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

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[Intervention Review]

Vitamin D supplementation for prevention of cancer in adults

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ABSTRACT

Background

The evidence on whether vitamin D supplementation is effective in decreasing cancers is contradictory.

Objectives

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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, Science Citation Index Expanded, and the Conference Proceedings Citation Index-Science to February 2014. We scanned bibliographies of relevant publications and asked experts and pharmaceutical companies for additional trials.

Selection criteria

We included randomised trials that compared vitamin D at any dose, duration, and route of administration versus placebo or no intervention in adults who were healthy or were recruited among the general population, or diagnosed with a specific disease. Vitamin D could have been administered as supplemental vitamin D (vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol)), or an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol), or 1,25-dihydroxyvitamin D (calcitriol)).

Data collection and analysis

Two review authors extracted data independently. We conducted random-effects and fixed-effect model meta-analyses. For dichotomous outcomes, we calculated the risk ratios (RRs). We considered risk of bias in order to assess the risk of systematic errors. We conducted trial sequential analyses to assess the risk of random errors.

Main results

Eighteen randomised trials with 50,623 participants provided data for the analyses. All trials came from high-income countries. Most of the trials had a high risk of bias, mainly for-profit bias. Most trials included elderly community-dwelling women (aged 47 to 97 years). Vitamin D was administered for a weighted mean of six years. Fourteen trials tested vitamin D_3, one trial tested vitamin D_2, and three trials tested calcitriol supplementation. Cancer occurrence was observed in 1927/25,275 (7.6%) recipients of vitamin D versus 1943/25,348 (7.7%) recipients of control interventions (RR 1.00 (95% confidence interval (CI) 0.94 to 1.06); P = 0.88; I^2 = 0%; 18 trials; 50,623 participants; moderate quality evidence according to the GRADE instrument). Trial sequential analysis (TSA) of the 18 vitamin D trials shows that the

futility area is reached after the 10th trial, allowing us to conclude that a possible intervention effect, if any, is lower than a 5% relative risk reduction. We did not observe substantial differences in the effect of vitamin D on cancer in subgroup analyses of trials at low risk of bias compared to trials at high risk of bias; of trials with no risk of for-profit bias compared to trials with risk of for-profit bias; of trials assessing primary prevention compared to trials assessing secondary prevention; of trials including participants with vitamin D levels below 20 ng/mL at entry compared to trials including participants with vitamin D levels of 20 ng/mL or more at entry; or of trials using concomitant calcium supplementation compared to trials without calcium. Vitamin D decreased all-cause mortality (1854/24,846 (7.5%) versus 2007/25,020 (8.0%); RR 0.93 (95% CI 0.88 to 0.98); P = 0.009; I^2 = 0%; 15 trials; 49,866 participants; moderate quality evidence), but TSA indicates that this finding could be due to random errors. Cancer occurrence was observed in 1918/24,908 (7.7%) recipients of vitamin D_3 versus 1933/24,983 (7.7%) in recipients of control interventions (RR 1.00 (95% CI 0.94 to 1.06); P = 0.88; I^2 = 0%; 14 trials; 49,891 participants; moderate quality evidence). TSA of the vitamin D_3 trials shows that the futility area is reached after the 10th trial, allowing us to conclude that a possible intervention effect, if any, is lower than a 5% relative risk reduction. Vitamin D_3 decreased cancer mortality (558/22,286 (2.5%) versus 634/22,206 (2.8%); RR 0.88 (95% CI 0.78 to 0.98); P = 0.02; I^2 = 0%; 4 trials; 44,492 participants; low quality evidence), but TSA indicates that this finding could be due to random errors. Vitamin D_3 combined with calcium increased nephrolithiasis (RR 1.17 (95% CI 1.03 to 1.34); P = 0.02; I^2 = 0%; 3 trials; 42,753 participants; moderate quality evidence). TSA, however, indicates that this finding could be due to random errors. We did not find any data on health-related quality of life or health economics in the randomised trials included in this review.

Authors' conclusions

There is currently no firm evidence that vitamin D supplementation decreases or increases cancer occurrence in predominantly elderly community-dwelling women. Vitamin D_3 supplementation decreased cancer mortality and vitamin D supplementation decreased all-cause mortality, but these estimates are at risk of type I errors due to the fact that too few participants were examined, and to risks of attrition bias originating from substantial dropout of participants. Combined vitamin D_3 and calcium supplements increased nephrolithiasis, whereas it remains unclear from the included trials whether vitamin D_3, calcium, or both were responsible for this effect. We need more trials on vitamin D supplementation, assessing the benefits and harms among younger participants, men, and people with low vitamin D status, and assessing longer duration of treatments as well as higher dosages of vitamin D. Follow-up of all participants is necessary to reduce attrition bias.

PLAIN LANGUAGE SUMMARY

Vitamin D supplementation for prevention of cancer in adults

Review question

Does vitamin D supplementation prevent cancer?

Background

The available evidence on vitamin D and cancer occurrence is intriguing but inconclusive. Many observational studies as well as randomised trials suggest that high vitamin D levels in the blood are related to reduced cancer occurrence. However, results of randomised trials testing the effect of vitamin D supplementation for cancer prevention are contradictory.

Study characteristics

The aim of this systematic review was to analyse the benefits and harms of the different forms of vitamin D especially on cancer occurrence. A total of 18 trials provided data for this review; 50,623 participants were randomly assigned to either vitamin D or placebo or no treatment. All trials were conducted in high-income countries.

Key results

The age range of the participants was 47 to 97 years and on average 81% were women. The majority of the included participants did not have vitamin D deficiency. Vitamin D administration lasted on average six years and most trial investigators used vitamin D_3 (cholecalciferol). We did not find firm evidence that vitamin D supplementation decreases or increases cancer occurrence in predominantly elderly community-dwelling women. We observed decreases in all-cause mortality and cancer-related mortality among the vitamin D/D_3 treated participants in comparison with the participants in the control groups. However, using trial sequential analysis, a statistical approach to reconfirm or question these findings, we conclude that these results could be due to random errors (play of chance). We also found evidence that combined vitamin D_3 and calcium supplements increased renal stone occurrence, but it remains unclear from the included trials whether vitamin D_3, calcium, or both were responsible for this effect. Moreover, these results could also be due to random errors (play of chance).

Quality of the evidence

A large number of the study participants left the trials before completion, and this raises concerns regarding the validity of the results. Most of the trials were judged not to be well and fairly conducted so that the results were likely to be biased (that is, possibly an overestimation of benefits and underestimation of harms).

Currentness of evidence

This evidence is up to date as of February 2014.

Summary of findings for the main comparison. Vitamin D versus placebo or no intervention for prevention of cancer in adults

Vitamin D versus placebo or no intervention for prevention of cancer in adults

Patient or population: healthy participants or recruited among the general population; individuals diagnosed with a specific disease in a stable phase or with vitamin D deficiency

Settings: outpatients
Intervention: vitamin D versus 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				
	Control	Vitamin D versus placebo or no intervention				
Cancer occurrence Follow-up: 0.5 to 7 years	**Study population**		**RR 1.00** (0.94 to 1.06)	50623 (18)	⊕⊕⊕⊖ **moderate**[a]	Trial sequential analysis of all vitamin D trials suggests that the futility area is reached after the 10th trial allowing us to conclude that any possible intervention effect, if any, is lower than a 5% relative risk reduction.
	77 per 1000	**77 per 1000** (72 to 81)				
	Moderate					
	28 per 1000	**28 per 1000** (26 to 30)				
Cancer occurrence in trials using vitamin D_3 (cholecalciferol) Follow-up: 0.5 to 7 years	**Study population**		**RR 1.00** (0.94 to 1.06)	49891 (14)	⊕⊕⊕⊖ **moderate**[a]	Trial sequential analysis of all vitamin D trials suggests that the futility area is reached after the 10th trial allowing us to conclude that any possible intervention effect, if any, is lower than a 5% relative risk reduction.
	77 per 1000	**77 per 1000** (73 to 82)				
	Moderate					
	28 per 1000	**28 per 1000** (26 to 30)				
All-cause mortality Follow-up: 0.5 to 7 years	**Study population**		**RR 0.93** (0.88 to 0.98)	49866 (15)	⊕⊕⊖⊖ **low**[b]	Trial sequential analysis of all trials irrespective of bias risks showed that the required information size had not yet been reached and that the
	80 per 1000	**75 per 1000**				

		(71 to 79)				cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit.
	Moderate					
	16 per 1000	**15 per 1000** (14 to 16)				
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)	44492 (4)	⊕⊕⊝⊝ **low**[b]	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 did not cross the trial sequential monitoring boundary for benefit.
	29 per 1000	**25 per 1000** (22 to 28)				
	Moderate					
	37 per 1000	**33 per 1000** (29 to 36)				
Adverse events: nephrolithiasis in trials using vitamin D_3(cholecalciferol) combined with calcium Follow-up: 0.5 to 7 years	**Study population**		**RR 1.17** (1.03 to 1.34)	42753 (3)	⊕⊕⊝⊝ **low**[b]	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 did not cross the trial sequential monitoring boundary for benefit.
	18 per 1000	**21 per 1000** (18 to 24)				
	Moderate					
	1 per 1000	**1 per 1000** (1 to 1)				
Health-related quality of life	See comment					Not investigated.
Health economics	See comment					Not investigated.

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

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

[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

Vitamin D is a fat-soluble vitamin, which maintains calcium and phosphorus homeostasis (Holick 2007; Horst 2005; Lips 2006). Vitamin D_3 (cholecalciferol) is synthesised in the skin from 7-dehydrocholesterol during exposure to sunlight. Alternatively, vitamin D, in the form of either vitamin D_3 or D_2, can be obtained from dietary sources. Vitamin D_3 (cholecalciferol) is the predominant form of vitamin D in humans. Vitamin D_2 (ergocalciferol) is derived mainly from irradiated plants. Vitamin D, as either D_3 or D_2, does not have biological activity. It must be metabolised within the liver to 25-hydroxycalciferol (calcidiol) and in the kidney to the biologically active form known as 1,25-dihydroxycalciferol (calcitriol) (Holick 2007; Horst 2005; Lips 2006). Current interest in vitamin D is engendered by the hypothesis that it may prevent cancer and prolong life (Bjelakovic 2014; Davis 2007; Giovannucci 2005). The evidence on whether vitamin D is effective in decreasing cancers is contradictory.

Description of the condition

Vitamin D status is determined by the measurement of the serum 25-hydroxyvitamin D level (Bischoff-Ferrar 2009c; Dawson-Hughes 2005; Lips 2004). There is controversy about the definition of optimal vitamin D status (Bouillon 2013; Hilger 2014). The Institute of Medicine recently recommended a target serum 25-hydroxyvitamin D level of 20 ng/ml (50 nmol/L) (IOM 2011). Based upon the systematic review prepared by the Institute of Medicine there are insufficient data to determine the safe upper limit of serum 25-hydroxyvitamin D level (IOM 2011). However, serum 25-hydroxyvitamin D level concentrations above 50 ng/mL (125 nmol/L) were considered potentially harmful (IOM 2011). The International Osteoporosis Foundation and the Endocrine Society Task Force recommend a target serum 25-hydroxyvitamin D level of 30 ng/ml (75 nmol/L) (Dawson-Hughes 2010; Holick 2011). The worldwide prevalence of suboptimal vitamin D status is estimated to be high (Hilger 2014; Holick 2007; Lamberg-Allardt 2006; Lips 2010: Van Schoor 2011; Zittermann 2003). The major causes of vitamin D deficiency are insufficient exposure to sunlight, decreased dietary intake, skin pigmentation, obesity, and advanced age (Lips 2006). Vitamin D deficiency in childhood results in rickets, while in adults it precipitates or exacerbates osteopenia and osteoporosis, and induces osteomalacia (Holick 2007). It has been speculated that vitamin D insufficiency is related to increased risks of cancer and cardiovascular diseases (Chiang 2013; Freedman 2007; Garland 2007; Giovannucci 2005; Gorham 2007; Michos 2008; Norman 2014; Schwartz 2007; Zittermann 2005; Zittermann 2006), the leading causes of death in middle- and high-income countries (Mathers 2006). Vitamin D insufficiency might also be the consequence of a disease, but not the cause (Marshall 2008).

Description of the intervention

Vitamin D supplementation prevents osteoporosis, osteomalacia, and fractures (Holick 2007; Lamberg-Allardt 2006). It has been postulated that vitamin D may have additional health effects beyond prevention of bone diseases (Bikle 2009; Sutton 2003). Ecologic studies have found that living at higher altitudes with lower exposure to sunlight is linked to increased cancer risk (Apperly 1941; Garland 1980). Most observational studies have associated increased vitamin D intake with decreased risk of cancer (Garland 2007; Gorham 2007; Schwartz 2007). Although high vitamin D status was connected with increased pancreatic cancer risk (Helzlsouer 2010; Stolzenberg-Solomon 2006; Stolzenberg-Solomon 2010), the range of 25-hydroxyvitamin D levels associated with the cancer risk was below that considered to reflect hypervitaminosis D (Krstic 2011).

How the intervention might work

The active form of vitamin D functions as a steroid-like hormone (Horst 2005). The effects of vitamin D are mediated by its binding to a vitamin D receptor (Norman 2006; Wesley Pike 2005), which is present in most tissues and cells in the body (Lips 2006). Upon binding to its receptors, vitamin D may enhance cell differentiation and cell apoptosis, and may inhibit cell proliferation in a variety of cell types (Flynn 2006). In addition, vitamin D is required for a functional immune system which is important for an adequate physiological response to infections, inflammatory diseases, immune-system-mediated diseases, and cancer (Bikle 2009; Cutolo 2009; Hart 2011; Sutton 2003). Thus, vitamin D supplementation could reduce cancer development.

Adverse effects of the intervention

Vitamin D toxicity is the result of excessive vitamin D intake. There is sparse evidence that ingestion of high quantities of vitamin D is harmful. The majority of the trials that reported hypercalcaemia, hypercalciuria, or nephrocalcinosis were conducted in participants with renal failure (Cranney 2007). We have shown that vitamin D_3 combined with calcium may increase nephrolithiasis, and that alfacalcidol and calcitriol may increase hypercalcaemia (Bjelakovic 2014).

Why it is important to do this review

The available evidence on vitamin D and cancer occurrence is intriguing but inconclusive. Results of recently completed randomised trials testing the influence of vitamin D supplementation for cancer prevention are contradictory. Lappe 2007 found that vitamin D supplementation is associated with significantly decreased cancer incidence. In contrast, another large randomised trial found no effect of vitamin D and calcium supplementation on cancer incidence (Brunner 2011). Although Chung 2011 found inconclusive evidence regarding vitamin D supplementation for the prevention of cancer in a recently updated meta-analysis, the same review suggests that hazard ratios and risk ratios are correlated better with the cancer mortality when compared to the cancer incidence rates (Krstic 2012). Our aim was to systematically review and statistically analyse the available evidence in order to assess the effects of vitamin D supplementation on cancer prevention in adults.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised trials, irrespective of blinding, publication status, or language.

Types of participants

Adult participants (aged 18 years or over) who were:

- healthy or were recruited from the general population;
- diagnosed with a specific disease in a stable phase;
- diagnosed with vitamin D deficiency.

We excluded trials including:

- people 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 are usually in need of vitamin D);
- people with cancer.

Types of interventions

We considered for inclusion randomised trials that compared vitamin D at any dose, duration, and route of administration versus placebo or no intervention.

The vitamin D was administered.

- As monotherapy.
- In combination with calcium.

Concomitant interventions were allowed if used equally in all intervention groups of the trial.

Types of outcome measures

Primary outcomes

- Cancer occurrence.
- All-cause mortality.
- Cancer mortality.

Secondary outcomes

- Adverse events depending on the availability of data, we attempted to classify adverse events as serious or non-serious. Serious adverse events were defined according to the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or was a congenital anomaly/birth defect, or any medical event, which might have jeopardised the patient, or required intervention to prevent it (ICH-GCP 1997). All other adverse events (that is, any medical occurrence not necessarily having a causal relationship with the treatment, but causing a dose reduction or discontinuation of the treatment) were considered as non-serious.
- Health-related quality of life.
- Health economics.

Covariates, effect modifiers, and confounders

We noted and recorded any possible covariates, effect modifiers, and confounders (for example, compliance or other medications).

Timing of outcome measurement

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

Search methods for identification of studies

Electronic searches

We used the following sources from inception to the specified date for identification of the trials.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (until February 2014).
- MEDLINE (until February 2014).
- EMBASE (until February 2014).
- LILACS (until February 2014).
- Science Citation Index Expanded (until February 2014).

We also searched databases of ongoing trials (www.clinicaltrials.gov/ and www.controlled-trials.com/ (with links to several databases) and the World Health Organization International Clinical Trials Registry Platform (ICTRP 2011)). For detailed search strategies, see Appendix 1. We included trials published in any language.

Searching other resources

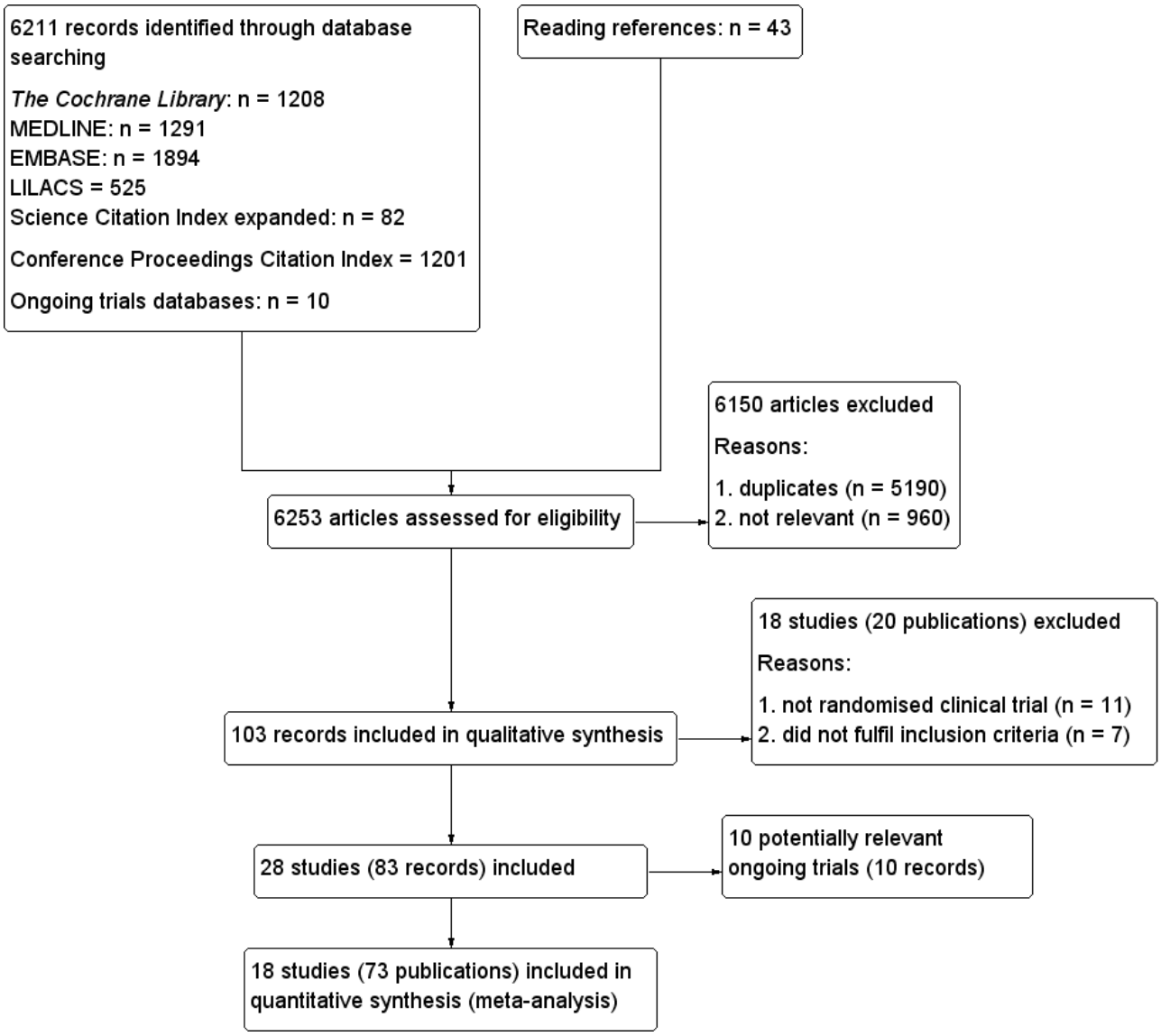
We have contacted the main manufacturers of vitamin D to ask for unpublished randomised trials. We tried to identify additional trials by searching the reference lists of included trials and (systematic) reviews, meta-analyses, and health technology assessment reports during the review preparation.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two review authors (GB and DN) independently scanned the abstract, title, or both sections of every record retrieved. We investigated all potentially relevant articles as full text. Where differences in opinion existed, we resolved them by recourse to a third party (CG). If resolving disagreement was not possible, we added the article to those 'awaiting assessment' and contacted the authors for clarification. An adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart of study selection is attached (Figure 1) (Liberati 2009).

