* OR neoplasm* OR tumor* OR tumour*) 3. #2 AND #1 4. TS=(random* OR blind* OR placebo* OR meta-analys*) 5. #4 AND #3

Appendix 2. Description of interventions

Characteristic **Study ID**	**Intervention(s)** **[route, frequency, total dose/day]**	**Control(s)** **[route, frequency, total dose/day]**
Aloia 2005	Vitamin D_3 (800 IU) plus calcium (1200 to 1500 mg) orally, daily	Matched placebo tablets plus calcium (1200 to 1500 mg) orally, daily
Avenell 2004	Vitamin D_3 (800 IU) orally, daily	No intervention
	Calcium (1000 mg) orally, daily	
	Vitamin D_3 (800 IU) plus calcium (1000 mg) orally, daily	

(*Continued*)

Avenell 2012	Vitamin D_3 (800 IU) orally, daily	Matched placebo tablets orally, daily
	Calcium (1000 mg) orally, daily	
	Vitamin D_3 (800 IU) plus calcium (1000 mg) orally, daily	
Baeksgaard 1998	Vitamin D_3 (560 IU) plus calcium (1000 mg) orally, daily	Matched placebo tablets orally, daily
	Vitamin D_3 (560 IU) plus calcium (1000 mg) plus multivitamin orally, daily	
Bischoff 2003	Vitamin D_3 (800 IU) plus calcium 1200 mg orally, daily	Calcium 1200 mg orally, daily
Bjorkman 2007	Vitamin D_3 (1200 IU) plus calcium (500 mg) orally, daily	Calcium (500 mg) orally, daily
	Vitamin D_3 (400 IU) plus calcium (500 mg) orally, daily	
Bolton-Smith 2007	Vitamin D_3 (400 IU) plus calcium 1000 mg orally, daily	Matched placebo orally, daily
	Vitamin D_3 (400 IU) plus calcium 1000 mg plus vitamin K_1 200 μg orally, daily	
	Vitamin K_1 200 μg orally, daily	
Brazier 2005	Vitamin D_3 (800 IU) plus calcium (1000 mg) orally, daily	Matched placebo tablets orally, daily
Broe 2007	Vitamin D_2 (800 IU) orally, daily	Matched placebo tablets orally, daily
	Vitamin D_2 (600 IU) orally, daily	
	Vitamin D_2 (400 IU) orally, daily	
	Vitamin D_2 (200 IU) orally, daily	
Brohult 1973	Vitamin D_3 (100,000 IU) daily	Placebo daily
Burleigh 2007	Vitamin D_3 (800 IU) plus calcium (1200 mg) orally, daily	Calcium (1200 mg) orally, daily
Campbell 2005	Home safety assessment and modification programme	Social visits

(*Continued*)

	Exercise programme plus vitamin D_3 100,000 IU initially and then 50,000 IU orally, monthly	
	Both interventions	
Chapuy 1992	Vitamin D_3 (800 IU) plus calcium (1200 mg) orally, daily	Double placebo orally, daily
Chapuy 2002	Vitamin D_3 (800 IU) plus calcium (1200 mg) (fixed combination) orally, daily	Double placebo orally, daily
	Vitamin D_3 (800 IU) plus calcium (1200 mg), (separate combination) orally, daily	
Chel 2008	Vitamin D_3 (600 IU) orally, daily	Matched placebo tablets orally, daily
	Vitamin D_3 (4200 IU) orally, weekly	Matched placebo tablets orally, weekly
	Vitamin D_3 (18,000 IU) orally, monthly	Matched placebo powder orally, monthly
Cherniack 2011	Vitamin D_3 2000 IU plus calcium 1200 mg orally, daily	Matched placebo plus calcium 1200 mg orally, daily
Cooper 2003	Vitamin D_2 (10,000 IU) orally, weekly plus calcium (1000 mg) orally, daily	Calcium (1000 mg) orally, daily
Coreless 1985	Vitamin D_2 (9000 IU) orally, daily	Placebo orally, daily
Daly 2006	Calcium-vitamin D_3-fortified milk containing vitamin D_3 (800 IU) plus calcium (1000 mg) daily	No intervention
Dawson-Hughes 1997	Vitamin D_3 (700 IU) plus calcium (500 mg) orally, daily	Double placebo orally, daily
Dukas 2004	Alfacalcidol (1 μg) orally, daily	Placebo orally, daily
Flicker 2005	Vitamin D_3 (10,000 IU) weekly and thereafter vitamin $D_3$1000 IU daily plus calcium (600 mg) orally, daily	Calcium (600 mg) orally, daily
Gallagher 2001	Calcitriol (0.5 μg) daily	Matched placebo pills orally, daily
	Conjugated oestrogens 0.625 mg/daily plus medroxyprogesterone acetate 2.5 mg orally, daily	
	Calcitriol (0.5 μg daily) plus conjugated oestrogens 0.625 mg/daily plus medroxyprogesterone acetate 2.5 mg orally, daily	

(*Continued*)