Figure 1. Study flow diagram.



Data extraction and management

For studies that fulfilled our inclusion criteria, two review authors (GB and DN) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details, see 'Characteristics of included studies'; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6), resolving any disagreements by discussion, or if required by recourse to a third party. We sought any relevant missing information on the trial from the study author(s) of the article, if required.

Dealing with duplicate publications and companion papers

In the case of duplicate publications and companion papers of a primary study, we tried to maximise our yield of information by simultaneous evaluation of all available data.

Assessment of risk of bias in included studies

Due to the risk of overestimation of beneficial intervention effects in randomised trials of unclear or inadequate methodological quality (Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012a; Savović 2012b; 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 reporting, selective outcome reporting, and other apparent biases (Higgins 2011). We used the following definitions:

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 were 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 (for example, 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: there was insufficient information to assess whether blinding was likely to induce bias into the results.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were 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: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias into the results.
- High risk of bias: the results were likely to be biased due to 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.

For a trial to be assessed with low risk of bias in the selective outcome reporting domain, the trial should have been registered either on the www.clinicaltrials.gov website or a similar register, or there should be a protocol, e.g., published in a paper journal. In the case of a trial being run and published in 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 publications results section, then the trial was considered to be at low risk of bias in the selective outcome reporting domain.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other kind of for-profit support that may manipulate the trial design, conduct, or results of the trial.
- Uncertain risk of bias: the trial may or may not be free of for-profit bias, as no information on clinical trial support or sponsorship is provided.
- High risk of bias: the trial is sponsored by the industry or has received some other kind of for-profit support.

Other bias

- Low risk of bias: the trial appears to be free of other components (for example, academic bias) 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: there are other factors in the trial that could put it at risk of bias (for example, authors have conducted trials on the same topic, etc).

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

Dealing with missing data

We tried to obtain relevant missing data from authors whenever we lacked important numerical data such as number of screened or randomised participants, or lack of data regarding the performance of intention-to-treat (ITT) analyses, or data on as-treated or per-protocol participant analyses in order to perform our analyses as rigorously as possible. We investigated attrition rates, (for example, dropouts, losses to follow-up, and withdrawals) and critically appraised issues of missing data (for example, last-observation-carried-forward (LOCF)) and imputation methods.

Regarding the primary outcomes, we included participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios (Hollis 1999).

- Extreme case analysis favouring the experimental intervention ('best-worst' case scenario: none of the dropouts/participants lost from the experimental arm, but all of the dropouts/participants lost from the control arm experienced the outcome, including all randomised participants in the denominator.
- Extreme case analysis favouring the control ('worst-best' case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomised participants in the denominator.

Assessment of heterogeneity

We identified heterogeneity by 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 specifically examined heterogeneity with the I^2 statistic (Higgins 2002), where I^2 values of 50% or more indicated a substantial level of heterogeneity

(Higgins 2003). For the heterogeneity adjustment of the required information size in the trials sequential analyses, we used diversity (D^2), as I^2 used for this purpose consistently underestimates the required information size (Wetterslev 2009).

When we found heterogeneity, we attempted to determine the potential reasons for it by examining the individual trial and subgroup characteristics.

Assessment of reporting biases

We used funnel plots in an exploratory data analysis to assess the potential existence of bias in small trials. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design of small trials, and publication bias. We performed adjusted rank correlation (Begg 1994) and a regression asymmetry test (Egger 1997) for detection of bias. We considered a P value less than 0.10 significant in the latter analyses. We carefully interpreted results of funnel plots (Lau 2006).

Data synthesis

We performed statistical analyses according to the statistical guidelines referenced in the latest version of *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

For the statistical analyses, we used Review Manager 5 (RevMan 2012), Trial Sequential Analysis version 0.9 beta (TSA 2011; www.ctu.dk/tsa), STATA 8.2 (STATA Corp, College Station, Texas), and Sigma Stat 3.0 (SPSS Inc, Chicago, Ill). We analysed the data with both fixed-effect (DeMets 1987) and random-effects (DerSimonian 1986) model meta-analyses. In the review text, we present the results of the random-effects model analyses. For dichotomous outcomes, we calculated the Mantel-Haenszel risk ratios (RRs). For all association measures, we used 95% confidence intervals (CIs). We conducted the analyses using the intention-to-treat principle, including all randomised participants irrespective of completeness of data. We included participants with missing data in the analyses using a carry forward of the last observed response. Accordingly, we counted participants who had been lost to follow-up as being alive.

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

For trials using a factorial design, we performed 'at the margins' analysis, combining all participants randomised to vitamin D (McAlister 2003). Due to the risk of interaction between different treatment regimens, we also performed 'inside the table' analysis in which we compared vitamin D only with placebo or no intervention. In the trials with a parallel group design with more than two arms and additional therapy, we compared the vitamin D arm alone with placebo or no intervention.

Trial sequential analysis

Meta-analyses may result in type 1 errors due to sparse data and repeated significance testing when meta-analyses are updated with new trials (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009). In a single trial, interim analysis increases the risk of type 1 errors. To avoid type 1 errors (rejecting the null hypothesis when it is in fact true) group sequential monitoring boundaries (Lan 1983) are applied to decide whether a trial could be terminated early because of a sufficiently small P value, that is, when the cumulative Z-curve crosses the alpha-spending monitoring boundary. Sequential monitoring boundaries can be applied to meta-analyses as well and are called trial sequential monitoring boundaries. In 'trial sequential analysis' (TSA), the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to decide whether additional trials are needed (Wetterslev 2008). So far, several meta-analyses and reviews have been published, including an increasing number of trial results as new trials have been published. It therefore seems appropriate to adjust new meta-analyses for sparse accumulating data and multiple testing to control the overall type 1 error risk in a cumulative meta-analysis (Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2008). The idea behind TSA is that if the cumulative Z-curve crosses a trial sequential monitoring boundary (TSMB), a sufficient level of evidence is reached and no further trials may be needed. However, there is insufficient evidence to reach a conclusion if the cumulative Z-curve does not cross the TSMB or does not surpass the futility boundaries before the required information size is reached. To construct the TSMBs, a required information size is needed which is calculated as the least number of participants needed in a well-powered single trial (Brok 2008; Pogue 1998; Wetterslev 2008). We adjusted the required information size to account for statistical between-trial heterogeneity with a diversity adjustment factor (Wetterslev 2009).

We performed trial sequential analysis to avoid random errors due to repetitive analyses of accumulated data and to prevent premature statements of superiority of intervention or lack of effect of an intervention (TSA 2011). We used the diversity-adjusted required information size estimated from a control event proportion of the included trials and an a priori intervention effect of 5% and 10% relative risk reduction (RRR) (Wetterslev 2009), and the diversity which was estimated in the included trials.

Subgroup analysis and investigation of heterogeneity

We mainly performed subgroup analyses if one of the primary outcomes demonstrated statistically significant differences between the intervention groups. In any other case, subgroup analyses were clearly marked as a hypothesis-generating exercise.

We conducted the following subgroup analyses.

- Trials with a low risk of bias compared to trials with a high risk of bias.
- Trials without risk of for-profit bias compared to trials with risk of for-profit bias
- Primary prevention trials compared to secondary prevention trials.
- Trials including participants with vitamin D insufficiency compared to trials with vitamin D adequacy.
- Vitamin D_3 compared to placebo or no intervention.
- Trials that administered vitamin D_3 singly compared to trials that administered vitamin D_3 combined with calcium.
- Vitamin D_2 compared to placebo or no intervention.
- Calcitriol compared to placebo or no intervention.

Sensitivity analysis

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

- Best-worst case scenario analyses.
- Worst-best case scenario analyses.

We also tested the robustness of the results by repeating the analysis using different statistical models (fixed- and random-effects model meta-analyses).

Summary of findings tables

We used GRADE (tech.cochrane.org/revman/other-resources/gradepro) to construct a 'Summary of findings' table for vitamin D for all of the review outcomes. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias (Andrews 2013a; Andrews 2013b; Balshem 2011; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2011i; ; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013). We used results obtained withTSA for the rating for imprecision. If there is insufficient evidence to reach a conclusion, i.e., if the TSA indicates that the required information size had not been reached, we downgraded the quality of the evidence by one level. In addition, we used risk of attrition bias for the rating for imprecision. If there was significant risk of attrition bias, we further downgraded the quality of the evidence by one level.

RESULTS

Description of studies

Results of the search

We identified a total of 6211 references of possible interest through searching *The Cochrane Library* (n = 1208), MEDLINE (n = 1291), EMBASE (n = 1894), LILACS (n = 525), Science Citation Index Expanded (n = 82), Conference Proceedings Citation Index-Science (n = 1201), and reference lists (n = 43). We identified an additional 10 ongoing trials through searching databases of ongoing trials. We will include data from the ongoing trials in future updates of this review. We then excluded 5190 duplicates and 960 clearly irrelevant references through reading the abstracts. Accordingly, we retrieved 103 references for further assessment. Of these, we excluded 20 references describing 18 studies because they were not randomised trials or did not fulfil the inclusion criteria of our review. We list reasons for exclusion in the table Characteristics of excluded studies. In total, 18 randomised trials described in 74 references fulfilled the inclusion criteria (Figure 1). The trials included a total of 50,623 participants.

We contacted eight authors for missing information and received answers from all of them.

Included studies

A detailed description of the characteristics of included studies is presented elsewhere (see Characteristics of included studies and appendices). The following is a succinct overview:

Trial characteristics

Out of the 18 trials reporting cancer occurrence, 14 trials used a parallel-group design and four trials (Avenell 2012; Bolton-Smith 2007; Gallagher 2001; Komulainen 1999) used a 2-by-2 factorial design (Pocock 2004). The trials were published between 1989 and 2013.

In 16 trials, vitamin D was provided free of charge by pharmaceutical companies. Two trials were not funded by industry (Trivedi 2003; Wood 2012).

The trials were conducted in Europe (n = 8) (Avenell 2012; Bolton-Smith 2007; Janssen 2010; Komulainen 1999; Larsen 2012; Trivedi 2003; Witham 2013; Wood 2012), North America (n = 5) (Brunner 2011; Gallagher 2001; Grady 1991; Lappe 2007; Ott 1989), and Oceania (n = 5) (Daly 2008; Glendenning 2012; Murdoch 2012; Prince 2008; Sanders 2010). All 18 trials were conducted in high-income countries.

Participants

A total of 50,623 participants were randomly assigned in the 18 trials reporting cancer occurrence (Table 1). The number of participants in each trial ranged from 70 to 36,282 (median 313). The mean age of participants was 69 years (range 47 to 97 years). The mean proportion of women was 81%.

Sixteen trials were primary prevention trials, that is, included healthy participants, or participants from the general population. Of these, 11 trials included elderly and postmenopausal women (Bolton-Smith 2007; Brunner 2011; Gallagher 2001; Glendenning 2012; Janssen 2010; Komulainen 1999; Lappe 2007; Ott 1989; Prince 2008; Sanders 2010; Wood 2012), three trials included elderly people (Avenell 2012; Grady 1991; Trivedi 2003), and two trials included healthy volunteers (Daly 2008; Murdoch 2012).

Two trials were secondary prevention trials that included participants with cardiovascular disease (arterial hypertension) (Larsen 2012; Witham 2013).

Of the 18 trials reporting cancer occurrence, 16 (89%) reported the baseline vitamin D status of participants based on serum 25-hydroxyvitamin D levels. Participants in nine trials (Bolton-Smith 2007; Daly 2008; Gallagher 2001; Glendenning 2012; Grady 1991; Larsen 2012; Murdoch 2012; Ott 1989; Trivedi 2003) had baseline 25-hydroxyvitamin D levels at or above vitamin D adequacy (20 ng/ml). Participants in the other seven trials had baseline 25-hydroxyvitamin D levels considered vitamin D insufficient (< 20 ng/ml) (Avenell 2012; Brunner 2011; Janssen 2010; Prince 2008; Sanders 2010; Witham 2013; Wood 2012). Two trials did not report the baseline vitamin D status of participants (Komulainen 1999; Lappe 2007).

The main outcomes in the trials were cancer occurrence, all-cause mortality, bone mineral density, and number of falls and fractures.

Experimental interventions

Vitamin D_3 - cholecalciferol

Vitamin D was administered as vitamin D_3 (cholecalciferol) in 14 trials (49,891 participants; 78% women; mean age 67 years). Vitamin D_3 was tested singly in seven trials (Glendenning 2012; Murdoch 2012; Sanders 2010; Trivedi 2003; Witham 2013; Wood 2012) and combined with calcium in six trials. One trial tested vitamin D_3 singly and combined with calcium (Avenell 2012). Vitamin D_3 was administered orally in all trials. Vitamin D_3 was given daily in nine trials and at intervals in five trials (monthly

(Murdoch 2012); three-monthly (Glendenning 2012; Witham 2013); four-monthly (Trivedi 2003); and yearly (Sanders 2010)). The daily dose of the vitamin D_3 was 300 IU to 3333 IU (mean daily dose 1146 IU; median daily dose 810 IU). The duration of supplementation in trials using vitamin D_3 was five months to seven years (weighted mean 6.0 years), and the duration of the follow-up period was five months to seven years (weighted mean 6.3 years).

Vitamin D_2 - ergocalciferol

Vitamin D was administered as vitamin D_2 (ergocalciferol) in one trial (302 participants; 100% women; mean age 77.2 years). Vitamin D_2 was tested in a dose of 1000 IU, combined with 1000 mg of calcium, orally, and daily for a one-year period.

Calcitriol - 1,25-dihydroxyvitamin D

Vitamin D was administered as calcitriol in three trials (430 participants; 85% women; aged 50 to 97 years). Calcitriol was tested singly in two trials and combined with calcium in one trial (Ott 1989). Calcitriol was tested orally and daily in all trials. The dose of calcitriol was 0.5 µg in two trials (Gallagher 2001; Grady 1991); while two doses of calcitriol (0.5 µg and 2 µg) were tested in another trial (Ott 1989). The duration of supplementation in trials using calcitriol was two to five years (weighted mean 2.5 years) and the duration of the follow-up period was two to five years (weighted mean 4.0 years).

Comparator interventions

Seventeen trials used placebo, and one trial used no intervention in the control group (Daly 2008).

Co-interventions

Seven trials used calcium combined with vitamin D in the experimental intervention groups. Two trials tested calcium separately in one of the intervention groups (Avenell 2012; Lappe 2007). Calcium was administered orally and daily in all trials. The dose of calcium was 500 mg to 1500 mg (mean 883 mg; median 1000 mg).

Three trials used calcium in the control group, combined with vitamin D placebo, in a dose of 500 mg to 1000 mg (mean 833 mg; median 1000 mg). These trials used an equal dose of calcium in the experimental intervention groups. One trial with a 2-by-2 factorial design tested a combination of vitamin D_3, vitamin K_1, and calcium in one group (Bolton-Smith 2007). The factorial design of this trial allowed us to compare only the vitamin D_3 plus calcium group with the placebo group of this trial. Two trials with a 2-by-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.

Excluded studies

A detailed description of the characteristics of included studies is presented elsewhere (see Characteristics of excluded studies and appendices).

Risk of bias in included studies

Two trials (11%) were considered to be at low risk of bias. The remaining 16 trials had unclear bias control in one or more of the components assessed (Figure 2; Figure 3). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 4). The adjusted-rank correlation test (P = 1.00) found no significant evidence of bias, while the regression asymmetry test found significant evidence of bias (P = 0.007).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

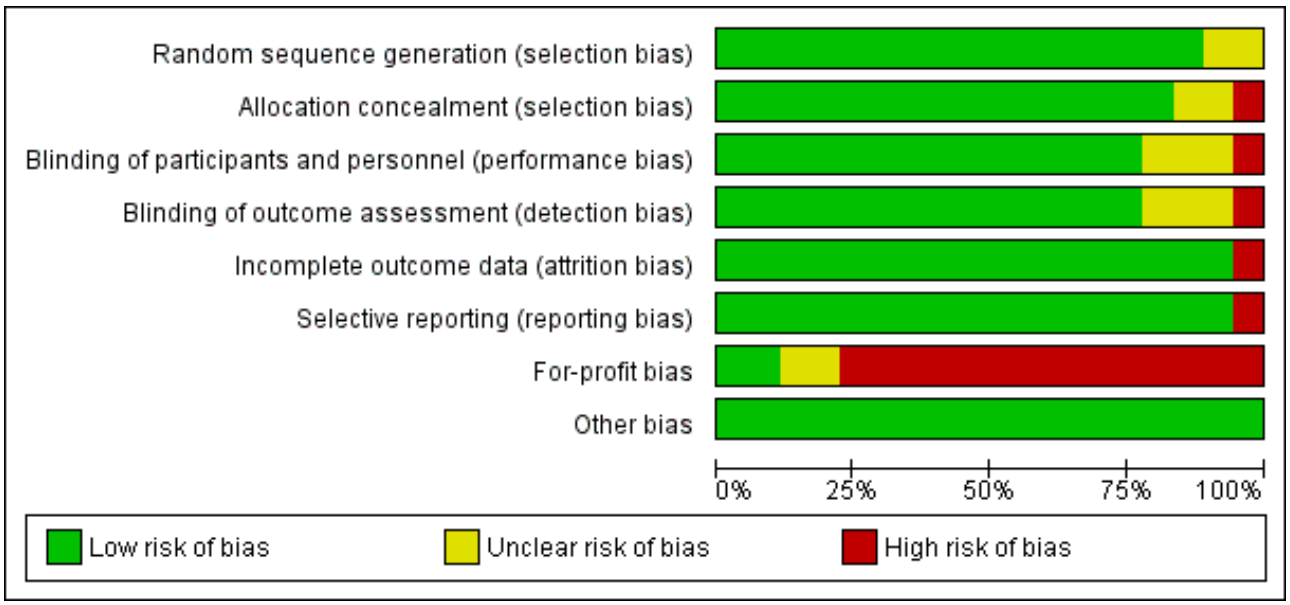


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

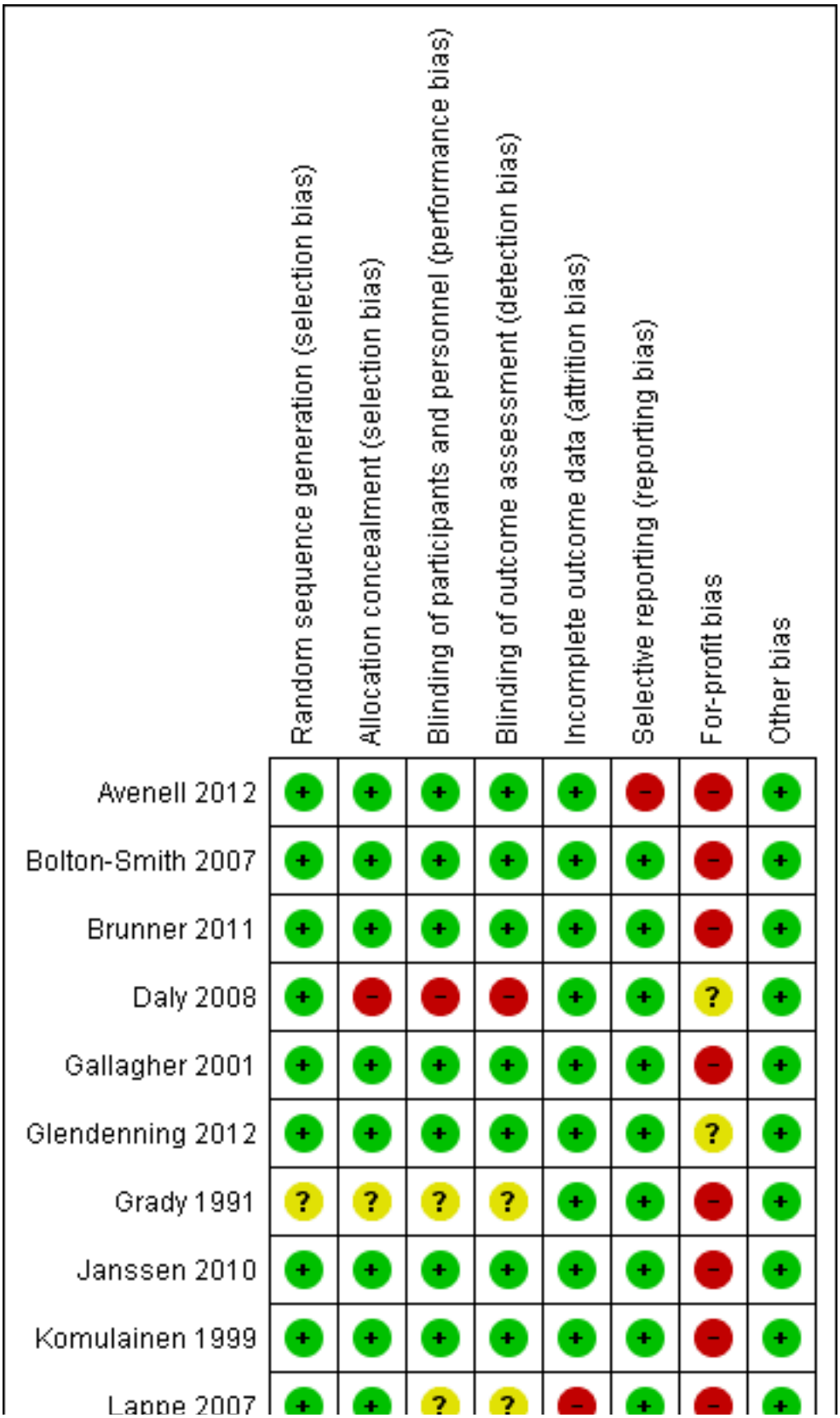


Figure 3. (Continued)

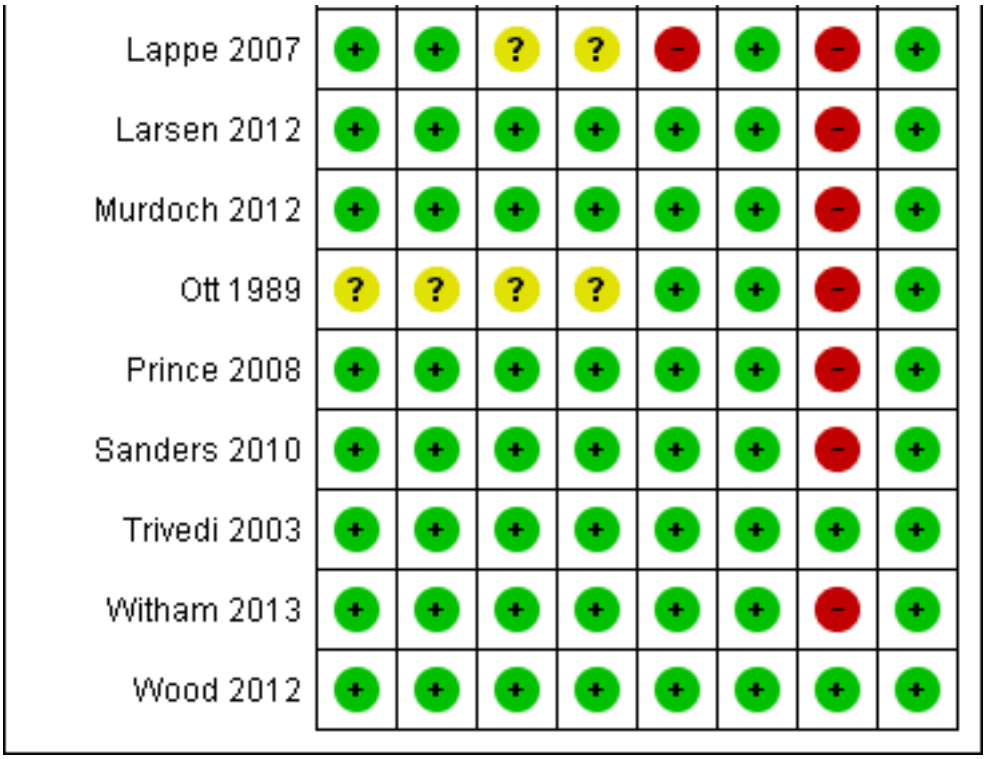
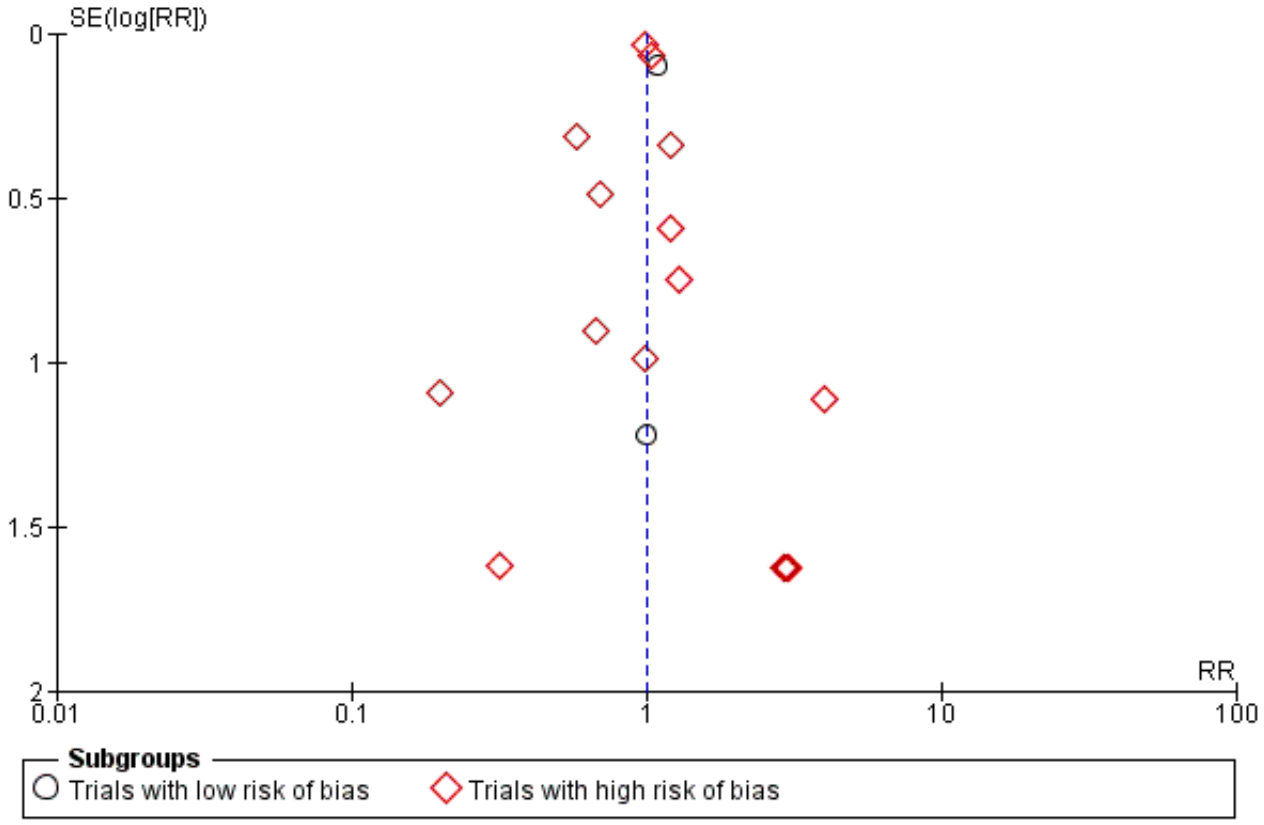


Figure 4. Funnel plot of comparison: 1 Vitamin D versus placebo or no intervention, outcome: 1.1 Cancer occurrence in trials with a low or high risk of bias.



Allocation

The generation of the allocation sequence was adequately described in 16 trials. The remaining two trials (Grady 1991; Ott 1989) were described as randomised, but the method used for sequence generation was not described.

The method used to conceal allocation was adequately described in 15 trials. We judged the method used for allocation concealment to be unclear in two trials (Grady 1991; Ott 1989) and inadequate in one trial (Daly 2008).

Blinding

The method of blinding was adequately described in 14 trials. The method of blinding was unclear in three trials (Grady 1991; Lappe 2007; Ott 1989). One trial was not blinded (Daly 2008).

Incomplete outcome data

Incomplete data were addressed adequately in 17 trials. In one trial, 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 introduce bias into the estimate of effect (Lappe 2007).

Selective reporting

Predefined primary and secondary outcomes were reported in all trials.

For-profit bias

Two trials were not funded by industry (Trivedi 2003; Wood 2012). Fifteen trials were funded by industry (Avenell 2012; Bolton-Smith 2007; Brunner 2011; Daly 2008; Gallagher 2001; Grady 1991; Komulainen 1999; Janssen 2010; Lappe 2007; Larsen 2012; Murdoch 2012; Ott 1989; Prince 2008; Sanders 2010; Witham 2013). The source of funding is not clear for one trial (Glendenning 2012).

Other potential sources of bias

All included trials appear 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 versus placebo or no intervention for prevention of cancer in adults

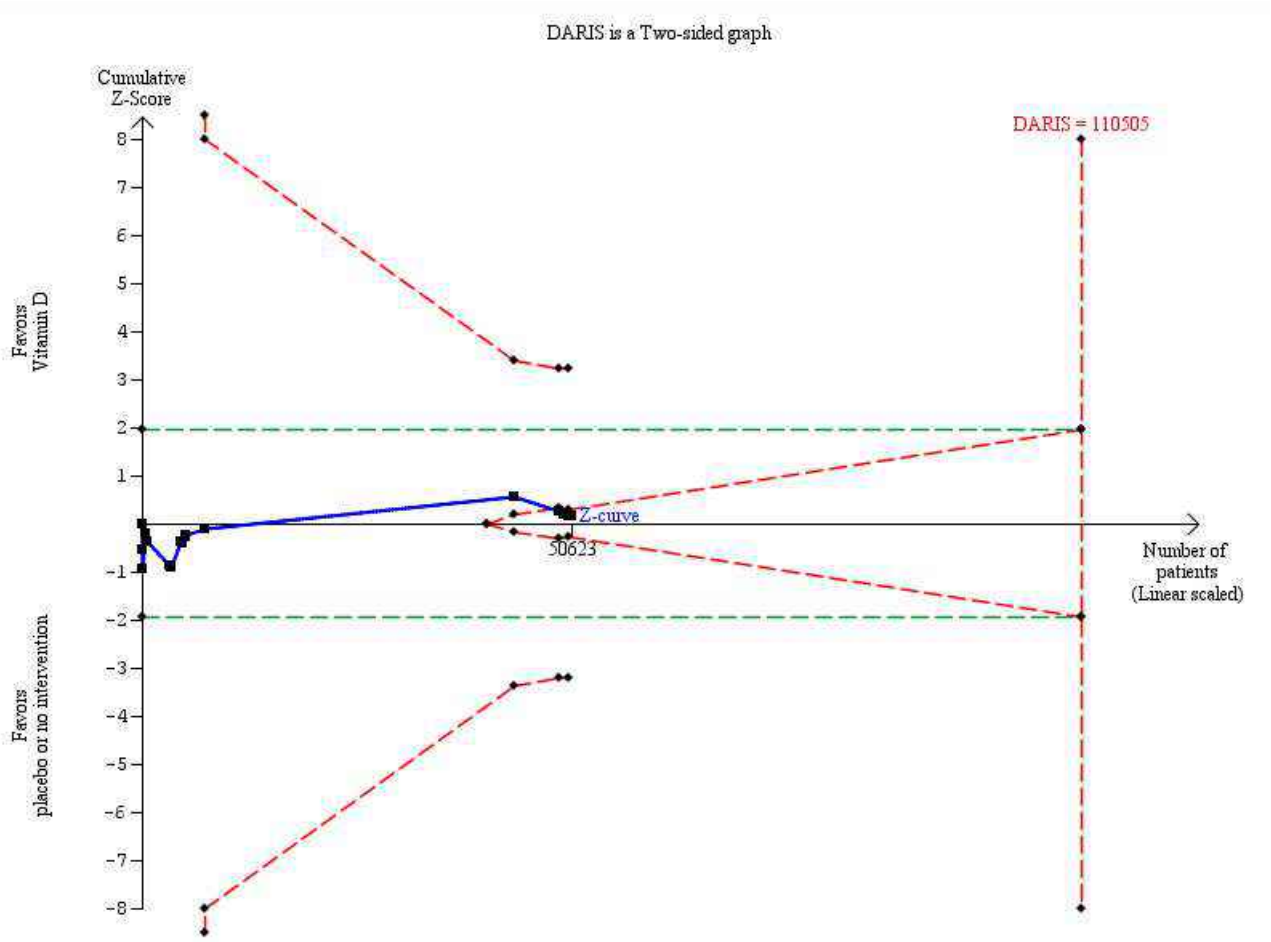
Primary outcomes

Cancer occurrence

Overall, vitamin D had no statistically significant effect on cancer occurrence (risk ratio (RR) 1.00 (95% CI 0.94 to 1.06); P = 0.88; I^2 = 0%; 18 trials; 50,623 participants; Analysis 1.1). A total of 1927 of 25,275 participants (7.6%) randomised to the vitamin D group and 1943 of 25,348 participants (7.7%) randomised to the placebo or no intervention group had cancer at the end of follow-up. Trial sequential analysis of all vitamin D trials suggests that we reached the futility area after the 10th trial, allowing us to conclude that any

possible intervention effect, if any, is lower than a 5% relative risk reduction (Figure 5).

Figure 5. Trial sequential analysis on cancer occurrence in the 18 vitamin D trials was performed based on cancer occurrence of 10% in the control group, a relative risk reduction of 5% with vitamin D supplementation, a type I error of 5%, and a type II error of 20% (80% power). There was no diversity. This resulted in a required information size of 110,505 participants. Trial sequential analysis of all vitamin D trials suggests that the futility area is reached after the 10th trial allowing us to conclude that any possible intervention effect, if any, is lower than a 5% relative risk reduction. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries. The red inward sloping lines represent the trial sequential monitoring boundaries.



Intervention effects according to bias risk of trials

Vitamin D had no statistically significant effect on cancer occurrence in trials with a low risk of bias (RR 1.08 (95% CI 0.89 to 1.31); P = 0.41; I^2 = 0%; 2 trials; 2991 participants), nor in trials with a high risk of bias (RR 0.99 (95% CI 0.93 to 1.05); P = 0.67; I^2 = 0%; 16 trials; 47,632 participants; Analysis 1.1). The difference between the effect estimate of vitamin D on cancer in trials with low risk of bias and trials with a high risk of bias was not statistically significant (P = 0.36); (Analysis 1.1).

Trials without risk of for-profit bias compared to trials with risk of for-profit bias

Vitamin D had no significant effect on cancer occurrence in the trials without risk of for-profit bias (RR 1.08 (95% CI 0.89 to 1.31); P = 0.41; I^2 = 0%; 2991 participants; 2 trials; Analysis 1.2). Vitamin D had no significant effect on cancer occurrence in the trials with risk of for-profit bias (RR 0.99 (95% CI 0.93 to 1.05); P = 0.67; I^2 = 0%; 47,632 participants; 16 trials; Analysis 1.2). The difference between the estimate of the effect of vitamin D on cancer occurrence in the trials without risk of for-profit bias and the trials with risk of for-profit bias was not statistically significant by the test of interaction (P = 0.36; Analysis 1.2).

Primary prevention compared to secondary prevention

Vitamin D had no significant effect on cancer occurrence in the primary prevention trials (RR 1.00 (95% CI 0.94 to 1.06); P = 0.87; I^2 = 0%; 50,334 participants; 16 trials; Analysis 1.3). Vitamin D had no statistically significant effect on cancer occurrence in the secondary

prevention trials (RR 1.33 (95% CI 0.26 to 6.96); P = 0.73; I^2 = 0%; 289 participants; 2 trials; Analysis 1.3). The difference between the estimates of the effect of vitamin D on cancer occurrence in the primary prevention and the secondary prevention trials was not statistically significant by the test of interaction (P = 0.73; Analysis 1.3).

Intervention effects according to vitamin D status

Vitamin D had no statistically significant effect on cancer occurrence in participants with vitamin D insufficiency (RR 0.99 (95% CI 0.93 to 1.05); P = 0.68; I^2 = 0%; 7 trials; 44,668 participants), nor in participants with vitamin D adequacy (RR 1.12 (95% CI 0.94 to 1.34); P = 0.21; I^2 = 0%; 9 trials; 4544 participants; Analysis 1.4). The difference between the estimates of vitamin D on cancer in trials including participants with vitamin D adequacy and trials including participants with vitamin D insufficiency was not statistically significant (P = 0.19; Analysis 1.4).

Sensitivity analyses taking attrition into consideration

Of the 18 trials reporting cancer occurrence, 17 trials reported the exact numbers of participants with missing outcomes in the intervention and control groups. One trial did not report losses to follow-up for the intervention groups separately (Lappe 2007). A total of 849 of 24,829 participants (3.4%) had missing outcomes in the vitamin D group versus 791 of 24,615 participants (3.2%) in the control group.

'Best-worst case' scenario

If we assume that all participants lost to follow-up in the experimental intervention group had no cancer and all those with missing outcomes in the control intervention group developed cancer, vitamin D supplementation significantly decreased cancer occurrence (RR 0.41 (95% CI 0.31 to 0.54); P < 0.00001; I^2 = 82%; 49,444 participants; 17 trials; Analysis 1.5).

'Worst-best case' scenario

If we assume that all participants lost to follow-up in the experimental intervention group developed cancer and all those with missing outcomes in the control intervention group had no cancer, vitamin D supplementation significantly increased cancer occurrence (RR 2.76 (95% CI 1.97 to 3.86); P < 0.00001; I^2 = 88%; 49,444 participants; 17 trials; Analysis 1.5).

Intervention effects according to administered form of vitamin D

Vitamin D_3 (cholecalciferol)

Vitamin D_3 was tested in 14 trials (49,891 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry). The adjusted-rank correlation test found no significant evidence of bias (P = 0.59), while a regression asymmetry test found significant evidence of bias (P = 0.01). Overall, vitamin D_3 had no statistically significant effect on cancer (RR 1.00 (95% CI 0.94 to 1.06); P = 0.88; I^2 = 0%; Analysis 1.6). Vitamin D_3 had no statistically significant effect on cancer in trials with a low risk of bias (RR 1.08 (95% CI 0.89 to 1.31); P = 0.41; I^2 = 0%; 2 trials; 2991 participants), nor in trials with a high risk of bias (RR 0.99 (95% CI 0.93 to 1.05); P = 0.67; I^2 = 0%; 12 trials; 46,900 participants; Analysis 1.6). The difference between the estimates of vitamin D_3 on cancer in trials with low risk of bias versus trials with a high risk of bias was not statistically significant (P = 0.36).

Vitamin D_3 and calcium

Vitamin D_3 administered singly versus placebo had no statistically significant effect on cancer (RR 1.03 (95% CI 0.90 to 1.17); P = 0.69; I^2 = 0%; 9200 participants; 8 trials; Analysis 1.7). Vitamin D_3 combined with calcium versus placebo or no intervention had no statistically significant effect on cancer (RR 0.97 (95% CI 0.91 to 1.04); P = 0.36; I^2 = 0%; 40,670 participants; 7 trials; Analysis 1.7).

Cancer site occurrence in trials using vitamin D_3

Vitamin D_3 had no significant effect on lung cancer (RR 0.86 (95% CI 0.69 to 1.07); P = 0.17; I^2 = 0%; 5 trials; 45,509 participants; Analysis 1.8); breast cancer (RR 0.97 (95% CI 0.86 to 1.09); P = 0.61; I^2 = 0%; 7 trials; 43,669 participants; Analysis 1.9); colorectal cancer (RR 1.11 (95% CI 0.92 to 1.34); P = 0.26; I^2 = 0%; 5 trials; 45,598 participants; Analysis 1.10); or pancreatic cancer (RR 0.91 (95% CI 0.57 to 1.46); P = 0.69; I^2 = 0%; 2 trials; 36,405 participants; Analysis 1.11). Vitamin D_3 had no significant effect on prostate, uterine, ovarian, oesophageal, stomach, or liver cancer (one trial each) (Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15, Analysis 1.16; Analysis 1.17).

Vitamin D_2 (ergocalciferol)

Vitamin D_2 was tested in one trial (302 participants). Vitamin D_2 had no statistically significant effect on cancer (RR 0.20 (95% CI 0.02 to 1.69); P = 0.14; Analysis 1.18).

Calcitriol (1,25-dihydroxyvitamin D)

Calcitriol was tested in three trials (430 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry). Overall, calcitriol had no statistically significant effect on cancer (RR 1.45 (95% CI 0.52 to 4.06); P = 0.48; I^2 = 0%; Analysis 1.19).

Cancer site occurrence in trials using calcitriol

Calcitriol had no significant effect on breast, uterine, or stomach cancer (one trial each) (Analysis 1.20; Analysis 1.21; Analysis 1.22)

All-cause mortality

Overall, vitamin D significantly decreased all-cause mortality (RR 0.93 (95% CI 0.88 to 0.98); P = 0.009; I^2 = 0%; 15 trials; 49,866 participants; Analysis 1.23). A total of 1854 of the 24,846 participants (7.5%) randomised to the vitamin D group and 2007 of the 25,020 participants (8.0%) randomised to the placebo or no intervention group died. In a trial with low risk of bias, mortality was not significantly changed (RR 0.90 (95% CI 0.77 to 1.07); P = 0.23; 1 trial; 2686 participants). In trials with a high risk of bias, mortality was significantly decreased in the vitamin D group (RR 0.93 (95% CI 0.88 to 0.99); P = 0.02; I^2 = 0%; 14 trials; 47,180 participants; Analysis 1.23). The difference between the effect estimate of vitamin D on mortality in trials with low risk of bias and in trials with a high risk of bias was not statistically significant (P = 0.75; Analysis 1.23). Trial sequential analysis on mortality in the 15 vitamin D trials was performed based on a mortality rate in the control group of 10%, a relative risk reduction (RRR) of 5% in the experimental group, a type I error of 5%, and type II error of 20% (80% power). There was no diversity. The required information size was 110,505 participants. The cumulative Z-curve did not cross the trial sequential monitoring boundary for benefit after the 15th trial.