Glendenning 2012	Cholecalciferol 150,000 three-monthly	Placebo vitamin D three-monthly
Grady 1991	Calcitriol (0.5 μg) orally, daily	Placebo vitamin D orally, daily
Grimnes 2011	Vitamin D_3 (20,000 IU) orally, twice weekly	Placebo orally, twice weekly.
Harwood 2004	Single injection of 300,000 IU of vitamin D_2	No intervention
	Single injection of 300,000 IU of vitamin D_2 plus oral calcium (1000 mg) daily	
	Oral vitamin D_3 (800 IU) plus calcium (1000 mg) daily	
Jackson 2006	Vitamin D_3 (400 IU) plus calcium (1000 mg) orally, daily	Matched placebo orally, daily
Janssen 2010	Vitamin D_3 (400 IU) plus calcium (500 mg) orally, daily	Matched placebo vitamin D_3 plus calcium (500 mg) orally, daily
Komulainen 1999	Sequential combination of 2 mg oestradiol valerate (days 1 to 21) and 1 mg cyproterone acetate (days 12 to 21) and a treatment-free interval (days 22 to 28)	Placebo
	Vitamin D_3 (300 IU) plus calcium (500 mg) daily [a]	
	Sequential combination of 2 mg oestradiol valerate (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) orally, daily	
Krieg 1999	Vitamin D_3 (880 IU) plus calcium (1000 mg) orally, daily	No treatment
Kärkkäinen 2010	Vitamin D_3 800 IU plus calcium 1000 mg orally, daily	No intervention
Lappe 2007	Vitamin D_3 (1000 IU) plus calcium (1400 to 1500 mg) orally, daily	Double placebo tablets, orally, daily
	Calcium (1400 to 1500 mg) plus a vitamin D placebo orally, daily	
Larsen 2004	Home safety inspection	No intervention

(*Continued*)

	Vitamin D_3 (400 IU) plus calcium (1000 mg) orally, daily	
	Both interventions	
Latham 2003	Resistance exercise	Matched placebo tablets, orally
	Attention control	
	Vitamin D_3 (300,000 IU) single dose, orally	
Law 2006	Vitamin D_2 100,000 IU every three months, orally	No intervention
Lehouck 2012	Vitamin D_3 100,000 IU monthly, orally	Matched placebo orally, monthly
Lips 1996	Vitamin D_3 400 IU orally, daily	Matched placebo orally, daily
Lips 2010	Vitamin D_3 8400 IU orally, weekly	Matched placebo orally, weekly.
Lyons 2007	Vitamin D_2 100,000 IU four-monthly, orally	Matched placebo tablets four-monthly, orally
Meier 2004	Vitamin D_3 (500 IU) orally, daily	No intervention
Mochonis 2006	Vitamin D_3 300 IU plus calcium 1200 mg orally, daily	No intervention
	Calcium 1200 mg, orally, daily	
Ooms 1995	Vitamin D_3 400 IU orally, daily	Matched placebo orally, daily
Ott 1989	Vitamin D_3 17.2 IU plus calcium 1000 mg	Matched placebo vitamin D plus calcium 1000 mg orally, daily
Porthouse 2005	Vitamin D_3 (800 IU) plus calcium (1000 mg), orally, daily	No intervention[b]
Prince 2008	Vitamin D_2 1000 IU plus calcium 1000 mg orally, daily	Matched placebo tablets of vitamin D plus calcium 1000 mg orally, daily
Sanders 2010	Vitamin D_3 500,000 IU orally, yearly	Matched placebo tablets of vitamin D orally, yearly
Sato 1997	Vitamin D (alfacalcidol) (1 μg) plus calcium 300 mg orally, daily	Matched placebo tablets of vitamin D and calcium orally, daily
Sato 1999a	Vitamin D (alfacalcidol) (1 μg) orally, daily	Matched placebo tablets of vitamin D orally, daily
Sato 1999b	Vitamin D (alfacalcidol) (1 μg) orally, daily	No treatment

(*Continued*)

	Ipriflavone 600 mg orally, daily	
Sato 2005a	Vitamin D_2 (1000 IU) orally, daily	Matched placebo tablets of vitamin D daily
Schleithoff 2006	Vitamin D_3 2000 IU plus calcium 500 mg orally, daily	Matched placebo vitamin D plus calcium 500 mg orally, daily
Smith 2007	Vitamin D_2 300,000 IU intramuscular injection, yearly	Matched placebo intramuscular injection yearly
Trivedi 2003	Vitamin D_3 100,000 IU every four months orally	Matched placebo vitamin D every four months orally
Witham 2010	Vitamin D_2 (10,000 IU) orally, daily	Matched placebo tablets orally, daily
Zhu 2008	Vitamin D_2 (1000 IU) plus calcium (1200 mg) orally, daily	Matched placebo vitamin D and placebo calcium orally, daily
	Calcium 1200 mg plus placebo vitamin D orally, daily	

Footnotes
[a] No intake during June to August; the vitamin D_3 dosage was lowered to 100 IU/d after four years of treatment
[b] Information leaflet on dietary calcium intake and prevention of falls

Appendix 3. Baseline characteristics (I)