Sensitivity analyses taking attrition into consideration

Of the 15 trials reporting mortality, 14 trials reported the exact numbers of participants with missing outcomes in the intervention

and control groups. One trial did not report losses to follow-up for the intervention groups separately (Lappe 2007). A total of 797 of 24,400 participants (3.3%) had missing outcomes in the vitamin D group versus 757 of 24,287 participants (3.1%) 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 supplementation significantly decreased mortality (RR 0.43 (95% CI 0.31 to 0.60); P < 0.00001; I^2 = 89%; 48,687 participants; 14 trials; Analysis 1.24).

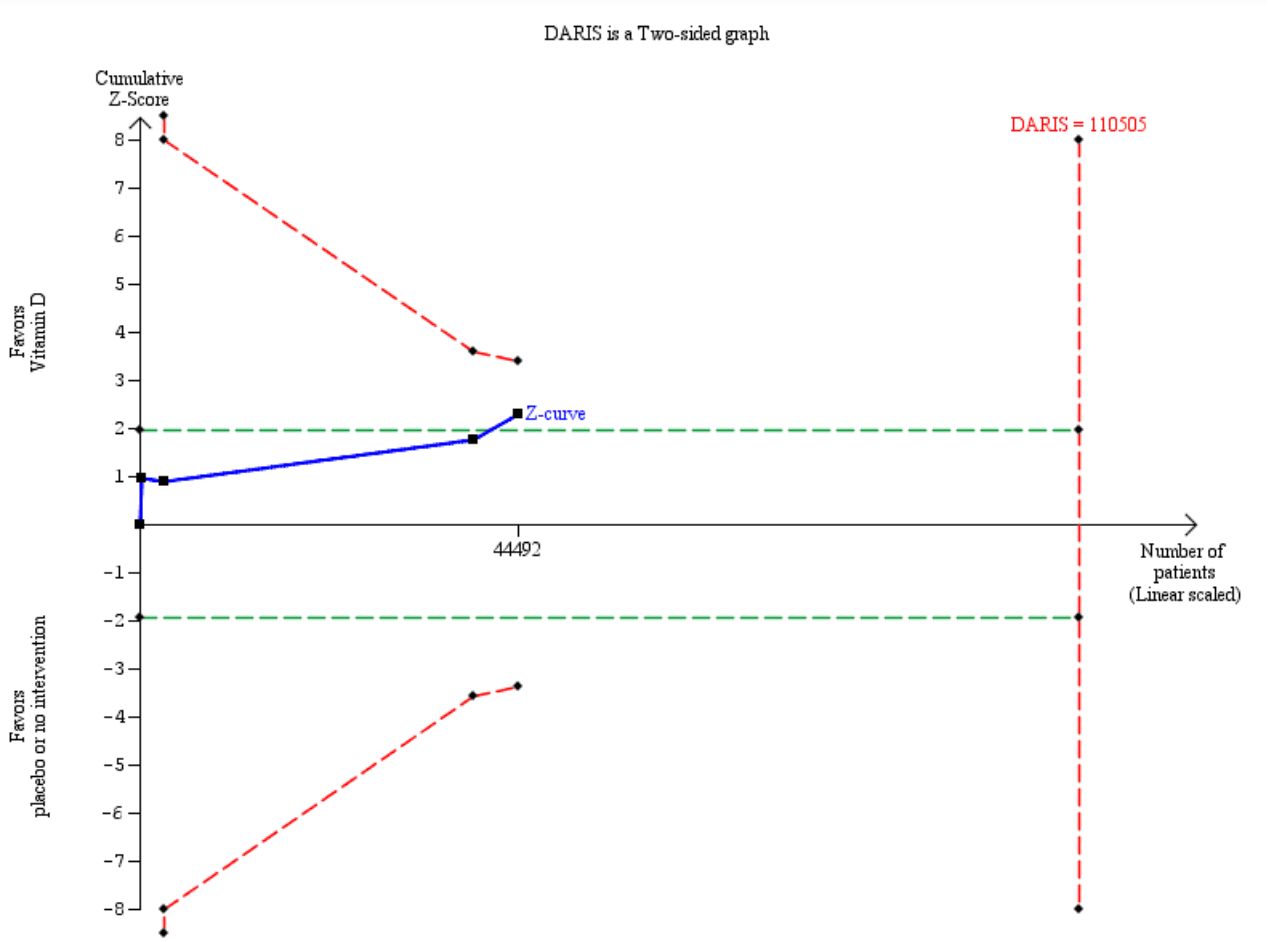
'Worst-best case' scenario

If we assume that all participants lost to follow-up in the experimental intervention group died and all those with missing outcomes in the control intervention group survived, vitamin D supplementation significantly increased mortality (RR 2.03 (95% CI 1.47 to 2.80); P < 0.0001; I^2 = 89%; 48,687 participants; 14 trials; Analysis 1.24).

Cancer mortality

Vitamin D_3 may decrease cancer mortality (RR 0.88 (95% CI 0.78 to 0.98); P = 0.02; I^2 = 0%; 4 trials; 44,492 participants; Analysis 1.25). However, we lack firm evidence for even a 10% RRR since the required information size of 110,505 participants has not yet been reached for such an effect, and the cumulative Z-curve did not cross the monitoring boundaries (Figure 6).

Figure 6. Trial sequential analysis on cancer mortality in the four vitamin D trials was performed based on cancer mortality of 3% in the control group, a relative risk reduction of 10% with vitamin D_3 supplementation, a type I error of 5%, and a type II error of 20% (80% power). There was no diversity. The required information size was 110,505 participants. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundary (red line) after the fourth trial. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries. The red inward sloping lines represent the trial sequential monitoring boundaries.



Sensitivity analyses taking attrition into consideration

All four trials reporting cancer mortality reported the exact numbers of participants with missing outcomes in the intervention and control groups. A total of 613 of 22,286 participants (2.8%) had missing outcomes in the vitamin D group versus 600 of 22,206 participants (2.7%) 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 from cancer, vitamin D supplementation significantly decreased mortality (RR 0.48 (95% CI 0.33 to 0.70); P < 0.0001; I^2 = 88%; 44,492 participants; 4 trials; Analysis 1.26).

'Worst-best case' scenario

If we assume that all participants lost to follow-up in the experimental intervention group died from cancer and all those with missing outcomes in the control intervention group survived, vitamin D supplementation significantly increased mortality (RR 1.69 (95% CI 1.04 to 2.75); P < 0.03; I^2 = 93%; 44,492 participants; 4 trials; Analysis 1.26).

Secondary outcomes

Adverse events

Several adverse events were reported (for example, hypercalcaemia, nephrolithiasis, hypercalciuria, renal insufficiency, cardiovascular disorders, gastrointestinal disorders, and psychiatric disorders). The supplemental forms of vitamin D (D_3 and D_2) (RR 1.41 (95% CI 0.64 to 3.09); P = 0.39; I^2 = 0%; 4 trials; 5879 participants), and active form of vitamin D (calcitriol) (RR 4.03 (95% CI 0.56 to 29.22); P = 0.17; I^2 = 53%; 2 trials; 332 participants) had no statistically significant effect on the risk of hypercalcaemia (Analysis 1.27).

Combined vitamin D_3 and calcium supplements significantly increased nephrolithiasis (RR 1.17 (95% CI 1.03 to 1.34); P = 0.02; I^2 = 0%; 3 trials; 42,753 participants; Analysis 1.27). Calcitriol had no statistically significant effect on nephrolithiasis (RR 0.33 (95% CI 0.01 to 8.10); P = 0.50; 1 trial; 246 participants; Analysis 1.27). The effect of vitamin D on the other adverse events was not statistically significant: hypercalciuria (RR 12.49 (95% CI 0.72 to 215.84); P = 0.08; 1 trial; 98 participants); renal insufficiency (RR 0.65 (95% CI 0.23 to 1.82); P = 0.41; I^2 = 4%; 3 trials; 5549 participants); cardiovascular disorders (RR 0.95 (95% CI 0.86 to 1.05); P = 0.28; I^2 = 0%; 8 trials; 4938 participants); gastrointestinal disorders (RR 1.19 (95% CI 0.88 to 1.59); P = 0.26; I^2 = 3%; 7 trials; 1624 participants); and psychiatric disorders (RR 1.42 (95% CI 0.46 to 4.38); P = 0.54; I^2 = 0%; 2 trials; 332 participants; Analysis 1.27).

Health-related quality of life and health economics

We did not find any data on health-related quality of life or health economics in the randomised trials included in this review.

DISCUSSION

Summary of main results

Our systematic review contains a number of important findings. We have found evidence that vitamin D supplements in the form of vitamin D_3, vitamin D_2, or calcitriol have no clear effect on occurrence of cancer in mainly elderly community-dwelling women. This effect does not seem to be due to random errors ('play of chance'). Vitamin D supplements have no clear effect on any specific cancer type. Vitamin D supplements decreased cancer mortality and all-cause mortality, but these estimates are at risk of type I errors due to the fact that too few participants were examined and to substantial attrition bias. Combined vitamin D_3 and calcium supplements increased nephrolithiasis, but it remains unclear from the included trials whether vitamin D_3, calcium, or both were responsible for this effect. Vitamin D supplements have no clear effects on other adverse events.

Overall completeness and applicability of evidence

Our published protocol described our plan to analyse the effect of vitamin D on cancer in primary and secondary prevention randomised trials in adults. We included all eligible randomised trials up to February 2014. All trials were conducted in high-income countries. Participants of both genders were included. Most of the participants were elderly community-dwelling women. The 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 of secondary prevention with low participation rates were included, so our ability to say anything about such patients is severely limited. We included randomised trials with both vitamin D–deficient participants and those who seemed to have adequate vitamin D levels at entry. We were unable to detect substantial differences regarding these variables on the estimated intervention effect on cancer. We found surprisingly little statistical heterogeneity in any of our analyses. Most trials assessed vitamin D_3, and our major conclusions relate to this intervention. Most of the trials were considered to be at high risk of bias, mainly for-profit bias. Our analyses revealed that outcome reporting was missing on more than 3% of participants. This number is too high when cancer occurrence is about 7% in the placebo or no intervention/placebo 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 on cancer. Although these extreme sensitivity analyses are unlikely, they reveal how few missing participants would need to have developed cancer to substantially change our findings of modest benefit into a null effect or maybe even harm. We therefore 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 2008). It represents a comprehensive review of the topic, including 18 randomised trials with more than 50,000 participants. This increases the precision and power of our analyses (Higgins 2011; Turner 2013). We were not able to find in the literature earlier meta-analyses of preventive trials of vitamin D on cancer occurrence. We conducted a thorough review in accordance with The Cochrane Collaboration methodology (Higgins 2011) and implementing findings of methodological studies (Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012a; Savović 2012b; Schulz 1995; Wood 2008). Between-trial statistical heterogeneity is almost absent from our meta-analyses, which enhances the consistency of our findings.

We conducted a number of subgroup analyses. We observed no statistically significantly different effects of the intervention of vitamin D supplementation on cancer in subgroup analyses of trials

at low risk of bias compared to trials at high risk of bias; of trials at no risk of for-profit bias compared to trials at risk of for-profit bias; of trials assessing primary prevention compared to trials assessing secondary prevention; of trials including participants with vitamin D level below 20 mg/mL at entry compared to trials including participants with normal vitamin D levels at entry; and of vitamin D_3 trials using concomitant calcium supplementation compared to vitamin D_3 trials without calcium.

We also performed trial sequential analyses to control for 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 obstacle in many of the included trials is the relatively large proportion of about 3% of participants with missing outcomes in both experimental and control groups. This opens the way 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. Our 'best-worst case' and 'worst-best case' scenario analyses revealed much more extreme confidence limits for cancer occurrence (95% CI 0.31 to 3.76) compared to our 'complete-case' scenario analysis (95% CI 0.94 to 1.06); for all-cause mortality (95% CI 0.31 to 2.80) compared to our 'complete-case' scenario analysis (95% CI 0.88 to 0.98), and for cancer mortality (0.33 to 2.75) compared to our 'complete-case' scenario analysis (95% CI 0.78 to 0.98). Those analyses convey a message of a noticeable degree of uncertainty regarding our results. This observation calls for more comprehensive meta-analyses of individual participant data.

We used GRADE to construct a 'Summary of findings' table for vitamin D for the review outcome measures. Results obtained by use of TSA were applied for the rating for imprecision. If there was insufficient evidence to reach a conclusion, i.e., if the TSA indicates that the required information size had not been reached, we downgraded the quality of the evidence by one level. We also used risk of attrition bias for the rating for imprecision. As the cumulative Z-curve for the intervention effect on cancer occurrence has reached the futility area for a 5% relative risk reduction (RRR) even though the required information size for such an effect has not been reached, there is precision enough to refute a 5% RRR. However, if, for example, a 2.5% RRR is still a clinically relevant effect, there may still be imprecision for detecting or rejecting such an effect of 2.5% RRR. If we consider a 2.5% RRR, which is equivalent to a number needed to treat for an additional beneficial outcome (NNTB) of 400, a worthwhile effect, then the downgrading for imprecision seems appropriate for the ability to refute a 5% RRR of cancer occurrence.

Potential biases in the review process

Most of the included trials are at high risk of bias, which undermines the validity of our results (Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012a; Savović 2012b; Schulz 1995; Wood 2008). Our meta-analyses show a lack of statistical heterogeneity, which may emphasise the consistency of our findings but should also raise concern (Ioannidis 2006). Statistical homogeneity may be due to inappropriate inferences of the asymptotic Q test with sparse data (Ioannidis 2006). We have also performed trial sequential analyses, based on the estimation of the diversity-adjusted required information size in order to avoid an undue risk of random errors in a cumulative meta-analysis and to prevent premature statements of superiority of vitamin D or of lack of effect (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009).

Certain potential limitations of this review warrant consideration. As with all systematic reviews, our findings and interpretations are limited by the quality and quantity of available evidence on the effects of vitamin D on cancer. Despite extensive speculations in the literature and a large number of epidemiological studies that claim cancer preventive effects of vitamin D, few randomised trials have been conducted assessing cancer occurrence. The duration of supplementation and duration of follow-up was short in some of the included trials compared to the long process of carcinogenesis. This may make it difficult to detect any effects, beneficial or harmful. Among the 18 included randomised trials, cancer occurrence was the primary prespecified outcome in few of them. Different forms of vitamin D were used for supplementation. The majority of included trials used vitamin D_3, one trial tested vitamin D_2, and three trials tested calcitriol. Our subgroup analyses found that the effect of vitamin D on cancer was neutral, irrespective of the form of vitamin D used for supplementation. Most trials investigated the effects of vitamin D administered at lower doses than those recently suggested as cancer-preventive (Garland 2011). All the included trials came from high-income countries, and the majority of them included participants without overt deficiencies of vitamin D. Accordingly, we are unable to assess how vitamin D affects cancer in populations with specific needs.

Agreements and disagreements with other studies or reviews

We found that vitamin D had neutral effect on cancer occurrence. This finding is in accord with the result of our previous review (Bjelakovic 2014), and contradicts the results of epidemiological studies (Bikle 2014; Garland 2006; Giovannucci 2005; Ordóñez-Mena 2013; Redaniel 2014; Woloszynska-Read 2011; Yin 2013). Our results are in accord 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 found no substantive differences regarding the effect of vitamin D on cancer in trials including participants with vitamin D insufficiency (25-hydroxyvitamin D level less than 20 ng/mL) compared to trials including participants with optimal vitamin D status. Optimal vitamin D status has been linked to decreased incidence of several types of cancer (Garland 2007; Gorham 2007). However, a number of observational studies have also suggested that high vitamin D status might be connected with increased oesophageal (Chen 2007), pancreatic (Stolzenberg-Solomon 2006), breast (Goodwin 2009), and prostate cancer risks (Ahn 2008). One should consider the possibility of a U-shaped relationship between vitamin D status and cancer risk (Toner 2010; Tuohimaa 2012). Once again, we may be witnessing the flawed inferences that are sometimes drawn from observational epidemiological data (Jakobsen 2013).

We have examined the influence of different forms of vitamin D on cancer occurrence. We have found neutral effect irrespective of the form of vitamin D used. Our previous systematic review on vitamin D and mortality has found weak evidence that only vitamin D_3 may be of benefit for survival (Bjelakovic 2014). We found no evidence for vitamin D_2, alfacalcidol, and calcitriol affecting mortality, but these estimates are at risk of type II errors (the chance of not rejecting the null hypothesis when it is in fact false) due to the fact that small groups of participants were examined. A number of recently published clinical trials (Armas 2004; Heaney 2011; Lehmann 2013; Leventis 2009; Logan 2013; Romagnoli 2008; Trang 1998), and the systematic review (Tripkovic 2012) found evidence that vitamin D_3 increases serum 25-hydroxyvitamin D more efficiently than vitamin D_2. Several clinical trials have been conducted to examine the effects of alfacalcidol and calcitriol on different health outcomes. These trials have mostly included women with osteoporosis (Ott 1989; Shiraki 2004) and people with chronic kidney disease (Palmer 2009). Due to the lack of a demonstrable effect, and observed adverse events (hypercalcaemia), the active forms of vitamin D are increasingly being replaced with the supplemental forms of vitamin D (cholecalciferol and ergocalciferol). Three trials included in our present systematic review tested calcitriol. The evidence for an effect on cancer is inconclusive, but the sample size was too small to exclude possible effects. We were not able to identify trials testing alfacalcidol that reported cancer occurrence at the end of the follow-up period.

The effect of vitamin D_3 on cancer occurrence was not statistically significant in trials using vitamin D_3 singly or trials using vitamin D_3 combined with calcium. Because of the small number of included trials assessing vitamin D_3 alone or combined with calcium, the findings could be due to a type II error. Our finding seems consistent with the result obtained by Bristow 2013, who found that calcium supplements did not affect cancer, but contradict 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. 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 no evidence for an effect 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 non-institutionalised postmenopausal women (Moyer 2013).The complex interactions between vitamin D and calcium make it difficult to separate their effects (Lips 2012). More clinical research seems needed.

We have examined the influence of vitamin D supplementation on different cancer types. Vitamin D showed no substantive effect on any specific cancer type. Our results are in accord with the results of the recently published systematic review and meta-analysis investigating the role of vitamin D supplementation on breast cancer (Sperati 2013). Our results contradict earlier speculations in the literature about the preventive effects of vitamin D on certain cancer types (Fleet 2012; Woloszynska-Read 2011).

We have found no evidence for an effect of vitamin D supplements on cancer occurrence. However, vitamin D supplements seemed to decrease cancer mortality. Epidemiological studies that examined the relationship between vitamin D status and cancer mortality have shown mixed results. Pilz and coworkers found that optimal vitamin D status seems to be related to decreased cancer mortality in some studies (Pilz 2009; Pilz 2013). On the other hand, Freedman 2010 found no overall relationship between vitamin D status and cancer mortality in the general population. Our finding of no evidence that vitamin D has an effect on cancer occurrence seems to be at odds with the statistically significant beneficial effect of vitamin D on cancer mortality. However, due to low participation rates in the included trials, the decreased cancer mortality could be a random error as indicated by our trial sequential analysis. One should also consider that as yet unknown preventive effects of vitamin D supplementation on premature death, which may not necessarily influence cancer incidence, might play a role (Bjelakovic 2014).

Vitamin D supplements decreased all-cause mortality. This is in accord with the results of our previous review of the role of vitamin D in mortality prevention (Bjelakovic 2014), in which we disregarded the risks of random error and attrition bias. However, if these risks are considered, we do not yet know whether vitamin D affects mortality.

Combined vitamin D_3 and calcium supplements increased nephrolithiasis. This is in accord with the results of our previous review (Bjelakovic 2014). Other adverse events, including elevated urinary calcium excretion; renal insufficiency; cardiovascular, gastrointestinal, or psychiatric disorders, were not substantively influenced by vitamin D supplementation.

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

Despite biological plausibility for the role of vitamin D in the prevention of cancer, the available evidence does not seem to support this possibility. Several recently published evidence reports have assessed the influence of vitamin D and calcium on different health outcomes (Bolland 2014; Chung 2011; Cranney 2007; Moyer 2013; Rosen 2012). The majority of the findings on different health outcomes including cancer were equivocal. The US Institute of Medicine reported that available evidence supports a role for vitamin D and calcium in skeletal health (IOM 2011). The evidence was, however, considered insufficient and inconclusive for extraskeletal outcomes including cancer (IOM 2011). Most recent systematic review and meta-analyses concluded that vitamin D supplementation for osteoporosis prevention in free-living adults without specific risk factors for vitamin D deficiency seems to be inappropriate (Reid 2014). In the same vein, the recently updated Systematic Evidence Review for the US Preventive Service Task Force found no evidence of benefit from vitamin supplementation for the prevention of cancer and cardiovascular disease (Fortmann 2013). Accordingly, these comprehensive reports are compatible with our findings.