Characteristic Study ID	Duration of interv ention [years]	Duration of follow-up [years]	Participating population	Country	Setting	Ethnic groups
Aloia 2005	3	3	Postmenopausal African-American women	USA	Outpatients	All black
Avenell 2004	1	1	Elderly people with an osteoporotic fracture within the past 10 years	UK	Outpatients	-
Avenell 2012	3.75	6.2	Elderly people with low-	UK	Outpatients	-

(*Continued*)

			trauma, osteoporotic fracture in the previous 10 years			
Baeksgaard 1998	2	2	Postmenopausal women	Demark	Outpatients	-
Bischoff 2003	0.25	0.25	Elderly women living in institutional care	Switzerland	Inpatients	-
Bjorkman 2007	0.5	0.5	Chronically bedridden patients	Finland	-	-
Bolton-Smith 2007	2	2	Elderly non-osteoporotic women	UK	Outpatients	-
Brazier 2005	1	1	Elderly vitamin D-insufficient women	France	Outpatients	-
Broe 2007	0.42	0.42	Nursing home residents	USA	Inpatients	-
Brohult 1973	1	1	Patients with rheumatoid arthritis	Sweden	Outpatients	-
Burleigh 2007	0.08	0.08	Elderly people	UK	Inpatients	-
Campbell 2005	1	1	Elderly people with visual impairment	New Zealand	Outpatients	-
Chapuy 1992	1.5	4	Healthy ambulatory women	France	Outpatients	-
Chapuy 2002	2	2	Elderly people living in institutional care	France	Outpatients	-
Chel 2008	0.33	0.33	Nursing home residents	Netherlands	Inpatients	-
Cherniack 2011	0.5	0.5	Elderly people	USA	Outpatients	-

(*Continued*)

Cooper 2003	2	2	Postmenopausal women	Australia	Outpatients	All white
Coreless 1985	0.75	0.75	Elderly patients from geriatric wards	UK	Inpatients	-
Daly 2006	2	3.5	Healthy ambulatory men	Australia	Outpatients	-
Dawson-Hughes 1997	3	3	Healthy ambulatory participants	USA	Outpatients	-
Dukas 2004	0.75	0.75	Elderly people	Switzerland	Outpatients	-
Flicker 2005	2	2	Elderly people living in institutional care	Australia	Inpatients	-
Gallagher 2001	3	5	Elderly women	USA	Outpatients	-
Grady 1991	0.5	0.5	Elderly people	USA	Outpatients	-
Glendenning 2012	0.5	0.75	Elderly women	Australia	Outpatients	-
Grimnes 2011	0.5	0.5	Healthy people with low vitamin D status	Norway	Outpatients	-
Harwood 004	1	1	Elderly women	UK	Outpatients	-
Jackson 2006	7	7	Postmenopausal women	USA	Outpatients	-
Janssen 2010	1	1	Elderly vitamin D-insufficient women	Netherlands	Outpatients	-
Komulainen 1999	5	5	Postmenopausal women	Finland	Outpatients	-
Krieg 1999	2	2	Elderly institutionalised women	Switzerland	Outpatients	-
Kärkkäinen 2010	3	3	Postmenopausal women	Finland	Outpatients	-

(*Continued*)

Lappe 2007	4	4	Postmenopausal women	USA	Outpatients	All white
Larsen 2004	3.5	3.5	Elderly people	Denmark	Outpatients	-
Latham 2003	0.003	0.5	Elderly people	New Zealand	Outpatients	-
Law 2006	0.83	0.83	Elderly people	UK	Inpatients	-
Lehouck 2012	1	1	Patients with chronic obstructive pulmonary disease	Belgium	Outpatients	-
Lips 1996	3.5	3.5	Elderly people	Netherlands	Outpatients	-
Lips 2010	0.31	0.31	Elderly people with vitamin D insufficiency	Netherlands	Outpatients	-
Lyons 2007	3	3	Elderly people living in institutional care	UK	Inpatients	-
Meier 2004	0.5	1	Healthy volunteers	Germany	Outpatients	-
Mochonis 2006	1	1	Postmenopausal women	Greece	Outpatients	-
Ooms 1995	2	2	Elderly people	Netherlands	Outpatients	-
Ott 1989	2	2	Postmenopausal women	USA	Outpatients	-
Porthouse 2005	2	2	Elderly women	UK	Outpatients	-
Prince 2008	1	1	Elderly women with vitamin D insufficiency	Australia	Outpatients	-
Sanders 2010	2.96	2.96	Elderly women	Australia	Outpatients	-
Sato 1997	0.5	0.5	Patients with hemiplegia after stroke	Japan	Outpatients	-

(*Continued*)

Sato 1999a	1.5	1.5	Elderly patients with Parkinson's disease	Japan	Outpatients	-
Sato 1999b	1	1	Patients with hemiplegia after stroke	Japan	Outpatients	-
Sato 2005a	2	2	Elderly women with hemiplegia after stroke	Japan	Outpatients	-
Schleithoff 2006	0.75	1.25	Patients with congestive heart failure	Germany	Inpatients	-
Smith 2007	3	3	Elderly people	UK	Outpatients	-
Trivedi 2003	5	5	Elderly people	UK	Outpatients	-
Witham 2010	0.38	0.38	Patients with systolic heart failure	UK	Outpatients	-
Zhu 2008	5	5	Elderly women	Australia	Outpatients	-

Footnotes
"-" denotes not reported.

Appendix 4. Baseline characteristics (II)

Characteristic Study ID	Duration of disease [mean years (SD) / range]	Sex [female %]	Age [mean years (SD) / range]	Co-medications/ Co-interventions	Co-morbidities
Aloia 2005	-	100	60 (50 to 75)	-	-
Avenell 2004	-	83	77	-	-
Avenell 2012	-	85	77	-	Low-trauma osteoporotic fracture in the previous 10 years

(*Continued*)

Baeksgaard 1998	-	100	62.5 (58 to 67)	-	-
Bischoff 2003	-	100	85.3	-	-
Bjorkman 2007	-	82	84.5 (65 to 104)	-	-
Bolton-Smith 2007	-	100	68		
Brazier 2005	-	100	74.6	-	-
Broe 2007		73	89		
Brohult 1973	2 (2 to 7)	68	52 (18 to 69)	-	Rheumatoid arthritis
Burleigh 2007	-	59	83	-	-
Campbell 2005	-	68	83.6 (75 to 96)	-	-
Chapuy 1992	-	100	84 (69 to 106)	-	-
Chapuy 2002	-	100	85 (64 to 99)	-	-
Chel 2008	-	77	84	-	-
Cherniack 2011	-	2	80	-	-
Cooper 2003	-	100	56	-	-
Coreless 1985	-	78	82.4	-	-
Daly 2006	-	0	61.9	-	-
Dawson-Hughes 1997		55	71	-	-
Dukas 2004	-	51	71	-	-
Flicker 2005	-	95	83.4	-	-
Gallagher 2001	-	100	71.5	-	-
Glendenning 2012	-	100	76.7	-	-
Grady 1991	-	54	79.1 (70 to 97)	-	-
Grimnes 2011	-	49	52	-	-

(*Continued*)

Harwood 2004	-	100	81.2 (67 to 91)	-	-
Jackson 2006	-	100	62.4 (50 to 79)		
Janssen 2010	-	100	80.8	-	-
Komulainen 1999	-	100	52.7 (47 to 56)	-	-
Krieg 1999	-	100	84.5 (62 to 98)	-	-
Kärkkäinen 2010	-	100	67 (65 to 71)	-	-
Lappe 2007	-	100	66.7	-	-
Larsen 2004	-	60	75 (66 to 103)	-	-
Latham 2003	-	53	85 (64 to 99)	-	-
Law 2006	-	76	85	-	-
Lehouck 2012	-	20	68	-	Chronic obstructive pulmonary disease
Lips 1996	-	74	80 (70 to 97)	-	-
Lips 2010	-	-	78	-	-
Lyons 2007	-	76	84 (62 to 107)	-	-
Meier 2004	-	65	56.5 (33 to 78)	-	-
Mochonis 2006	-	100	60.3 (55 to 65)	-	-
Ooms 1995	-	100	80.3	-	-
Ott 1989	-	100	67.5	-	-
Porthouse 2005	-	100	76.8	-	-
Prince 2008	-	100	77.2 (70 to 90)	-	-
Sanders 2010	-	100	76.0	-	-
Sato 1997	-	45	68.5	-	Hemiplegia after stroke
Sato 1999a	-	78	70.6 (65 to 88)	-	Parkinson's disease

(*Continued*)

Sato 1999b	-	56	70.7	Ipriflavone	Hemiplegia after stroke
Sato 2005a	-	100	74.1	-	Hemiplegia after stroke
Schleithoff 2006	-	17	51 (50 to 63)	-	Congestive heart failure
Smith 2007	-	54	79.1	-	-
Trivedi 2003	-	24	74.7 (65 to 85)	-	-
Witham 2010	-	34	79.7	-	Systolic heart failure
Zhu 2008	-	100	75 (70 to 80)	-	-

Footnotes
"-" denotes not reported
SD: standard deviation

Appendix 5. Matrix of study endpoints

Characteristic Study ID	Primary endpoint(s) [time of measurement]	Secondary endpoint(s) [time of measurement]	Other endpoint(s) [time of measurement]
Aloia 2005	Bone mineral density (6, 12, 18, 24 mo)	-	Overall mortality (24 mo)
Avenell 2004	Recruitment, compliance and retention within a randomised trial (12 mo)	-	Overall mortality (12 mo)
Avenell 2012	Fractures	Overall mortality, vascular disease mortality, cancer mortality and cancer occurrence (3.75, 6.2 yr)	-
Baeksgaard 1998	Bone mineral density (0, 12, 24 mo	Serum calcium, serum phosphate and serum intact parathyroid hormone (0, 24 mo)	Overall mortality (24 mo)
Bischoff 2003	Falls	Musculoskeletal function and bone remodeling (3 mo)	Overall mortality (3 mo)

(*Continued*)