It seems that health claims are again ahead of the evidence. It is very likely that low vitamin D status is not the cause, but rather the consequence of disease (Autier 2014; Guallar 2010; Guallar

2013; Harvey 2012; Kupferschmidt 2012). Results of several large ongoing randomised trials that assess vitamin D supplementation for different health outcomes will likely help us to elucidate the role of vitamin D.

AUTHORS' CONCLUSIONS

Implications for practice

We found no evidence that vitamin D, irrespective of the form used, has an effect on cancer occurrence in predominantly elderly community-dwelling women. Vitamin D decreased cancer mortality and all-cause mortality, but these estimates are at risk of type I errors due to the fact that too few participants were examined. Combined vitamin D_3 and calcium supplements increased nephrolithiasis.

Implications for research

We need more evidence before drawing firm conclusions on the effect of vitamin D on cancer. More randomised trials are needed on the effects of vitamin D_3 on cancer in younger persons, in men, and in people with low vitamin D status. More randomised trials assessing a longer duration of vitamin D intervention and higher dosages of vitamin D may also be needed. The effects of vitamin D on health-related quality of life and cost effectiveness deserve further investigation. Future trials should be designed according to the SPIRIT guidelines (Chan 2013) and reported according to the CONSORT guidelines (www.consort-statement.org). Future trials should reduce attrition bias to a minimum.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

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	**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 < 7; 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 < 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 (1000 mg) daily (n = 1311) Intervention group 3: vitamin D_3 (800 IU) plus calcium (1000 mg) daily (n = 1306)

Avenell 2012 *(Continued)*

	Comparator 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	**Outcomes reported in abstract of publication** **Primary outcomes:** all-new low-energy fractures including clinical, radiologically-confirmed vertebral fractures, but not those of the face or skull. **Secondary outcomes:** none defined.
Stated aim of study	Quote from the publication: "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." „The United Kingdom Medical Research Council funded the central organization of the RECORD Trial (Grant G9706483). In the last two years, Roger M. Francis has received lecture fees from Shire Pharmaceuticals Group plc. All other authors have nothing to declare in the last two years. Before this, all authors received research grant support to their institutions from the United Kingdom Medical Research Council, Shire Pharmaceuticals Group plc, and Nycomed AS for the RECORD Trial.“ 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	Quote from the publication: "Randomization was centralized, computer generated, stratified by canter, and minimized by age (under 80 yr or 80 yr and over), gender, time since fracture (previous 3 months or longer), and type of enrolling fracture (proximal femur, distal forearm, clinical vertebral, and other)." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "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)." Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "All outcomes were reported or verified by people who were masked to the allocation scheme. Tablets varied in size and taste, and so each had matching placebos. Calcium and calcium and vitamin D tablets were large, and those for vitamin D were small. Placebos matched in size were provided for each of these three types of tablets."

Avenell 2012 *(Continued)*

		Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "All outcomes were reported or verified by people who were masked to the allocation scheme. Tablets varied in size and taste, and so each had matching placebos. Calcium and calcium and vitamin D tablets were large, and those for vitamin D were small. Placebos matched in size were provided for each of these three types of tablets." Comment: 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)	Low risk	Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	High risk	Comment: predefined, or clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "Shire Pharmaceuticals co-funded the drugs together with Nycomed who also manufactured the drugs." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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	**Number of participants randomised:** 244 healthy, nonosteoporotic women, aged 60 years or over (mean 68). **Inclusion criteria:** healthy, non-osteoporotic women, aged 60 years or over. **Exclusion criteria:** clinical osteoporosis or chronic disease (e.g., diabetes mellitus, cardiovascular disease, cancer, fat malabsorption syndromes), routine medication that interferes with vitamin K, vitamin D, or bone metabolism (notably warfarin and steroids), and consumption of nutrient supplements that provided in excess of 30 µg vitamin K, 400 IU vitamin D, or 500 mg calcium daily.
Interventions	Participants were randomly assigned to receive: Intervention group 1: vitamin D_3 (400 IU) plus calcium 1000 mg daily (n = 62) Intervention group 2: vitamin D_3 (400 IU) plus calcium 1000 mg plus vitamin K_1 200 µg daily (n = 61) Intervention group 3: vitamin K_1 200 µg daily (n = 60) Comparator group: matched placebo daily (n = 61), for a 2-year period.
Outcomes	**Outcomes reported in abstract of publication.:** **Primary outcomes:** bone mineral density. **Secondary outcomes:** possible interaction with vitamin K, of vitamin D and calcium.

Bolton-Smith 2007 *(Continued)*

Stated aim of study	Quote from the publication: "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%)." This study was supported by a contract (N05001) from the UK Food Standards Agency. 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	Quote from the publication: "An independent statistician at Hoffmann-La Roche, who had no other connection to the study, provided a computer-generated randomisation list to the researchers Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "An independent statistician at Hoffmann-La Roche, who had no other connection to the trial, provided a randomisation list to the researchers." Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: 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)	Low risk	Quote from the publication: "A flow chart with the numbers of subjects randomly assigned and retained in each treatment arm at successive 6-month visits is shown in Fig. 1. Of the 244 eligible women randomised into the study, 209 (85.6%) completed the two-year study, with good supplement adherence based on pill count (median, 99; interquartile range, 97.3 to 99.8%). Reasons for withdrawal were illness unrelated to the study (n = 17); volunteer preference, noncompliance, or other violations of the inclusion criteria (n = 14); and low BMD necessitating further medical intervention (n = 4)." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: predefined, or clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "Hoffmann-La Roche Vitamins Division (now DSM Nutritional Products), Basel, Switzerland provided the supplementation tablets." Comment: the trial was sponsored by the industry.

Bolton-Smith 2007 *(Continued)*

Other bias	Low risk	Comment: the trial appears to be free of other components that could put it at risk of bias.

Brunner 2011

Methods	Women's Health Initiative (WHI) Multicentre, randomised, double-blind, placebo-controlled trial using parallel group design (2 intervention groups)
Participants	**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 < 3 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	**Number of study centres:** 40 Participants were randomly assigned to receive: Intervention group: vitamin D_3 (400 IU) plus calcium (1000 mg) daily (n = 18,176) Comparator group: matched placebo daily (n = 18,106), for a 7-year period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** hip fracture. **Secondary outcomes:** other fractures and colorectal cancer**.**
Stated aim of study	Quote from the publication: "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

Brunner 2011 *(Continued)*

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."

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We extracted data about cancer incidence and cancer mortality from the following 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	Quote from the publication: "Eligible women were randomly assigned in a double-blind fashion to receive supplements or placebo (provided by GlaxoSmithKline) in equal proportions with use of a permuted-block algorithm stratified according to clinical canter and age." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "Eligible women were randomly assigned in a double-blind fashion to receive supplements or placebo." Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "Blinding of the study was achieved by bottle labeling" Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "Blinding of the study was achieved by bottle labeling" Comment: 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)	Low risk	Quote from the publication: "Ninety-seven percent of participants were followed to study completion. At the time the study ended, 352 women assigned to calcium with vitamin D supplements and 332 women assigned to placebo had withdrawn; 144 and 152, respectively, had been lost to follow-up; and 744 and 807, respectively, had died."

Brunner 2011 *(Continued)*

		Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: predefined, or clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "The active trial drug and placebo were supplied by GlaxoSmithKline Consumer Healthcare (Pittsburgh)." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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 (2 intervention groups)
Participants	**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 4 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: calcium-vitamin D_3-fortified milk containing vitamin D_3 (800 IU) plus calcium (1000 mg) daily (n = 85) Comparator group: usual diet (n = 82), for a 2-year period; participants were followed for additional 1½ years.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** bone mineral density. **Secondary outcomes:** none defined.
Stated aim of study	Quote from the publication: "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%." "None of the authors had a personal or financial conflict of interest." Additional information on mortality was received through personal communication with Professor Robin Daly (04.02.2009).

Risk of bias

Daly 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "Within each stratum, participants were randomised to either the milk supplementation or control group from computer generated random number lists." Comment: sequence generation was achieved using a computer-generated random number list.
Allocation concealment (selection bias)	High risk	Quote from the publication: "Men randomised to receive the calcium-vitamin D3–fortified milk were asked to consume 400 ml (2 × 200-ml tetra packs) of reduced-fat (~1%) ultra high temperature (UHT) milk specifically formulated by Murray Goulburn Cooperative Co. (Brunswick, Australia). Participants assigned to the control group continued with their usual diet." Comment: the allocation sequence was known to the investigators who assigned participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: trial was not blinded, so that the allocation was known during the trial. Placebo was not used.
Incomplete outcome data (attrition bias)	Low risk	Quote from the publication: "The reasons for not attending the follow-up visit in the milk supplementation group were that the subject was not interested (n = 12), had been diagnosed with cancer (n = 2), could not be contacted (n = 4), had moved away (n = 2), or had died (n=1). For the control group, the main reasons were that the subject was not interested (n = 13), had been diagnosed with cancer (n = 2), could not be contacted (n = 2), or had moved away (n = 2)." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: predefined, or clinically relevant and reasonably expected outcomes were reported.
For-profit bias	Unclear risk	Quote from the publication: "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)."
Other bias	Low risk	Comment: 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	**Number of participants randomised:** 489 healthy elderly women 65 to 77 (mean 71.5) years of age.

Gallagher 2001 *(Continued)*

	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) Comparator group: matched placebo daily (n = 123) for a 3-year period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** change in bone mineral density of the femoral neck and spine. **Secondary outcomes:** incidence of non-vertebral fractures.
Stated aim of study	Quote from the publication: "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 oestrogens, 86% and 92%; medroxyprogesterone acetate, 91% and 94%; calcitriol, 87% and 93%; placebos, 94% and 92%." This study was primarily supported by the NIH (Grants UO1- AG10373 and RO1-AG10373). Additional support was provided 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	Quote from the publication: "The study assigned subjects to treatment groups using simple randomization stratified on hysterectomy status." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "An independent statistical group performed the blinding and randomization." Comment: 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.

Gallagher 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "All investigators and staff conducting the study remained blinded throughout the treatment period." Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "All investigators and staff conducting the study remained blinded throughout the treatment period." Comment: 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)	Low risk	Quote from the publication: "The major reasons given for discontinuing medication were bleeding problems (21), breast tenderness (13), other significant health problems (21), lost interest in the study (19), cerebrovascular incident, cerebral thrombosis, cerebral haemorrhage, transient Ischaemic attack (15), and gastrointestinal problems (14). Five of the subjects died during study from causes unrelated to study medication. There were four deaths from congestive heart failure, one from each treatment group, and one case of sudden death due to myocardial infarct on the combination treatment." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: predefined, or clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "The active trial drug and placebo were supplied by Wyeth-Ayerst Laboratories, Inc Pharm, Hoffman-LaRoche Inc and Pharmacia & Upjohn, Inc." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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 (2 intervention groups)
Participants	**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 4 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 were not suitable for the study.
Interventions	Participants were randomly assigned to receive: Intervention group: cholecalciferol 150,000 3-monthly (n = 353) Comparator group: placebo vitamin D 3-monthly (n = 333),

Glendenning 2012 *(Continued)*

	for a 9-month period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** falls, muscle strength, and mobility. **Secondary outcomes:** serum 25-hydrohyvitamin D levels, and adverse events.
Stated aim of study	Quote from the publication: "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	"The study was supported by the Department of Health, Western Australia State Health Research Advisory Council Research Translation Project Grant, Sir Charles Gairdner Hospital Research Advisory Committee Grant, and Royal Perth Hospital Medical Research Foundation Grant."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "The study used a computer generated randomization sequence with a block size of 10 to assign participants to either cholecalciferol therapy or placebo in a ratio of 1:1." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "The randomization sequence was generated by a pharmacist at Captain Stirling Pharmacy, Perth, Western Australia, where participants were assigned to intervention and test capsules were appropriately labeled." Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "The study participants and researchers at the Sir Charles Gairdner Hospital responsible for recruitment and assessment of outcomes measures remained blinded to group assignment." Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "The study participants and researchers at the Sir Charles Gairdner Hospital responsible for recruitment and assessment of outcomes measures remained blinded to group assignment." Comment: 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)	Low risk	Quote from the publication: "Subject disposition is presented in Figure 1." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: pre-defined, or clinically relevant and reasonably expected outcomes were reported.

Glendenning 2012 *(Continued)*

For-profit bias	Unclear risk	Quote from the publication: "Captain Stirling Pharmacy formulated the test capsules." Comment: the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship is provided.
Other bias	Low risk	Comment: 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 (2 intervention groups)
Participants	**Number of participants randomised:** 98 elderly ambulatory men and women (54% women), aged 70 to 97 (mean 79.1) years of age **Inclusion criteria:** elderly ambulatory men and women. **Exclusion criteria:** serum calcium levels of 2.57 mmol/L or more, urinary calcium levels of 7.28 mmol/day or more, creatinine clearance less than 0.42 mmol/s, history of hypercalcaemia, nephrolithiasis, seizure disorder, hyperparathyroidism, treatment with calcium, vitamin D or thiazide diuretics, and average calcium intake greater than 1000 mg/day.
Interventions	Participants were randomly assigned to receive: Intervention group: calcitriol (0.5 µg) daily (n = 50) Comparator group: placebo vitamin D (n = 48), for a 6-months period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** muscle strength. **Secondary outcomes:** none defined.
Stated aim of study	Quote from the publication: "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."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Comment: 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 of participants and personnel (performance bias) All outcomes	Unclear risk	Quote from the publication: "We conducted a randomized controlled, double-blinded trial in 98 men and women volunteers over 69 yr old."

Grady 1991 *(Continued)*

		Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote from the publication: "We conducted a randomized controlled, double-blinded trial in 98 men and women volunteers over 69 yr old." Comment: 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)	Low risk	Quote from the publication: "One subject (assigned to treatment with 1,25-$(OH)_2$ $2D_3$) died following surgery for gastric cancer during the second month of the study. A second subject (assigned to placebo) suffered a stroke during the third month of the study and was unable to complete the protocol." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: predefined, or clinically relevant and reasonably expected outcomes are reported on.
For-profit bias	High risk	Quote from the publication: "Calcitriol and placebo capsules were provided by Hoffman-LaRoche (Nutley, NJ)." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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 (2 intervention groups)
Participants	**Number of participants randomised:** 70 geriatric women older than 65 years with serum 25 hydroxyvitamin D concentrations between 20 and 50 nmol/L **Inclusion criteria:** vitamin D-insufficient geriatric women able to walk and follow simple instructions. **Exclusion criteria:** treatment with vitamin D or steroids in the previous 6 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 participants' compliance (i.e., surgery planned).
Interventions	Participants were randomly assigned to receive: Intervention group: vitamin D_3 (400 IU) plus calcium (500 mg) daily (n = 36) Comparator group: placebo vitamin D_3 plus calcium (500 mg) daily (n = 34), for a 6-months period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** muscle strength, power and functional mobility. **Secondary outcomes:** none defined.

Janssen 2010 *(Continued)*

Stated aim of study	Quote from the publication: "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	"This study was financially supported by the Prevention Program (Project 96070602) of ZonMw, The Netherlands." Additional information on funding of the trial received through personal communication with Dr Henie C.J.P. Janssen (06.02.2014)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "Randomization was done in blocks of six, to minimize any seasonal influence between the treatment groups." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "Trial medication was provided by an independent hospital pharmacist who also performed the randomization." Comment: allocation was controlled by a central and independent randomisation unit.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "No person involved, i.e., subjects, investigators, or physicians who treated the subjects, had access to the randomization procedure." Comment: 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..
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "No person involved, i.e., subjects, investigators, or physicians who treated the subjects, had access to the randomization procedure." Comment: the outcome measurement is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Quote from the publication: "Eleven subjects withdrew from the trial: death (1), cognitive decline (4), a malignant lung tumor (1), recurrent upper urinary tract infections with malaise (2), acute emotional distress (1), hip fracture (1) and peritonitis (1)." Comment: the underlying reasons for missing data are unlikely to make treatment effects depart from plausible values.
Selective reporting (reporting bias)	Low risk	Comment: predefined, or clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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	**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:** non-osteoporotic, 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 (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 vitamin 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 (days 1 to 21) and 1 mg cyproterone acetate (days 12 to 21) and an intervention-free interval (days 22 to 28) plus vitamin D_3 (300 IU) and calcium (500 mg) daily (n = 116) Comparator group: placebo daily (n = 116), for a 5-year period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** bone mineral density. **Secondary outcomes:** none defined.
Stated aim of study	Quote from the publication: "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 dropouts 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)." "This work was supported by Leiras Oy, Finland and Schering AG, Germany."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "The women were randomized to the four different groups through use of a computer program." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "The group allocation was masked in data analysis."

Komulainen 1999 *(Continued)*

		Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "The personnel involved were unaware of the group allocations." Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "The personnel involved were unaware of the group allocations." Comment: 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)	Low risk	Quote from the publication: "Of the 464 women enrolled in the study, 435 (94%) eligible women completed it. Among the 29 drop-outs were 20 women who could not be contacted in the end of the study and 3 who died from unrelated causes during the study period. In addition, 6 osteoporotic women were withdrawn from the study after enrolment when subject eligibility data were available (baseline lumbar or femoral BMD above -2 SD of the mean of the whole study population)." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: predefined, or clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "The trial was supported by Leiras Oy, Finland and Schering AG, Germany; Hormone replacement therapy was provided by Climen, Schering AG, Germany; Vitamin D_3 by D-Calsor, Orion Ltd, Finland, and calcium by Rohto Ltd, Tampere, Finland." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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 (3 intervention groups)
Participants	**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 4 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)

Lappe 2007 *(Continued)*

	Intervention group 2: vitamin D_3 placebo plus calcium (1400 to 1500 mg) daily (n = 445) Comparator group: placebo, consisting of both vitamin D_3 placebo and a brand-specific calcium placebo daily (n = 288), for a 4-year period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** fracture incidence. **Secondary outcomes:** cancer incidence.
Stated aim of study	Quote from the publication: "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." „None of the authors was affiliated in any way with an entity involved with the manufacture or marketing of vitamin D. RRR has served on scientific advisory boards for Lilly, P&G, Merck, Roche, and Amgen. RPH has served on scientific advisory boards for the International Dairy Foods Association and ConAgra and on the speaker bureau for Merck and P&G.“ 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	Quote from the publication: "The study statistician generated the randomization sequence with the use of a computer-generated permuted blocks (n = 5) randomization scheme, and the study nurses enrolled the subjects and assigned them to groups." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "The study statistician generated the randomization sequence." Comment: 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 of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there was insufficient information to assess whether blinding was likely to introduce bias into the results.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there was insufficient information to assess whether blinding was likely to introduce bias into the results.
Incomplete outcome data (attrition bias)	High risk	Quote from the publication: "Of 1180 women enrolled, 1024 (86.8%) completed the 4 y of study. Most of the losses (n = 92) occurred within the first year." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were not described.

Lappe 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: predefined, or clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "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) Comment: the trial was sponsored by the industry."
Other bias	Low risk	Comment: the trial appears to be free of other components that could put it at risk of bias.

Larsen 2012

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (2 intervention groups)
Participants	**Number of participants randomised:** 130 participants with hypertension, mean age 60 years, 69% women. **Inclusion criteria:** arterial hypertension, white, and resident in Denmark (56° N). **Exclusion criteria:** 24-hour ambulatory blood pressure > 150 mm Hg systolic and/or 95 mm Hg diastolic, malignant disease, atrial flutter or fibrillation, hypercalcaemia, pregnancy or nursing, alcohol abuse (> 24 g of alcohol per day for women and > 36 for men), regular use of nonsteroidal anti-inflammatory drugs or glucocorticoids, daily vitamin D intake exceeding 10 µg of chole- or ergocalciferol, tanning bed usage, and changes in antihypertensive medication during trial period.
Interventions	Participants were randomly assigned to receive: Intervention group: cholecalciferol 3000 IU daily (n = 65) Comparator group: placebo vitamin D daily (n = 65), for a 20-week period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** 24-hour systolic blood pressure. **Secondary outcomes:** 24-hour diastolic blood pressure and heart rate, central blood pressure, central augmentation index, carotid-femoral pulse wave velocity, urinary calcium-creatinine ratio, and plasma levels of renin, angiotensin II, aldosterone, brain natriuretic peptide, 25(OH)D, intact parathyroid hormone, ionized calcium, phosphate, and fibroblast growth factor 23.
Stated aim of study	Quote from the publication: "to test the hypothesis that daily cholecalciferol supplementation in the winter lowers blood pressure in patients with hypertension."
Notes	Mean compliance by pill count was 99% in both groups. "This study was supported by The Danish Osteoporosis Association; The Local Health Service in Randers, Randers Central Hospital, Aarhus County; The Pharmacy Association of 1991; The Danish Health Foundation; and Nycomed DAK."

Risk of bias

Bias	Authors' judgement	Support for judgement

Larsen 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote from the publication: "Participants were allocated to treatment via permutated block randomization conducted at http://www.randomization.com."
Allocation concealment (selection bias)	Low risk	Quote from the publication: The hospital pharmacy generated the randomization sequence and labeled the bottles. The randomization code was kept in a sealed envelope until after the last visit of the last participant." Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "Investigators, participants, and other study personnel were blinded to treatment assignment for the duration of the study." Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "Investigators, participants, and other study personnel were blinded to treatment assignment for the duration of the study." Comment: the assessment of outcomes was not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Quote from the publication: "Eighteen patients were excluded due to withdrawal of consent (6), 24-h systolic blood pressure >150 mm Hg (5), inability to complete 24-h blood pressure measurement (2), changes in antihypertensive medication (2), ibuprofen treatment (1), cancer (1), and major surgery close to follow-up (1). Thus, 112 patients completed the trial." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: all clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "Cholecalciferol and placebo tablets were obtained from Ferrosan A/S, Soeborg, Denmark." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: the trial appears to be free of other components that could put it at risk of bias.

Murdoch 2012

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (2 intervention groups)
Participants	**Number of participants randomised:** 322 healthy adults mean age 47 years, 75% women **Inclusion criteria:** aged 18 years or older, able to give written informed consent, a resident of the Christchurch region for the study period. **Exclusion criteria:** use of vitamin D supplements other than as part of a daily multivitamin preparation (in which the daily intake was ≤ 400 IU); use of immunosuppressants or medications that interfere with vitamin D metabolism (e.g., thiazide diuretics, phenytoin, carbamazepine, primidone, phenobarbital, doses of prednisone > 10 mg/d, methotrexate, azathioprine, cyclosporin); history of hypercalcaemia

Murdoch 2012 *(Continued)*

	or nephrolithiasis; sarcoidosis; kidney disorders requiring dialysis or polycystic kidney disease; cirrhosis; current malignancy diagnosis in which the cancer was aggressive and prognosis was poor; baseline plasma calcium (corrected for plasma albumin concentration) greater than 10.4 mg/dL or less than 8.4 mg/dL; enrolment or planned enrolment in other research that would conflict with full participation in the study or confound the observation or interpretation of the study findings (e.g., in which 25-OHD levels were tested and results known by the participant; in which the participant was required to take conflicting medications; any investigations of viruses and antiviral treatments); and pregnancy or planned pregnancy during the study period
Interventions	Participants were randomly assigned to receive: Intervention group: an initial dose of 200,000 IU oral vitamin D_3, then 200,000 IU 1 month later, then 100,000 IU monthly (n = 161) Comparator group: placebo administered in an identical dosing regimen (n = 161), for a 1½-year period
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** number of upper respiratory tract infections episodes. **Secondary outcomes:** duration of upper respiratory tract infections episodes, severity of upper respiratory tract infections episodes, and number of days of missed work due to upper respiratory tract infections episodes.
Stated aim of study	Quote from the publication: "To determine the effect of vitamin D supplementation on incidence and severity of upper respiratory tract infections in healthy adults."
Notes	"The study was funded by the Health Research Council of New Zealand. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "Participants were assigned using computer-generated randomisation to receive either vitamin D_3 or placebo."
Allocation concealment (selection bias)	Low risk	Quote from the publication: "The randomization process and bottling of tablets were performed in Auckland, New Zealand, under the supervision of the study biostatistician (A.W.S.) to ensure that those running the study, including outcome assessors and those administering the intervention, were blinded to allocation." Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "Those running the study, including outcome assessors and those administering the intervention, were blinded to allocation." Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "Those running the study, including outcome assessors and those administering the intervention, were blinded to allocation."

Murdoch 2012 *(Continued)*

		Comment: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Quote from the publication: "Two hundred ninety-four participants (91%) completed the study treatment and follow-up, 18 (6%) withdrew from the study altogether, and 10 (3%) withdrew from treatment but completed the 18-month follow-up." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: all clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "Both vitamin D_3 and placebo tablets were sourced from Tishcon Corp." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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 (2 intervention groups)
Participants	**Number of participants randomised:** 86 postmenopausal women, 50 to 80 (mean 67.5) years of age. **Inclusion criteria:** postmenopausal women with at least 2 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: calcitriol 0.25 to 2 µg plus calcium 1000 mg (n = 43) Comparator group: placebo vitamin D plus calcium 1000 mg daily (n = 43), for a 2-year period.
Outcomes	**Outcomes reported in abstract of publication:** **Primary outcomes:** bone mass **Secondary outcomes:** adverse effects of calcitriol
Stated aim of study	Quote from the publication: "To determine if calcitriol is an effective treatment in postmenopausal osteoporosis."
Notes	"The study was supported by Hoffmann-La Roche Inc. Dr. Ott is the recipient of a National Institutes of Health (NIH) Clinical Investigator Award #AR-01244. The study used the General Clinical Research Center, funded by NIH grant #RR-00037."

Risk of bias

Bias	Authors' judgement	Support for judgement

Ott 1989 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: the trial is described as randomised but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Comment: 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 of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: 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)	Low risk	Quote from the publication: "Of the 86 women enrolled in the study, 76 completed at least one year and 72 completed 2 years. Four women on calcitriol discontinued the study within the 12 weeks for personal reasons. Four others discontinued after a year; 1 for personal reasons and 1 for multiple fractures; 1 was placed on corticosteroids for a pulmonary disease, and 1 developed clinical signs of chronic lymphocytic leukemia. Six women receiving placebo discontinued within 6 months: 4 for personal reasons, 1 for severe depression, and 1 woman died of myocardial infarction." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: all clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "Hoffman-La Roche (Nutley, New Jersey) supplied the vitamin D supplements." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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 (2 intervention groups)
Participants	**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 2-fold above the reference range); a fracture in the past 6 months; a Mini-Mental State Examination score of < 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:

Prince 2008 *(Continued)*

	Intervention group: vitamin D_2 1000 IU plus calcium 1000 mg daily (n = 151) Comparator group: matched placebo tablet of vitamin D plus calcium 1000 mg daily (n = 151), for a 1-year period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** risk of falls in older women at high risk of falling. **Secondary outcomes:** none defined.
Stated aim of study	Quote from the publication: "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." "This study was supported by a research grant from the National Health and Medical Research Council of Australia (project grant 353638)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "The randomization procedure used a random number generator with a block size of 10 to assign participants to ergocalciferol or placebo in a ratio of 1:1, thus ensuring equal recruitment to the 2 groups during the various seasons." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "The randomization schedule to ergocalciferol or placebo was generated by an independent research scientist (I.M.D.) and was kept in the pharmacy department of the Sir Charles Gairdner Hospital, where the bottles were labeled and dispensed to the subjects." Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "The study subjects and the study staff remained blinded to the treatment code until all the data had been entered, evaluated for accuracy, and the a priori hypotheses reviewed." Comment: 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,
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "The study subjects and the study staff remained blinded to the treatment code until all the data had been entered, evaluated for accuracy, and the a priori hypotheses reviewed." Comment: 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)	Low risk	Quote from the publication: "Participant flow through the study is shown in Figure 1."

Prince 2008 *(Continued)*

		Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: all clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "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." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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 (2 intervention groups); The Vital D study
Participants	**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 resident 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: vitamin D_3 500,000 IU yearly (n = 1131) Comparator group: matched placebo tablet of vitamin D yearly (n = 1127), for 3 - 5 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	**Outcomes reported in abstract of publication** **Primary outcomes:** falls and fractures. **Secondary outcomes:** serum 25-hydroxycholecalciferol and intact parathyroid hormone levels.
Stated aim of study	Quote from the publication: "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."

Sanders 2010 *(Continued)*

	"The study was supported by project grant No. 251682 from the National Health and Medical Research Council and by the Australian Government Department of Health and Ageing. Financial Disclosures: none reported"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "Allocation was performed by an independent statistician using computer generated randomization of numbers performed in blocks of 500." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "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." Comment: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "The participants and study staff were blinded to intervention group." Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "The participants and study staff were blinded to intervention group." Comment: the assessment of outcomes was not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	Quote from the publication: "Enrollment and outcomes are shown in Figure 1. There was no difference between the treatment groups in the proportion who withdrew nor in the reasons for withdrawal." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: all clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "Study medication was supplied by PSM Healthcare, Auckland, New Zealand." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: 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 (2 intervention groups)

Trivedi 2003 *(Continued)*

Participants	**Number of participants randomised:** 2686 elderly people (24% women) aged 65 to 85 (mean 74) years **Inclusion criteria:** elderly people living in the general community. **Exclusion criteria:** already taking vitamin D supplements and conditions that were contraindications to vitamin D supplementation (a history of renal stones, sarcoidosis, or malignancy).
Interventions	Participants were randomly assigned to receive: Intervention group: vitamin D_3 (100,000 IU) every 4 months orally (n = 1345) Comparator group: matched placebo every 4 months orally (n = 1341), for a 5-year period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** fracture incidence and total mortality by cause. **Secondary outcomes:** none defined.
Stated aim of study	Quote from the publication: "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%." "Funding: Start up grant from the Medical Research Council. Competing interests: None declared." Additional information received through personal communication with Professor Kay-Tee Khaw (23.05.2014).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "The randomisation was conducted by our computer associate who did this by computer." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "Ipswich Pharmacy kept the coding." Comment: 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 of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "Participants and investigators were blinded to the treatment until the end of the trial, when Ipswich Pharmacy revealed the coding." Comment: 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.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "Participants and investigators were blinded to the treatment until the study ended, when Ipswich Pharmacy revealed the coding."

Trivedi 2003 *(Continued)*

		Comment: 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)	Low risk	Quote from the publication: "A total of 631 (23.5%) participants, including those who died, did not complete the full five years to March 2002—22.8% (307) in the vitamin D group and 24.2% (324) in the placebo group (P = 0.41). No significant difference existed between the two groups in the number known to be alive but who withdrew (that is, discontinued questionnaire follow up) from the study: 5.7% (77) in the placebo group and 6.2% (83) in the active group (P = 0.64)." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: all clinically relevant and reasonably expected outcomes were reported.
For-profit bias	Low risk	Quote from the publication: "The 100,000 IU vitamin D supplement or placebo used in this trial was specially prepared by the Ipswich Hospital Pharmacy." Comment: the trial appears to be free of industry sponsorship or other kind of for-profit support that may manipulate the trial design, conductance, or results of the trial.
Other bias	Low risk	Comment: the trial appears to be free of other components that could put it at risk of bias.

Witham 2013

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (2 intervention groups)
Participants	**Number of participants randomised:** 159 community-dwelling people aged 70 years and over, mean age 77 years, with isolated systolic hypertension. **Inclusion criteria:** age 70 years and over, serum 25-hydroxyvitamin D level < 75 nmol/L; office systolic blood pressure > 140 mm Hg. **Exclusion criteria:** diastolic blood pressure > 90 mm Hg, systolic blood pressure > 180 mm Hg, hypertension known to be due to a correctable underlying medical or surgical cause; estimated glomerular filtration rate < 40 ml/min (by 4 variable Modified Diet in Renal Disease equation 1); any liver function test (alanine aminotransferase, bilirubin, alkaline phosphatase) > 3 times upper limit of local normal range; albumin-adjusted serum calcium > 2.60 mmol/L or < 2.15 mmol/L. We also excluded people with known metastatic malignancy or sarcoidosis, a history of renal calculi, diagnosis of heart failure with left ventricular systolic dysfunction, atrial fibrillation, and those already taking prescription vitamin D supplements.
Interventions	Participants were randomly assigned to receive: Intervention group 1: 100,000 IU oral vitamin D_3 3-monthly (n = 80) Comparator group: matched placebo vitamin D (n = 79), for a 1-year period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** between-group difference in office blood pressure at 3 months.

Witham 2013 *(Continued)*

	Secondary outcomes: 24-hour blood pressure, soluble markers of cardiovascular risk, endothelial function, pulse wave velocity, other biochemical measurements (glucose, total cholesterol, LDL and HDL cholesterol, triglycerides, serum albumin and calcium), exercise capacity and falls.
Stated aim of study	Quote from the publication: "To test whether high-dose, intermittent cholecalciferol supplementation lowers blood pressure in older patients with isolated systolic hypertension."
Notes	This study was supported by CSO grant CZB/4/300, a Chief Scientist Office, the Scottish Government, and NHS Education Scotland/CSO Clinician Scientist Award (to Dr Witham). Dr Witham has received grant funding for vitamin D research from the Scottish Government, Diabetes UK, Chest Heart and Stroke Scotland, Heart Research UK, and the ME Society. Dr Struthers has received grant funding for vitamin D research from the Scottish Government, Diabetes UK, and Chest Heart and Stroke Scotland. Dr McMurdo has received grant funding for vitamin D research from the Scottish Government." Additional information received through personal communication with Dr Miles D. Witham (04.02.2014)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "Stratified randomization was performed using a minimization algorithm, administered by the Robertson Centre for Biostatistics (Glasgow Clinical Trials Unit, University of Glasgow, United Kingdom) using a telephone-based system to conceal study allocation from investigators and participants." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "Stratified randomisation was performed using a telephone-based system to conceal study allocation from investigators and participants." Comment: allocation was controlled by a central and independent randomisation unit.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "Stratified randomisation was performed using a telephone-based system to conceal study allocation from investigators and participants. Identical, masked medication bottles were used." Comment: The allocation sequence was unknown to the investigators.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "All outcome measures were performed by researchers who were masked to treatment allocation." Comment: the outcome assessors were masked to treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: all clinically relevant and reasonably expected outcomes were reported.
For-profit bias	High risk	Quote from the publication: "Tablets containing cholecalciferol (Vigantol oil) or matching placebos (Mygliol oil) were produced by Merck KgAA." Comment: the trial was sponsored by the industry.
Other bias	Low risk	Comment: the trial appears to be free of other components that could put it at risk of bias

Wood 2012

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (3 intervention groups)
Participants	**Number of participants randomised:** 305 healthy postmenopausal women aged 60 to 70 years, mean age 64 years. **Inclusion criteria:** white postmenopausal women. **Exclusion criteria:** pre-existing cardiovascular disease, diabetes, asthma, malabsorption, hypertensive blood pressure measurements of at least 160 mm Hg systolic or 99 mm Hg diastolic, difficulty in swallowing tablets or capsules, or who were taking medications or supplements known to affect any dependent variable, current smokers or participants with abnormal blood biochemistry at screening
Interventions	Participants were randomly assigned to receive: Intervention group 1: 400 IU oral vitamin D_3 daily (n = 102) Intervention group 1: 1000 IU oral vitamin D_3 daily (n = 101) Comparator group: matched placebo capsule of vitamin D (n = 102), for a 1-year period.
Outcomes	**Outcomes reported in abstract of publication** **Primary outcomes:** serum lipid profile, estimate of insulin resistance, inflammatory biomarkers, and blood pressure. **Secondary outcomes:** none defined.
Stated aim of study	Quote from the publication: "to test whether daily doses of vitamin D_3 at 400 or 1000 IU/d for one year affected conventional markers of cardiovascular disease risk."
Notes	"This work was funded by the UK Department of Health. The authors have nothing to disclose."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the publication: "Randomization was computer generated. Research nurses assigned participants to one of three intervention groups using an automated telephone service (Health Services Research Unit, University of Aberdeen, UK)." Comment: sequence generation was achieved using computer random number generation.
Allocation concealment (selection bias)	Low risk	Quote from the publication: "Capsules containing vitaminD_3 (400 or 1000 IU) or identical placebo were purchased (Pure Encapsulations, Sudbury, MA), packaged into white plastic coded containers, and sealed in sequentially numbered study packs (Bilcare, Powys, UK)." Comment: the allocation was controlled by a central and independent randomisation unit.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote from the publication: "Both participants and study investigators were blinded to intervention groupings throughout the study." Comment: The allocation sequence was unknown to the investigators.

Wood 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the publication: "Both participants and study investigators were blinded to intervention groupings throughout the study." Comment: the outcome assessors were masked to treatment allocation.
Incomplete outcome data (attrition bias)	Low risk	Quote from the publication: "A total of 305 women were randomly assigned to one of three study interventions. In total, 40 withdrew (six due to personal reasons, 34 due to clinical reasons)." Comment: the numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	Comment: all clinically relevant and reasonably expected outcomes were reported.
For-profit bias	Low risk	Quote from the publication: "Capsules containing vitamin D_3 (400 or 1000 IU) or identical placebo were purchased (Pure Encapsulations, Sudbury, MA)." Comment: the trial appears to be free of industry sponsorship or other kind of for-profit support that may manipulate the trial design, conductance, or results of the trial.
Other bias	Low risk	Comment: the trial appears to be free of other components that could put it at risk of bias.

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

Study	Reason for exclusion
Anderson 2010	Not a randomised trial.
Chadha 2010	Randomised controlled trial that included participants with cancer.
Crew 2009	Not a randomised trial.
Diamond 2013	All participants were supplemented with vitamin D.
Fedirko 2010	Randomised controlled trial without clinical outcomes.
Garland 2011	Not a randomised trial.
Glossmann 2011	Not a randomised trial.
Hermann 2013	All participants were supplemented with vitamin D.
Holt 2006	Not a randomised trial.
Jacobs 2011	Not a randomised trial.
Kampman 2000	Not a randomised trial.
Lagari 2012	All participants were supplemented with vitamin D.
Peppone 2011	Not a randomised trial.

Study	Reason for exclusion
Rheem 2010	Not a randomised trial.
Tellioglu 2012	All participants were supplemented with vitamin D.
Vashi 2010	Not a randomised trial.
Vieth 2009	Not a randomised trial.
Zabihiyeganeh 2013	All participants were supplemented with vitamin D.

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

ACTRN12611000402943

Trial name or title	ViDA (Vitamin D Assessment) Trial
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (2 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 4-year study period **Exclusion criteria:** current use of vitamin D supplements (> 600 IU per day if aged 50 to70 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 last 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: Vitamin D3 200,000 IU oral capsule at baseline, then 100,000 IU oral capsule monthly (aside from 200,000 IU oral capsule in each June) Comparator 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	April 2011
Contact information	Robert Scragg (r.scragg@auckland.ac.nz)
Notes	

ISRCTN17873085

Trial name or title	The impact of vitamin D supplementation in chronic heart failure

ISRCTN17873085 *(Continued)*

Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (2 intervention groups)
Participants	**Country:** United Kingdom **Estimated number of participants:** 100 **Inclusion criteria:** participants aged 18 years or over with class II and III heart failure due to left ventricular systolic dysfunction (left ventricular ejection fraction ≤ 40%); stable symptoms for 3 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 3 months) calcium or other vitamin supplements; currently prescribed amlodipine or other calcium channel antagonists (intake of spironolactone will be recorded); chronic heart failure due to untreated valvular heart disease; history of primary hyperparathyroidism, sarcoidosis, tuberculosis or lymphoma; vitamin D levels greater than 50 nmol/L
Interventions	Participants will be randomly assigned to receive: Intervention group: vitamin D_3 (4000 IU) daily Comparator group: placebo daily for a period of 1 year
Outcomes	The primary outcome measure 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, 1, 4, 8, 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, 1, 4, 8, 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, 1, 4, 8, and 12 months; B-type natriuretic peptide, measured at baseline, 1, 4, 8, and 12 months
Starting date	January 2009; expected completion December 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	

Manson 2009

Trial name or title	Vitamin D and Omega-3 Trial (VITAL)
Methods	Randomised, double-blind, placebo-controlled trial using 2-by-2 factorial design
Participants	**Country:** United States **Estimated number of participants**: 20,000 **Inclusion criteria:** men aged 50 or more or women aged 55 or more 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 coro-

Manson 2009 *(Continued)*

	nary intervention; history of renal failure or dialysis, hypercalcaemia, hypo- 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 Comparator group: vitamin D placebo and omega-3 placebo orally, daily for a 2-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	

NCT00585637

Trial name or title	Vitamin D for chemoprevention
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (4 intervention groups)
Participants	**Country:** United States **Estimated number of participants:** 320 **Inclusion criteria:** healthy black participants 30 to 80 years of age; comfortable communicating in English; currently has a primary care physician; willing to discontinue vitamin D or calcium supplements; willing to have all protocol-specific tests run. **Exclusion criteria:** plans on taking a vacation or travel to a sunny region within 3 months of vitamin supplementation period except for a short period (i.e., 1 weekend); pregnant or breast feeding or planning on becoming pregnant in the following year; pre-existing calcium (including hypercalcaemia), parathyroid conditions (including hyperparathyroidism), sarcoidosis; no concurrent active malignancies (other than non-melanoma skin cancer) or previous diagnosis of prostate cancer; cognitively impaired; active thyroid disease (e.g., Graves, Hashimoto's or thyroiditis); history of nephrolithiasis, chronic liver disease, chronic renal disease, or renal dialysis
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (1000 IU) daily Intervention group 2: vitamin D_3 (2000 IU) daily Intervention group 3: vitamin D_3 (4000 IU) daily

NCT00585637 *(Continued)*

	Comparator group: placebo daily for a period of 3 month; participants will be followed for 6 months
Outcomes	The primary outcome measures will be: among Blacks, identify a dose of oral vitamin D supplementation that will result in levels of plasma 25-hydroxyvitamin D that would be predicted to reduce colorectal cancer occurrence. Secondary outcome measures will be: the influence of oral vitamin D supplementation on inflammatory markers and compare germline polymorphic variation in Vitamin D pathway genes between Blacks and a cohort of Whites
Starting date	October 2007; expected completion October 2009
Contact information	Charles Fuchs, MD tel: (617) 632-5840 Charles_Fuchs@dfci.harvard.edu
Notes	