Bjorkman 2007	Parathyroid function and bone mineral density (0, 6 mo)	-	Overall mortality (6 mo)
Bolton-Smith 2007	Bone mineral density (6, 12, 18, 24 mo)	Markers of bone turnover and vitamin status (0, 24 mo)	Overall mortality (24 mo)
Brazier 2005	Bone mineral density (0, 12 mo)	Clinical and laboratory safety of treatment (0, 12 mo)	Overall mortality (12 mo)
Broe 2007	Falls (5 mo)	-	Overall mortality (5 mo)
Brohult 1973	Objective and subjective improvement (12 mo)	-	Overall mortality (12 mo)
Burleigh 2007	Falls (1 mo)	-	Overall mortality (1 mo)
Campbell 2005	Numbers of falls, injuries resulting from falls (3, 6, 12 mo)	Costs of implementing the home safety programme	Overall mortality (3, 6, 12 mo)
Chapuy 1992	Fractures (6, 12, 18 mo)	Adverse events (6, 12, 18 mo)	Overall mortality (18 mo)
Chapuy 2002	Biochemical variables of calcium homeostasis, femoral neck bone mineral density and hip fracture risk (3, 6, 9, 12, 15, 18, 21, 24 mo)	-	Overall mortality (24 mo)
Chel 2008	Efficacy of different doses and intervals of oral vitamin D_3 supplementation with the same total dose (4 mo)	Effect of calcium supplementation following vitamin D supplementation on serum PTH and markers of bone turnover (4 mo)	Overall mortality (4 mo)
Cherniack 2011	Serum calcium, 25-hydroxyvitamin D, parathyroid hormone and 24-hour urinary calcium (6, 12 mo)	-	Overall mortality (18 mo)
Cooper 2003	Bone mineral density (0, 6, 12, 18, 24 mo)	-	Overall mortality (24 mo)
Coreless 1985	Abilities to carry out basic activities of daily life (2, 9 mo)	-	Overall mortality (9 mo)
Daly 2006	Bone mineral density	-	Overall mortality (24 mo)

(*Continued*)

Dawson-Hughes 1997	Bone mineral density, biochemical measures of bone metabolism and the incidence of nonvertebral fractures (1, 6, 18, 24, 30, 36 mo)	-	Overall mortality (36 mo)
Dukas 2004	Falls (9 mo)	Serum concentrations of 25-hydroxyvitamin D, 1,25 dihydroxyvitamin D and intact parathormone (0, 3, 6 mo)	Overall mortality (9 mo)
Flicker 2005	Falls and fractures (24 mo)	-	Overall mortality (24 mo)
Gallagher 2001	Bone mineral density (1.5, 3, 6, 12, 18, 24, 30, 36 mo)	-	Overall mortality (24 mo)
Glendenning 2012	Falls, muscle strength and mobility (0, 3, 6, 9 mo)	Serum 25-hydroxyvitamin D levels and adverse events (0, 3, 6, 9 mo)	Overall mortality (9 mo)
Grady 1991	Muscle strength (1, 2, 4, 8, 12, 18, 24 wk)	-	Overall mortality (24 mo)
Grimnes 2011	Insulin sensitivity and secretion (6 mo)	Blood lipid levels (6 mo)	Adverse events (6 mo), overall mortality (6 mo)
Harwood 2004	Bone biochemical markers, bone mineral density and rate of falls (3, 6, 12 mo)	-	Overall mortality (12 mo)
Jackson 2006	Fractures, cancer occurrence, mortality (3, 7 yr)	-	-
Janssen 2010	Muscle strength, power and functional mobility (0, 6 mo)	-	Overall mortality (6 mo)
Komulainen 1999	Bone mineral density (0, 1, 2, 3, 4, 5 yr)	-	Adverse events (5 yr), overall mortality (5 yr)
Krieg 1999	Quantitative ultrasound parameters of bones and metabolic disturbances (0, 12, 24 mo)	-	Overall mortality (24 mo)
Kärkkäinen 2010	Bone mineral density (0, 3 yr)	Vitamin D status (0, 3 yr)	Overall mortality (0, 3 yr)
Lappe 2007	Fractures	Cancer occurrence (0, 6, 12, 18, 24, 30, 36, 42, 48 mo), vitamin D status (0, 12 mo)	Overall mortality (48 mo)

(*Continued*)

Larsen 2004	Falls (3.5 yr)	-	Overall mortality (3.5 yr)
Latham 2003	Physical health (3 mo), falls (6 mo)	Physical performance (6 mo), self-rated function (6 mo)	Overall mortality (6 mo)
Law 2006	Non-vertebral fractures (10 mo), falls (10 mo)	-	Overall mortality (10 mo)
Lehouck 2012	Time to first exacerbation	Exacerbation rate, time to first hospitalisation, time to second exacerbation, quality of life, overall mortality	-
Lips 1996	Fractures (1, 2, 3.5 yr)	Overall mortality (3.5 yr)	-
Lips 2010	Mediolateral body sway with eyes open (4 mo)	Short physical performance battery (4 mo), vitamin D status (4 mo), calcium concentration (4 mo), phosphate concentration (4 mo), adverse events (4 mo)	-
Lyons 2007	Incidence of first fracture	Hip fractures, fractures at common osteoporotic sites (hip, wrist, forearm, vertebrae) (3 yr), overall mortality (3 yr)	-
Meier 2004	Circannual changes in bone turnover and bone mass (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 mo)	-	Overall mortality (12 mo)
Mochonis 2006	Bone mineral density (0, 6, 12 mo)	-	Overall mortality (12 mo)
Ooms 1995	Bone mineral density (0, 6, 12, 18, 24 mo), biochemical markers of bone turnover (0, 6, 12, 18, 24 mo)	-	Overall mortality (24 mo)
Ott 1989	Bone mass (0, 6, 12, 18, 24 mo)	Adverse events (24 mo)	Overall mortality (24 mo)
Porthouse 2005	Fractures (excluding those of the digits, rib, face and skull) (0, 6, 12, 18, 25 mo)	Hip fracture; quality of life, visits to the doctor, hospital admissions, falls, fear of falling (0, 6, 12, 18, 25 mo), overall mortality (25 mo)	-