NCT00662844

Trial name or title	Vitamin D supplementation in younger women
Methods	Randomised, double-blind, placebo controlled trial using parallel group design (5 intervention groups)
Participants	**Country:** United States **Estimated number of participants**: 200 **Inclusion criteria:** premenopausal white 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 **Exclusion criteria:** cancer (exceptions: basal cell carcinoma or if cancer occurred more than 10 years ago) or terminal illness; previous hip fracture; hemiplegia; uncontrolled type I diabetes ± significant proteinuria or fasting blood sugar > 140 mg in type II diabetes; kidney stones more than 2 in a lifetime; chronic renal failure (serum creatinine > 1.4 mg/dl); evidence of chronic liver disease, including alcoholism; physical conditions such as severe osteoarthritis, rheumatoid arthritis, heart failure severe enough to prevent reasonable physical activity; previous treatment with bisphosphonates (more than 3 months), parathyroid hormone (PTH) or PTH derivatives, (e.g., teriparatide or fluoride in the last 6 months; previous treatment within the last 6 months with calcitonin or oestrogen (except birth control pills); chronic high dose corticosteroid therapy (> 10 mg/day) for over 6 months and not within the last 6 months; anticonvulsant therapy. (Dilantin, Phenobarbital); high dose thiazide therapy (> 37.5 mg); 24-hour urine calcium > 290 mg on 2 baseline tests; serum calcium exceeding upper normal limit on 2 baseline tests; bone mineral density. T-score < -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 Comparator group: placebo daily

NCT00662844 *(Continued)*

	for a period of 1 year.
Outcomes	The primary outcome measures will be serum 25-hydroxyvitamin D, and parathyroid hormone. Secondary outcome measures will be serum and urine calcium levels
Starting date	October 2007; expected completion January 2012
Contact information	JC Gallagher, MD tel: 402-280-4518 bones@creighton.edu
Notes	

NCT00784511

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 (2 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 5 years; sarcoidosis, current pancreatitis, active tuberculosis, hemiplegia, gout; inflammatory bowel disease, colostomy, malabsorption; cancer other than basal cell skin cancer within 5 years; uncontrolled arrhythmia in past year; albinism or other condition associated with reduced skin pigmentation; pregnancy over the last 1 year; intent to become pregnant; menopause onset within 1 year; any other unstable medical condition laboratory tests; fasting plasma glucose < 100; haemoglobin A1c > 7%; laboratory evidence of liver disease (e.g., AST > 70 U/L or ALT > 72 IU/L); laboratory evidence of kidney disease (e.g., estimated glomerular filtration rate < 60 ml/min/1.73 m^2; elevated spot urine calcium to creatinine ratio > 0.38 mg/dl); abnormal serum calcium (serum calcium > 10.5 mg/dl); anaemia (hematocrit < 36% in men, < 33% in women); medications (use in past 3 months; oestrogen or testosterone); prescription vitamin D, lithium; oral corticosteroids; anti-seizure medications; unstable doses of psychotropics or phenothiazines; cholestyramine supplements (current use - may discontinue after screening); vitamin D supplements, cod liver oil, calcium supplements; body mass index less < 25 or > 39.9; consumption of more than 14 alcoholic drinks per week; inability to attend all 3 trial visits as scheduled; inability to provide written informed consent; age < 40 years; not African-American (by self designation); participation in another research intervention trial; corresponds to a 24-hour urinary calcium excretion > 400 mg
Interventions	Participants will be randomly assigned to receive: Intervention group: vitamin D_3 (4000 IU) daily Comparator group: placebo daily for a period of 12 weeks
Outcomes	The primary outcome measure will be insulin secretion, insulin sensitivity and glucose control
Starting date	July 2008; expected completion: February 2011
Contact information	Nancy Palermo, B.S. tel: 617-556-3073

NCT00784511 *(Continued)*

	nancy.palermo@tufts.edu
Notes	

NCT01052051

Trial name or title	Clinical trial of vitamin D3 to reduce cancer risk in postmenopausal women (CAPS)
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (2 intervention groups)
Participants	**Country:** United States **Estimated number of participants:** 2300 postmenopausal women **Inclusion criteria:** age: ≥ 55 years, last menstrual period ≥ 4 years, good general health, willingness to participate in this 4-year long study, able to give informed consent, able to live independently and travel to the Fremont Area Medical Center for study visits **Exclusion criteria:** history of cancer except superficial basal or squamous cell carcinoma of the skin, other malignancies treated curatively more than 10 years ago, history of renal calculi or chronic kidney disease, history of sarcoidosis, history of tuberculosis, participation in the previous Creighton cancer prevention study, Mini-Mental Status Exam (MMSE) score of ≤ 23
Interventions	Intervention group: vitamin D_3 and calcium 1200 mg daily Comparator group: calcium 1200 mg daily for a period of 5 years
Outcomes	Cancer, hypertension, cardiovascular disease, osteoarthritis, colonic adenomas, diabetes, upper respiratory infections, fractures and falls
Starting date	June 2009 expected completion June 2015
Contact information	Joan Lappe, Professor of Medicine, Creighton University
Notes	

NCT01176344

Trial name or title	VItamin D effect on osteoarthritis study VIDEO
Methods	Randomised, double-blind, placebo controlled trial using parallel group design (2 intervention groups)
Participants	**Country:** Australia **Estimated number of participants**: 400 **Inclusion criteria:** age 50 to 79 years old, men and women with symptomatic knee osteoarthritis for at least 6 months with a pain visual analogue scale of at least 20 mm, meet the America College of Rheumatology (ACR) criteria for symptomatic knee osteoarthritis (OA), have an ACR functional class rating of I, II and III, have relatively good health (0 - 2 according to the investigator's global assessment of disease status on a 5-point Likert scale, range 0 [very well] to 4 [very poor]), have serum vitamin D level of > 12.5 nmol/L and < 60 nmol/L, and is able to read, speak and understand

NCT01176344 *(Continued)*

	English, capable of understanding the study requirements and willing to co-operate with the study instructions. **Exclusion criteria:** severe radiographic knee OA (grade 3 according to Altman's atlas), people with severe knee pain (on standing more than 80 mm on a 100-mm VAS), any contra-indication to having an MRI, rheumatoid arthritis, psoriatic arthritis, lupus, or cancer, severe cardiac or renal function impairment, hypersensitivity to vitamin D, any condition possibly affecting oral drug absorption (e.g., gastrectomy or clinically significant diabetic gastroenteropathy), significant trauma to the knees including arthroscopy or significant injury to ligaments or menisci of the knee within 1 year preceding the study, anticipated need for knee or hip surgery in the next 2 years, having taken Vitamin D supplements in last 30 days, having taken an investigational drug in last 30 days.
Interventions	Intervention group: vitamin D_3 (50,000 IU) monthly Comparator group: placebo monthly for a period of 2 years.
Outcomes	Loss of knee cartilage volume, progression of knee cartilage defects, loss of limb muscle strength, enlargement of tibial bone area, central blood pressure, radial applanation tonometry, aortic stiffness, carotid to femoral pulse wave velocity.
Starting date	March 2010
Contact information	A/Prof Changhai Ding, Menzies Research Institute, 17 Liverpool St, Hobart 7000, Tasmania; Department of Epidemiology & Preventive Medicine, 99 Commercial Rd, Melbourne 3004, Victoria, Australia Tel: 61-3-62267730 Fax: 61-3-62267704 Email: chding@utas.edu.au
Notes	

NCT01463813

Trial name or title	The Finnish Vitamin D Trial (FIND)
Methods	Randomised, double-blind, placebo-controlled trial using parallel group design (3 intervention groups)
Participants	**Country:** Finland **Estimated number of participants:** 18,000 **Inclusion criteria:** men 60 years or older, women 65 years or older. **Exclusion criteria:** Cardiovascular disease (including myocardial infarction, stroke, transient ischaemic attack, angina pectoris, coronary artery bypass grafting, or percutaneous coronary intervention), cancer (except non-melanoma skin cancer), any disease or state that raises a vitamin D-related safety concern (such as chronic liver, thyroid or kidney disease, hypercalcaemia, sarcoidosis or other granulomatous diseases such as active chronic tuberculosis or Wegener's granulomatosis), use of supplements yielding vitamin D over 20 µg/day or calcium over 1200 mg/day and unwillingness to discontinue the use
Interventions	Participants will be randomly assigned to receive: Intervention group 1: vitamin D_3 (1600 IU) daily; Intervention group 1: vitamin D_3 (3000 IU) daily

NCT01463813 *(Continued)*

	Comparator group: placebo daily for a period of 5 years
Outcomes	The primary outcome measure will be cancer and cardiovascular diseases
Starting date	January 2012; expected completion December 2019
Contact information	Tomi-Pekka Tuomainen, MD, PhD 358 40 355 2956 tomi-pekka.tuomainen@uef.fi Jyrki Virtanen, PhD 358 40 355 2957 jyrki.virtanen@uef.fi
Notes	

Rees 2013

Trial name or title	Vitamin D/calcium polyp prevention study
Methods	Randomised, double-blind, placebo-controlled trial using 2-by-2 factorial design
Participants	**Country:** United States **Estimated number of participants:** 2200 **Inclusion criteria:** aged 45 to 75 years; 1 or more histologically verified neoplastic polyp (adenoma) that is at least 2 mm in size removed from the large bowel with the entire large bowel examined by colonoscopy and documented to be free of further polyps or areas suspicious for neoplasia within 120 days of trial entry; anticipated colonoscopic follow-up 3 or 5 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 5 years; current participation in any other clinical trial (intervention trial); pregnancy or lactation; a diagnosis of narcotic or alcohol dependence in the past 5 years; a diagnosis of dementia (e.g., Alzheimer's) in the past 5 years; a diagnosis of a significant psychiatric disability (e.g., schizophrenia, refractory bipolar disorder, current severe depression) in the past 5 years; any diagnosis of kidney stones; a diagnosis of granulomatous diseases, e.g., sarcoidosis, active chronic fungal or mycobacterial infections (tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis), berylliosis, Wegener's granulomatosis in the past 5 years; hyperparathyroidism or other serious disturbance of calcium metabolism in the past 5 years; a diagnosis of severe kidney disease, e.g., chronic renal failure in the past 5 years; unexplained hypercalcaemia in the past 5 years; osteoporosis with physician recommendation for treatment of low bone mass; 2 or more low trauma fractures in the past 5 years; medical condition requiring treatment with vitamin D (e.g., osteomalacia) in the past 5 years; invasive carcinoma of the large bowel (even if confined to a polyp); familial colorectal cancer syndromes, e.g., Familial Adenomatous Polyposis (FAP) (including Gardner syndrome, Turcot's syndrome), Hereditary Nonpolyposis Colorectal Cancer (HNPCC), Hamartomatous Polyposis syndromes (including Peutz-Jeghers or Familial Juvenile Polyposis); inflammatory bowel disease, e.g., Crohn's Disease, Ulcerative Colitis; a diagnosis of chronic intestinal malabsorption syndromes, e.g., celiac sprue, bacterial overgrowth, chronic pancreatitis, pancreatic insufficiency in the past 5 years; large bow-

Rees 2013 *(Continued)*

	el resection; a diagnosis of malignancy, other than non-melanoma skin cancer in the past 5 years; severe lung disease - class 3 or 4 (e.g., COPD or emphysema requiring; oxygen) in the past 5 years; severe heart disease: cardiovascular disease functional class 3 or 4 in the past 5 years; severe liver disease, e.g., cirrhosis; any HIV positive diagnosis; active hepatitis B, defined as : Hep B surface antigen positive; active hepatitis C, defined as: measurable HCV RNA; use of chronic oral corticosteroid therapy in the past 5 years; use of lithium in the past 5 years; use of phenytoins in the past 5 years; use of quinidine in the past 5 years; use of therapeutic vitamin D in the past 5 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 Comparator group: placebo daily; for a period of 5 years; women who decline to forego calcium supplementation will be randomised only to calcium alone or to calcium plus vitamin D intervention group
Outcomes	The primary outcome measure will be new adenomas detected on follow-up colonoscopy
Starting date	July 2004; expected completion: December 2017
Contact information	John A Baron, MD, Principal Investigator, Dartmouth-Hitchcock Medical Center
Notes	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMD: bone mass density; COPD: chronic obstructive pulmonary disease; HCV RNA: hepatitis C virus ribonucleic acid; HIV: human immunodeficiency virus

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 Cancer occurrence in trials with a low or high risk of bias	18	50623	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.06]
1.1 Trials with low risk of bias	2	2991	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.89, 1.31]
1.2 Trials with high risk of bias	16	47632	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
2 Cancer occurrence and risk of for-profit bias	18	50623	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.06]
2.1 Trials without risk of for-profit bias	2	2991	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.89, 1.31]
2.2 Trials with risk of for-profit bias	16	47632	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
3 Cancer occurrence in primary and secondary prevention trials	18	50623	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.06]

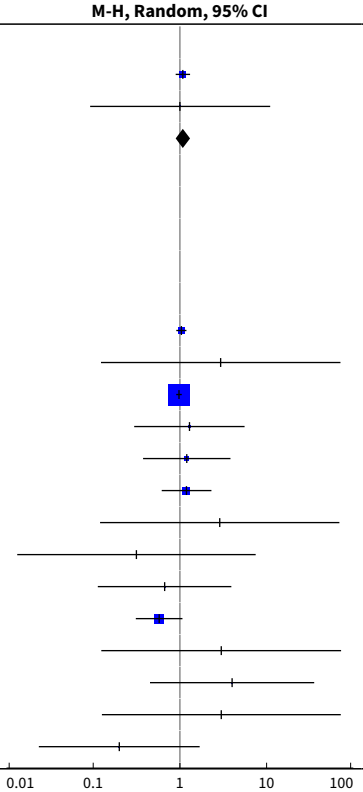
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Primary prevention trials	16	50334	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.06]
3.2 Secondary prevention trials	2	289	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.26, 6.96]
4 Cancer occurrence and vitamin D status	18	50623	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.06]
4.1 Vitamin D insufficiency	7	44668	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
4.2 Vitamin D adequacy	9	4544	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.94, 1.34]
4.3 Unknown vitamin status	2	1411	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.33, 1.05]
5 Cancer occurrence ('best-worst case' and 'worst-best case' scenario)	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 'Best-worst' case scenario	17	49444	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.31, 0.54]
5.2 'Worst-best' case scenario	17	49444	Risk Ratio (M-H, Random, 95% CI)	2.76 [1.97, 3.86]
6 Cancer occurrence in trials using vitamin D_3 (cholecalciferol)	14	49891	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.94, 1.06]
6.1 Vitamin D_3 trials with low risk of bias	2	2991	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.89, 1.31]
6.2 Vitamin D_3 trials with high risk of bias	12	46900	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
7 Cancer occurrence in trials using vitamin D_3 singly or combined with calcium	14	49870	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
7.1 Vitamin D_3 singly	8	9200	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.90, 1.17]
7.2 Vitamin D_3 combined with calcium	7	40670	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.04]
8 Lung cancer occurrence in trials using vitamin D_3 (cholecalciferol)	5	45509	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.69, 1.07]
9 Breast cancer occurrence in trials using vitamin D_3 (cholecalciferol)	7	43669	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.09]
10 Colorectal cancer occurrence in trials using vitamin D_3 (cholecalciferol)	5	45598	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.92, 1.34]
11 Pancreatic cancer occurrence in trials using vitamin D_3 (cholecalciferol)	2	36405	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.46]
12 Prostate cancer occurrence in trials using vitamin D_3 (cholecalciferol)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13 Uterine cancer occurrence in trials using vitamin D_3 (cholecalciferol)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

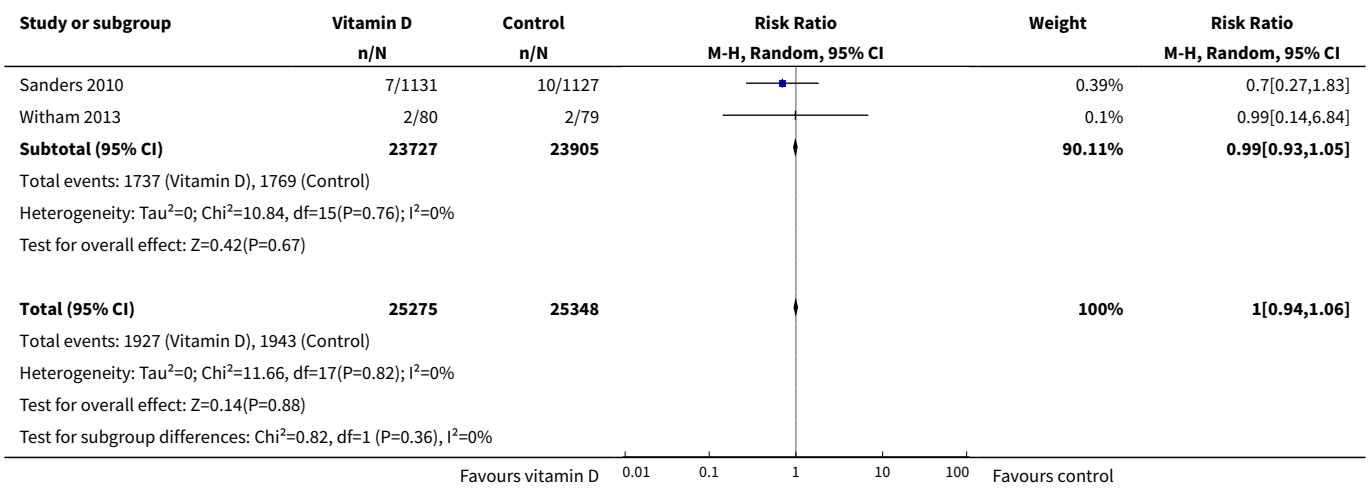
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Ovarian cancer occurrence in trials using vitamin D_3 (cholecalciferol)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15 Oesophageal cancer occurrence in trials using vitamin D_3 (cholecalciferol)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16 Stomach cancer occurrence in trials using vitamin D_3 (cholecalciferol)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17 Liver cancer occurrence in trials using vitamin D_3 (cholecalciferol)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18 Cancer occurrence in trials using vitamin D_2 (ergocalciferol)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19 Cancer occurrence in trials using calcitriol	3	430	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.52, 4.06]
20 Breast cancer occurrence in trials using calcitriol	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21 Uterine cancer occurrence in trials using calcitriol	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22 Stomach cancer occurrence in trials using calcitriol	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
23 All-cause mortality in trials with a low or high risk of bias	15	49866	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.98]
23.1 Trials with low risk of bias	1	2686	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.07]
23.2 Trials with high risk of bias	14	47180	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.99]
24 All-cause mortality ('best-worst case' and 'worst-best case' scenario)	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 'Best-worst' case scenario	14	48687	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.31, 0.60]
24.2 'Worst-best' case scenario	14	48687	Risk Ratio (M-H, Random, 95% CI)	2.03 [1.47, 2.80]
25 Cancer mortality	4	44492	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.98]
26 Cancer mortality ('best-worst case' and 'worst-best case' scenario)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 'Best-worst' case scenario	4	44492	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.70]
26.2 'Worst-best' case scenario	4	44492	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.04, 2.75]
27 Adverse events	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 Hypercalcaemia in trials using supplemental forms of vitamin D	4	5879	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.64, 3.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.2 Hypercalcaemia in trials using active forms of vitamin D	2	332	Risk Ratio (M-H, Random, 95% CI)	4.03 [0.56, 29.22]
27.3 Nephrolithiasis in trials using vitamin D_3 combined with calcium	3	42753	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.03, 1.34]
27.4 Nephrolithiasis in trials using calcitriol	1	246	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.10]
27.5 Hypercalciuria	1	98	Risk Ratio (M-H, Random, 95% CI)	12.49 [0.72, 215.84]
27.6 Renal insufficiency	3	5549	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.23, 1.82]
27.7 Cardiovascular disorders	8	4938	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.86, 1.05]
27.8 Gastrointestinal disorders	7	1624	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.88, 1.59]
27.9 Psychiatric disorders	2	332	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.46, 4.38]

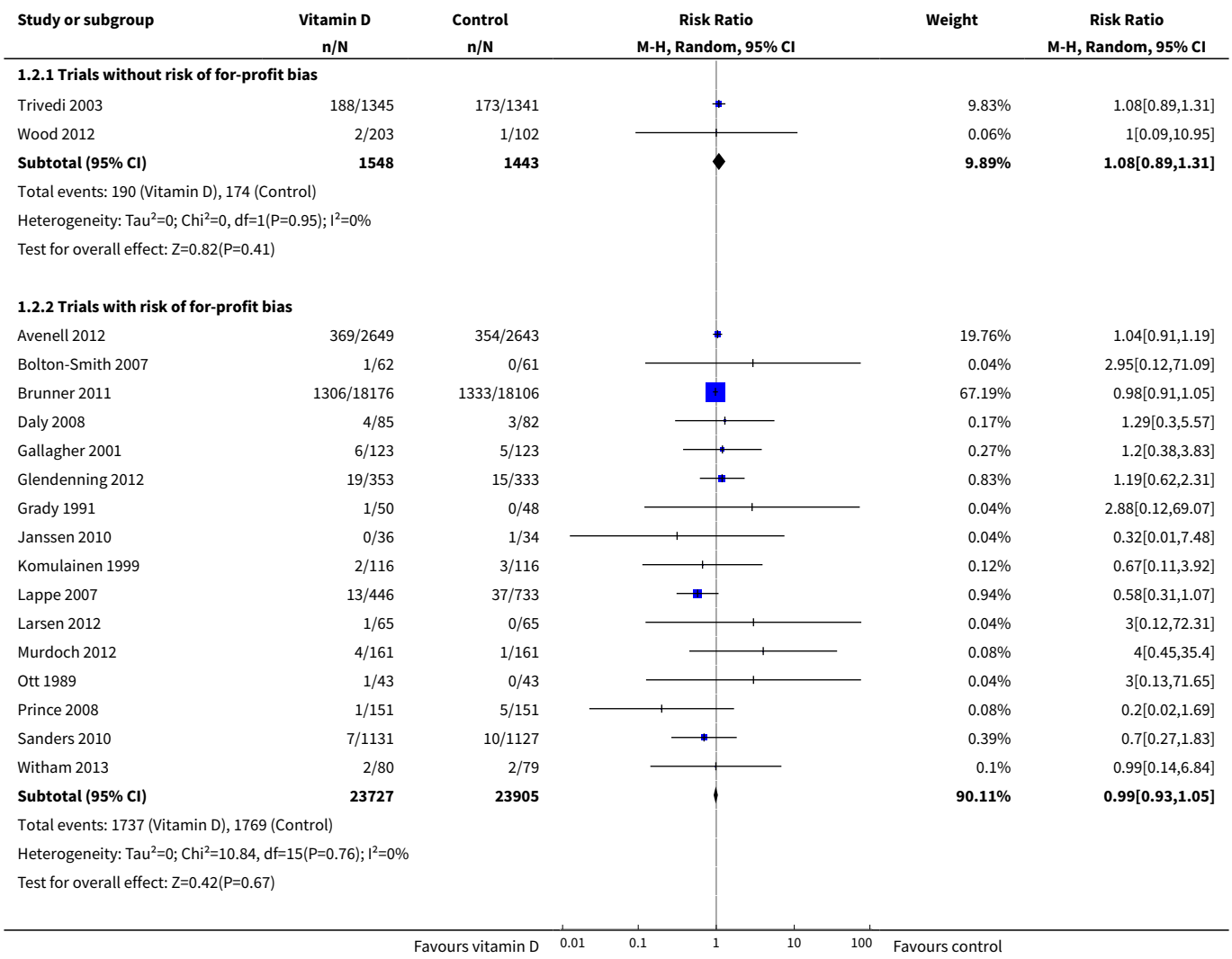
Analysis 1.1. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 1 Cancer occurrence in trials with a low or high risk of bias.