(*Continued*)

Prince 2008	Falls (12 mo)	Adverse events (12 mo)	Overall mortality (12 mo)
Sanders 2010	Falls and fractures (3, 9, 15, 24, 27, 36 mo)	Adverse events (36 mo)	Overall mortality (36 mo)
Sato 1997	Bone mineral density, hip fractures (6 mo)	-	Overall mortality (6 mo)
Sato 1999a	Non-vertebral fractures (18 mo)	Progression of osteopenia (0, 18 mo)	Overall mortality (0, 18 mo)
Sato 1999b	Bone mineral density (0, 12 mo)	-	Overall mortality (12 mo)
Sato 2005a	Falls (24 mo)	Muscular strength, morphological changes of muscle (0, 24 mo)	Overall mortality (24 mo)
Schleithoff 2006	Overall mortality (15 mo], biochemical variables (15 mo)	Left ventricular ejection fraction (15 mo], left ventricular end-diastolic diameter (15 mo), the cardiothoracic ratio (15 mo), maximal oxygen intake (15 mo) and blood pressure (15 mo)	Vitamin D status (15 mo)
Smith 2007	Non-vertebral fractures (0, 6, 12, 18, 24, 30, 36 mo)	Fractures of the hip or wrist, falls (0, 6, 12, 18, 24, 30, 36 mo)	Overall mortality (36 mo)
Trivedi 2003	Fractures (5 yr], cause-specific mortality (5 yr)	Cancer occurrence (5 yr), cardiovascular disease (5 yr)	Overall mortality (5 yr)
Witham 2010	Six-minute walk test (0, 10, 20 wk)	Timed get-up-and-go test (0, 10, 20 wk), daily physical activity levels (0, 10, 20 wk), health status (0, 10, 20 wk), cardiovascular and inflammatory markers (0, 10, 20 wk), adverse events (20 wk)	Overall mortality (20 wk)
Zhu 2008	Bone mineral density (0, 1, 3, 5 yr], plasma 25-hydroxyvitamin D (0, 1, 3, 5 yr), biomarkers of bone turnover (0, 1, 3, 5 yr), parathyroid hormone (0, 1, 3, 5 yr), intestinal calcium absorption (0, 1, 3, 5 yr)	Adverse events (5 yr)	Overall mortality (5 yr)

Footnotes
Primary or secondary endpoint(s) refer to verbatim statements in the publication; other endpoints relate to outcomes that were not specified as 'primary' or 'secondary' outcomes in the publication
"-" denotes not reporte

(*Continued*)

mo: month; wk: weeks; yr: year

Appendix 6. Adverse events

Characteristic Study ID	Intervention(s) and control(s)	Deaths [n/N]	All adverse events [n/N (%)]	Severe/serious adverse events [n/N (%)]	Left study because of adverse events [n/N (%)]
Aloia 2005	I: vitamin D_3, calcium	1/104	-	8/104 (7.7)	-
	C: placebo	2/104	-	7/104 (6.7)	-
total:			222		
Avenell 2004	I: vitamin D_3	4/70	-	-	-
	C: no intervention	3/64	-	-	-
total:			8 (6)	-	
Avenell 2012	I: vitamin D_3	836/2649	363/2649 (13.7)	-	-
	C: matched placebo	881/2643	386/2643 (14.6)	-	-
total:				33 (0.6)	-
Baeksgaard 1998	I: vitamin D_3 plus calcium	0/80	2/80 (2.5)	-	-
	C: matched placebo	1/80	2/80 (2.5)	-	-
Bischoff 2003	I: vitamin D_3 plus calcium	1/62	2/62 (3.2)	-	-
	C: matched placebo plus calcium	4/60	0/60 (0.0)	-	-
Bjorkman 2007	I: vitamin D_3 plus calcium	27/150	-	-	-
	C: calcium	9/68	-	-	-
Bolton-Smith 2007	I: vitamin D_3 plus calcium	0/62	-	-	-

(*Continued*)

	C: matched placebo	1/60	-	-	-
Brazier 2005	I: vitamin D_3 plus calcium	3/95	15/95 (15.8)	8/95 (8.4)	8/95 (8.4)
	C: matched placebo	1/97	17/97 (17.5)	10/97 (10.3)	10/97 (10.3)
Broe 2007	I: vitamin D_2	5/99	-	-	-
	C: matched placebo	2/25	-	-	-
Brohult 1973	I: vitamin D_3	1/25	3/25 (12.0)	1/25 (4.0)	0/25 (0.0)
	C: placebo	0/25	0/25 (0)	0/25 (0)	0/25 (0.0)
Burleigh 2007	I: vitamin D_3 plus calcium	16/104	4/101 (4.0)	0/101 (0.0)	1/101 (1.0)
	C: matched placebo vitamin D_3 plus calcium	13/104	3/104 (2.9)	0/104 (0.0)	0/104 (0.0)
Campbell 2005	I: home safety programme	6/195	-	-	-
	C: social visits	10/196	-	-	-
Chapuy 1992	I: vitamin D_3 plus calcium	893/1634	40/1634 (2.4)	40/1634 (2.4)	40/1634 (2.4)
	C: double placebo	917/1636	28/1636 (1.7)	28/1636 (1.7)	28/1636 (1.7)
Chapuy 2002	I1: vitamin D_3 plus calcium	70/389	27/389 (6.9)	3/389 (0.8)	-
	I2: vitamin D_3 plus calcium	46/194	16/194 (8.2)	0/194 (8.2)	-
	C: double placebo			6/583 (1.0)	6/583 (1.0)
Chel 2008	I: vitamin D_3	-	-	-	-
	C: matched placebo	-	-	-	-
Cherniack 2011	I: vitamin D_3 plus calcium	1/23	4/23 (17.4)	3/23 (13.0)	3/23 (13.0)
	C: matched placebo plus calcium	0/23	4/23 (17.4)	4/23 (17.4)	4/23 (17.4)

(*Continued*)

Cooper 2003	I: vitamin D_2 plus calcium	0/93	8/93 (8.6)	-	8/93 (8.6)
	C: calcium	1/94	1/94 (1.1)	-	1/94 (1.1)
total:				6/187 (3.2)	
Coreless 1985	I: vitamin D_2	8/41	3/41 (7.3)	1/41 (2.4)	1/41 (2.4)
	C: matched placebo	8/41	0/41 (0.0)	0/41 (0.0)	0/41 (0.0)
Daly 2006	I: calcium-vitamin D_3-fortified milk plus calcium	1/85	9/85 (10.6)	9/85 (10.6)	9/85 (10.6)
	C: no intervention	0/82	2/82 (2.4)	2/82 (2.4)	2/82 (2.4)
Dawson-Hughes 1997	I: vitamin D_3 plus calcium	2/187	6/187 (3.2)	6/187 (3.2)	6/187 (3.2)
	C: placebo	2/202	3/202 (1.5)	3/202 (1.5)	3/202 (1.5)
Dukas 2004	I: alfacalcidol	1/192	75/192 (39.0)	0/192 (0.0)	0/192 (0.0)
	C: placebo	1/186	82/186 (44.1)	0/186 (0.0)	0/186 (0.0)
Flicker 2005	I: vitamin D_3 plus calcium	-	-	-	-
	C: calcium	-	-	-	-
Gallagher 2001	I: calcitriol	2/123	87/123 (71.0)	55/123 (45.0)	-
	C: matched placebo	1/123	56/123 (45.5)	46/123 (37.0)	-
Glendenning 2012	I: cholecalciferol 150,000 three-monthly	2/353	24/353 (6.8)	19/353 (5.4)	-
	C: placebo vitamin D three-monthly	0/333	21/333 (6.3)	15/333 (4.5)	-
Grady 1991	I: calcitriol	1/50	7/50 (14.0)	7/50 (14.0)	-
	C: placebo vitamin D	0/48	2/48 (4.2)	2/48 (4.2)	-
Grimnes 2011	I: vitamin D_3	0/51	45/51 (88.0)	-	-

(*Continued*)

	C: placebo	1/53	46/53 (87.0)	-	-
Harwood 2004	I: vitamin D_2 plus calcium	24/113	-	-	0/113 (0.0)
	C: no intervention	5/37	-	-	0/37 (0.0)
Jackson 2006	I: vitamin D_3 plus calcium	744/18176	449/18,176 (2.5)	449/18,176 (2.5)	-
	C: matched placebo	807/18106	381/18,106 (2.1)	381/18,106 (2.1)	-
Janssen 2010	I: vitamin D_3 plus calcium	0/36	-	-	-
	C: matched placebo vitamin D_3 plus calcium	0/34	-	-	-
Komulainen 1999	I: vitamin D_3 plus calcium	0/116	-	5/116 (4.3)	-
	C: placebo	1/116	-	4/116 (3.4)	-
Krieg 1999	I: vitamin D_3 plus calcium	21/124	21/124	10/124 (8.1)	-
	C: no treatment	26/124	26/124	2/124 (1.6)	-
Kärkkäinen 2010	I: vitamin D_3 plus calcium	15/1718	17/1718 (0.99)	-	-
	C: no intervention	13/1714	0/1714 (0.0)	-	-
Lappe 2007	I: vitamin D_3 plus calcium	4/446	1/446 (0.2)	13/446 (2.9)	-
	C: calcium plus vitamin D placebo	18/733	4/733 (0.5)	20/733 (2.7)	-
Larsen 2004	I: home safety inspection	832/4957	-	-	-
	C: vitamin D_3 plus calcium	839/4648	-	-	-
Latham 2003	I: vitamin D_3	11/121	-	-	-
	C: matched placebo	3/122	-	-	-

(*Continued*)

Law 2006	I: vitamin D_2	347/1762	-	28/1762 (1.6)	28/1762 (1.6)
	C: no intervention	322/1955	-	1955 (0.0)	1955 (0.0)
Lehouck 2012	I: vitamin D_3	9/91	4/91 (4.4)	-	-
	C: matched placebo	6/91	0/91 (0.0)	-	-
Lips 1996	I: vitamin D_3	282/1291	-	-	-
	C: matched placebo	306/1287	-	-	-
Lips 2010	I: vitamin D_3	1/114	24/114 (21.0)	3/114 (2.6)	3/114 (2.6)
	C: matched placebo	0/112	26/112 (23.2)	2/112 (2.7)	2/112 (2.7)
Lyons 2007	I: vitamin D_2	947/1725	-	-	-
	C: matched placebo	953/1715	-	-	-
Meier 2004	I: vitamin D_3 (500 IU) orally, daily	0/30	-	-	-
	C: no intervention	1/25	-	-	-
Mochonis 2006	I: vitamin D_3 plus calcium	0/42	0/42 (0.0)	-	0/42 (0.0)
	C: no intervention	1/70	4/70 (5.7)	-	4/70 (5.7)
Ooms 1995	I: vitamin D_3	11/177	2/177 (1.1)	-	-
	C: matched placebo	21/171	0/171 (0.0)	-	-
Ott 1989	I: vitamin D_3 plus calcium	0/43	11/43 (25.6)	-	-
	C: matched placebo vitamin D plus calcium	1/43	1/43 (2.3)	-	-
Porthouse 2005	I: vitamin D_3 plus calcium	57/1321	-	-	-
	C: no intervention	68/1993	-	-	-
Prince 2008	I: vitamin D_2 plus calcium	0/151	-	-	-

(*Continued*)

	C: matched placebo tablet of vitamin D plus calcium	1/151	-	-	-
Sanders 2010	I: vitamin D_3	40/1131	223/1131 (19.7)	244/1131 (19.7)	-
	C: matched placebo tablet	47/1127	201/1127 (17.8)	207/1127 (17.8)	-
Sato 1997	I: vitamin D (alfacalcidol) plus calcium	1/45	-	-	-
	C: matched placebo tablets of vitamin D and calcium	1/39	-	-	-
Sato 1999a	I: vitamin D (alfacalcidol)	1/43	-	-	-
	C: matched placebo tablet of vitamin D	0/43	-	-	-
Sato 1999b	I: vitamin D (alfacalcidol)	0/34	-	-	-
	C: matched placebo tablet of vitamin D	1/35	-	-	-
Sato 2005a	I: vitamin D_2	1/48	-	-	-
	C: matched placebo tablet of vitamin D	2/48	-	-	-
Schleithoff 2006	I: vitamin D_3 2000 IU plus calcium 500 mg orally, daily	7/61	-	-	-
	C: matched placebo vitamin D plus calcium	6/62	-	-	-
Smith 2007	I: vitamin D_2	355/4727	-	-	-
	C: matched placebo intramuscular injection	354/4713	-	-	-
Trivedi 2003	I: vitamin D_3	224/1345	-	-	-

(*Continued*)

	C: matched placebo vitamin D	247/1341	-	-	-
Witham 2010	I: vitamin D_2 (10, 000 IU) orally, daily	4/53	20/53 (37.7)	-	-
	C: matched placebo tablet	2/52	25/52 (48.1)	-	-
Zhu 2008	I: vitamin D_2 plus calcium	0/39	-	-	-
	C: calcium plus placebo vitamin D	2/81	-	-	-

Footnotes
"-" denotes not reported
C: control; I: intervention

WHAT'S NEW

Last assessed as up-to-date: 29 February 2012.

Date	Event	Description
5 April 2012	New search has been performed	The present review version is an update of the review published in 2011 (Bjelakovic 2011).
4 April 2012	New citation required but conclusions have not changed	New searches were performed in February 2012. We found and included six new randomised clinical trials with 1138 participants

CONTRIBUTIONS OF AUTHORS

Goran Bjelakovic (GB): performed the literature search, data extraction and statistical analyses and drafted the review.

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Denmark.

External sources

- Ministry of Science Republic of Serbia, Serbia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Difference between the last published review version and the present review version

We interpreted our results much more conservatively as the result of extensive discussion of the validity of our results among the review authors.

INDEX TERMS

Medical Subject Headings (MeSH)

*Mortality; Calcitriol [*therapeutic use]; Cause of Death; Cholecalciferol [*therapeutic use]; Dietary Supplements; Ergocalciferols [*therapeutic use]; Hydroxycholecalciferols [*therapeutic use]; Randomized Controlled Trials as Topic; Vitamins [*therapeutic use]

MeSH check words

Adolescent; Adult; Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged; Young Adult