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
1.1.1 Trials with low risk of bias					
Trivedi 2003	188/1345	173/1341		9.83%	1.08[0.89,1.31]
Wood 2012	2/203	1/102		0.06%	1[0.09,10.95]
Subtotal (95% CI)	**1548**	**1443**		**9.89%**	**1.08[0.89,1.31]**
Total events: 190 (Vitamin D), 174 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
1.1.2 Trials with high risk of bias					
Avenell 2012	369/2649	354/2643		19.76%	1.04[0.91,1.19]
Bolton-Smith 2007	1/62	0/61		0.04%	2.95[0.12,71.09]
Brunner 2011	1306/18176	1333/18106		67.19%	0.98[0.91,1.05]
Daly 2008	4/85	3/82		0.17%	1.29[0.3,5.57]
Gallagher 2001	6/123	5/123		0.27%	1.2[0.38,3.83]
Glendenning 2012	19/353	15/333		0.83%	1.19[0.62,2.31]
Grady 1991	1/50	0/48		0.04%	2.88[0.12,69.07]
Janssen 2010	0/36	1/34		0.04%	0.32[0.01,7.48]
Komulainen 1999	2/116	3/116		0.12%	0.67[0.11,3.92]
Lappe 2007	13/446	37/733		0.94%	0.58[0.31,1.07]
Larsen 2012	1/65	0/65		0.04%	3[0.12,72.31]
Murdoch 2012	4/161	1/161		0.08%	4[0.45,35.4]
Ott 1989	1/43	0/43		0.04%	3[0.13,71.65]
Prince 2008	1/151	5/151		0.08%	0.2[0.02,1.69]





Analysis 1.2. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 2 Cancer occurrence and risk of for-profit 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
Total (95% CI)	**25275**	**25348**		**100%**	**1[0.94,1.06]**
Total events: 1927 (Vitamin D), 1943 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.66, df=17(P=0.82); I^2=0%					
Test for overall effect: Z=0.14(P=0.88)					
Test for subgroup differences: Chi^2=0.82, df=1 (P=0.36), I^2=0%					

Favours vitamin D 0.01 0.1 1 10 100 Favours control

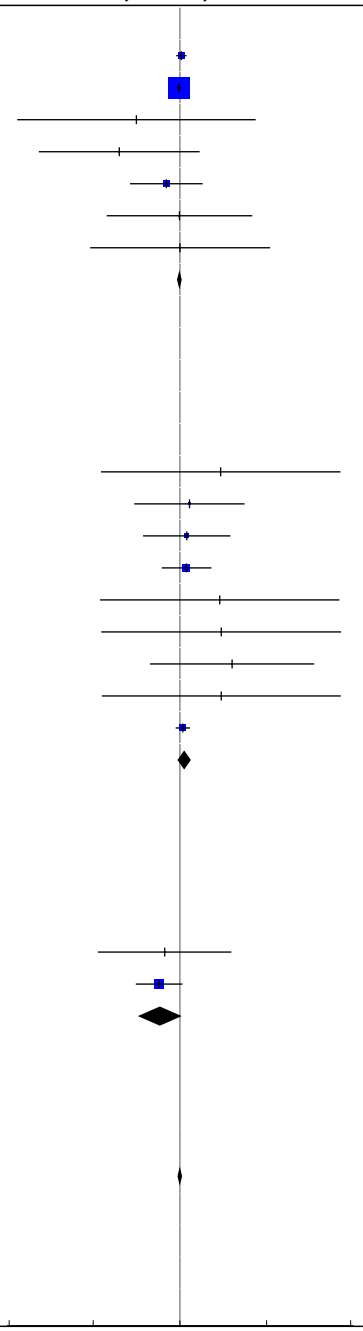
Analysis 1.3. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 3 Cancer occurrence in primary and secondary prevention trials.

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
1.3.1 Primary prevention trials					
Avenell 2012	369/2649	354/2643		19.76%	1.04[0.91,1.19]
Bolton-Smith 2007	1/62	0/61		0.04%	2.95[0.12,71.09]
Brunner 2011	1306/18176	1333/18106		67.19%	0.98[0.91,1.05]
Daly 2008	4/85	3/82		0.17%	1.29[0.3,5.57]
Gallagher 2001	6/123	5/123		0.27%	1.2[0.38,3.83]
Glendenning 2012	19/353	15/333		0.83%	1.19[0.62,2.31]
Grady 1991	1/50	0/48		0.04%	2.88[0.12,69.07]
Janssen 2010	0/36	1/34		0.04%	0.32[0.01,7.48]
Komulainen 1999	2/116	3/116		0.12%	0.67[0.11,3.92]
Lappe 2007	13/446	37/733		0.94%	0.58[0.31,1.07]
Murdoch 2012	4/161	1/161		0.08%	4[0.45,35.4]
Ott 1989	1/43	0/43		0.04%	3[0.13,71.65]
Prince 2008	1/151	5/151		0.08%	0.2[0.02,1.69]
Sanders 2010	7/1131	10/1127		0.39%	0.7[0.27,1.83]
Trivedi 2003	188/1345	173/1341		9.83%	1.08[0.89,1.31]
Wood 2012	2/203	1/102		0.06%	1[0.09,10.95]
Subtotal (95% CI)	**25130**	**25204**		**99.87%**	**1[0.94,1.06]**
Total events: 1924 (Vitamin D), 1941 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.2, df=15(P=0.74); I^2=0%					
Test for overall effect: Z=0.16(P=0.87)					
1.3.2 Secondary prevention trials					
Larsen 2012	1/65	0/65		0.04%	3[0.12,72.31]
Witham 2013	2/80	2/79		0.1%	0.99[0.14,6.84]
Subtotal (95% CI)	**145**	**144**		**0.13%**	**1.33[0.26,6.96]**
Total events: 3 (Vitamin D), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=0.34(P=0.73)					
Total (95% CI)	**25275**	**25348**		**100%**	**1[0.94,1.06]**
Total events: 1927 (Vitamin D), 1943 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.66, df=17(P=0.82); I^2=0%					
Test for overall effect: Z=0.14(P=0.88)					
Test for subgroup differences: Chi^2=0.12, df=1 (P=0.73), I^2=0%					

Favours vitamin D 0.01 0.1 1 10 100 Favours control

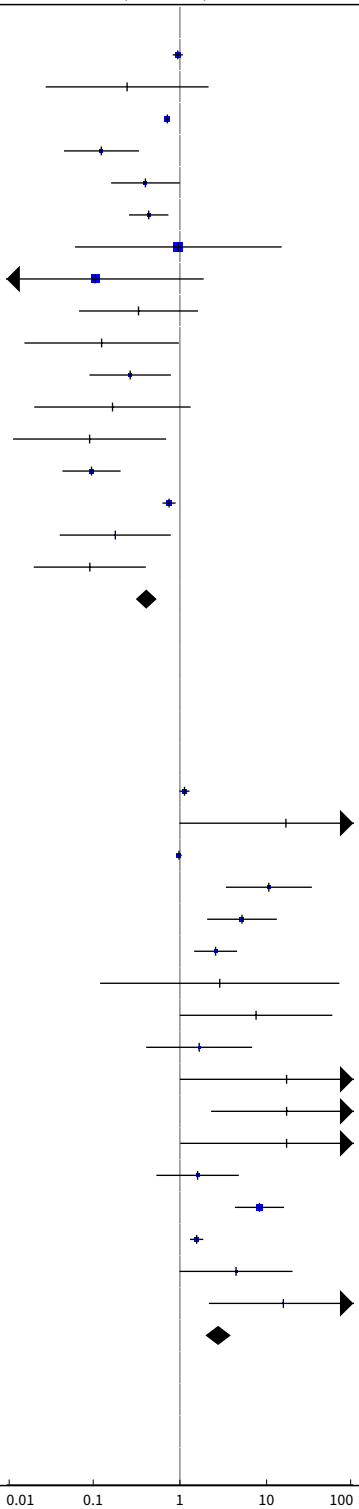
Analysis 1.4. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 4 Cancer occurrence and vitamin D status.

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
1.4.1 Vitamin D insufficiency					
Avenell 2012	369/2649	354/2643		19.76%	1.04[0.91,1.19]
Brunner 2011	1306/18176	1333/18106		67.19%	0.98[0.91,1.05]
Janssen 2010	0/36	1/34		0.04%	0.32[0.01,7.48]
Prince 2008	1/151	5/151		0.08%	0.2[0.02,1.69]
Sanders 2010	7/1131	10/1127		0.39%	0.7[0.27,1.83]
Witham 2013	2/80	2/79		0.1%	0.99[0.14,6.84]
Wood 2012	2/203	1/102		0.06%	1[0.09,10.95]
Subtotal (95% CI)	**22426**	**22242**		**87.62%**	**0.99[0.93,1.05]**
Total events: 1687 (Vitamin D), 1706 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.81, df=6(P=0.7); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
1.4.2 Vitamin D adequacy					
Bolton-Smith 2007	1/62	0/61		0.04%	2.95[0.12,71.09]
Daly 2008	4/85	3/82		0.17%	1.29[0.3,5.57]
Gallagher 2001	6/123	5/123		0.27%	1.2[0.38,3.83]
Glendenning 2012	19/353	15/333		0.83%	1.19[0.62,2.31]
Grady 1991	1/50	0/48		0.04%	2.88[0.12,69.07]
Larsen 2012	1/65	0/65		0.04%	3[0.12,72.31]
Murdoch 2012	4/161	1/161		0.08%	4[0.45,35.4]
Ott 1989	1/43	0/43		0.04%	3[0.13,71.65]
Trivedi 2003	188/1345	173/1341		9.83%	1.08[0.89,1.31]
Subtotal (95% CI)	**2287**	**2257**		**11.32%**	**1.12[0.94,1.34]**
Total events: 225 (Vitamin D), 197 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.96, df=8(P=0.94); I^2=0%					
Test for overall effect: Z=1.25(P=0.21)					
1.4.3 Unknown vitamin status					
Komulainen 1999	2/116	3/116		0.12%	0.67[0.11,3.92]
Lappe 2007	13/446	37/733		0.94%	0.58[0.31,1.07]
Subtotal (95% CI)	**562**	**849**		**1.06%**	**0.59[0.33,1.05]**
Total events: 15 (Vitamin D), 40 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=1.78(P=0.07)					
Total (95% CI)	**25275**	**25348**		**100%**	**1[0.94,1.06]**
Total events: 1927 (Vitamin D), 1943 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.66, df=17(P=0.82); I^2=0%					
Test for overall effect: Z=0.14(P=0.88)					
Test for subgroup differences: Chi^2=4.88, df=1 (P=0.09), I^2=59.05%					



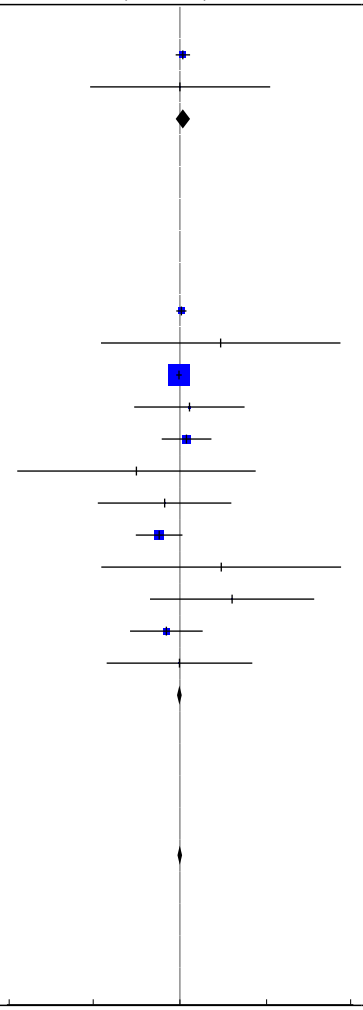
Analysis 1.5. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 5 Cancer occurrence ('best-worst case' and 'worst-best case' scenario).

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
1.5.1 'Best-worst' case scenario					
Avenell 2012	369/2649	390/2643		16.38%	0.94[0.83,1.08]
Bolton-Smith 2007	1/62	4/61		1.5%	0.25[0.03,2.14]
Brunner 2011	1306/18176	1817/18106		16.84%	0.72[0.67,0.77]
Daly 2008	4/85	31/82		5.34%	0.12[0.05,0.34]
Gallagher 2001	6/123	15/123		5.99%	0.4[0.16,1]
Glendenning 2012	19/353	41/333		10.61%	0.44[0.26,0.74]
Grady 1991	1/50	1/48		0.97%	0.96[0.06,14.92]
Janssen 2010	0/36	4/34		0.88%	0.11[0.01,1.88]
Komulainen 1999	2/116	6/116		2.62%	0.33[0.07,1.62]
Larsen 2012	1/65	8/65		1.66%	0.13[0.02,0.97]
Murdoch 2012	4/161	15/161		4.76%	0.27[0.09,0.79]
Ott 1989	1/43	6/43		1.62%	0.17[0.02,1.33]
Prince 2008	1/151	11/151		1.68%	0.09[0.01,0.7]
Sanders 2010	7/1131	73/1127		7.36%	0.1[0.04,0.21]
Trivedi 2003	188/1345	250/1341		15.95%	0.75[0.63,0.89]
Witham 2013	2/80	11/79		2.94%	0.18[0.04,0.78]
Wood 2012	2/203	11/102		2.89%	0.09[0.02,0.4]
Subtotal (95% CI)	**24829**	**24615**		**100%**	**0.41[0.31,0.54]**
Total events: 1914 (Vitamin D), 2694 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=87.19, df=16(P<0.0001); I^2=81.65%					
Test for overall effect: Z=6.31(P<0.0001)					
1.5.2 'Worst-best' case scenario					
Avenell 2012	400/2649	354/2643		14.21%	1.13[0.99,1.29]
Bolton-Smith 2007	8/62	0/61		1.28%	16.73[0.99,283.65]
Brunner 2011	1306/18176	1333/18106		14.43%	0.98[0.91,1.05]
Daly 2008	33/85	3/82		5.41%	10.61[3.39,33.26]
Gallagher 2001	26/123	5/123		6.91%	5.2[2.06,13.1]
Glendenning 2012	41/353	15/333		10.21%	2.58[1.46,4.57]
Grady 1991	1/50	0/48		1.04%	2.88[0.12,69.07]
Janssen 2010	8/36	1/34		2.31%	7.56[1,57.26]
Komulainen 1999	5/116	3/116		4.08%	1.67[0.41,6.81]
Larsen 2012	8/65	0/65		1.28%	17[1,288.56]
Murdoch 2012	17/161	1/161		2.35%	17[2.29,126.23]
Ott 1989	8/43	0/43		1.29%	17[1.01,285.6]
Prince 2008	8/151	5/151		5.71%	1.6[0.54,4.78]
Sanders 2010	83/1131	10/1127		9.39%	8.27[4.31,15.86]
Trivedi 2003	271/1345	173/1341		13.98%	1.56[1.31,1.86]
Witham 2013	9/80	2/79		3.72%	4.44[0.99,19.92]
Wood 2012	31/203	1/102		2.4%	15.58[2.16,112.49]
Subtotal (95% CI)	**24829**	**24615**		**100%**	**2.76[1.97,3.86]**
Total events: 2263 (Vitamin D), 1906 (Control)					
Heterogeneity: Tau^2=0.2; Chi^2=131.87, df=16(P<0.0001); I^2=87.87%					
Test for overall effect: Z=5.93(P<0.0001)					
Test for subgroup differences: Chi^2=73.87, df=1 (P<0.0001), I^2=98.65%					



Analysis 1.6. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 6 Cancer occurrence in trials using vitamin D_3 (cholecalciferol).

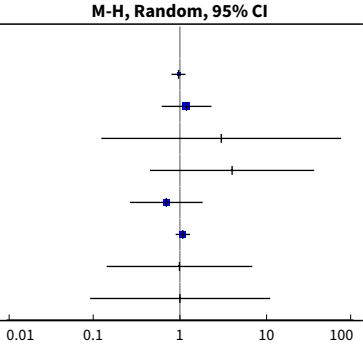
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Vitamin D_3 trials with low risk of bias					
Trivedi 2003	188/1345	173/1341		9.87%	1.08[0.89,1.31]
Wood 2012	2/203	1/102		0.06%	1[0.09,10.95]
Subtotal (95% CI)	**1548**	**1443**		**9.93%**	**1.08[0.89,1.31]**
Total events: 190 (Vitamin D), 174 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
1.6.2 Vitamin D_3 trials with high risk of bias					
Avenell 2012	369/2649	354/2643		19.85%	1.04[0.91,1.19]
Bolton-Smith 2007	1/62	0/61		0.04%	2.95[0.12,71.09]
Brunner 2011	1306/18176	1333/18106		67.48%	0.98[0.91,1.05]
Daly 2008	4/85	3/82		0.17%	1.29[0.3,5.57]
Glendenning 2012	19/353	15/333		0.84%	1.19[0.62,2.31]
Janssen 2010	0/36	1/34		0.04%	0.32[0.01,7.48]
Komulainen 1999	2/116	3/116		0.12%	0.67[0.11,3.92]
Lappe 2007	13/446	37/733		0.95%	0.58[0.31,1.07]
Larsen 2012	1/65	0/65		0.04%	3[0.12,72.31]
Murdoch 2012	4/161	1/161		0.08%	4[0.45,35.4]
Sanders 2010	7/1131	10/1127		0.39%	0.7[0.27,1.83]
Witham 2013	2/80	2/79		0.1%	0.99[0.14,6.84]
Subtotal (95% CI)	**23360**	**23540**		**90.07%**	**0.99[0.93,1.05]**
Total events: 1728 (Vitamin D), 1759 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.67, df=11(P=0.74); I^2=0%					
Test for overall effect: Z=0.42(P=0.67)					
Total (95% CI)	**24908**	**24983**		**100%**	**1[0.94,1.06]**
Total events: 1918 (Vitamin D), 1933 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.5, df=13(P=0.81); I^2=0%					
Test for overall effect: Z=0.14(P=0.88)					
Test for subgroup differences: Chi^2=0.82, df=1 (P=0.36), I^2=0%					



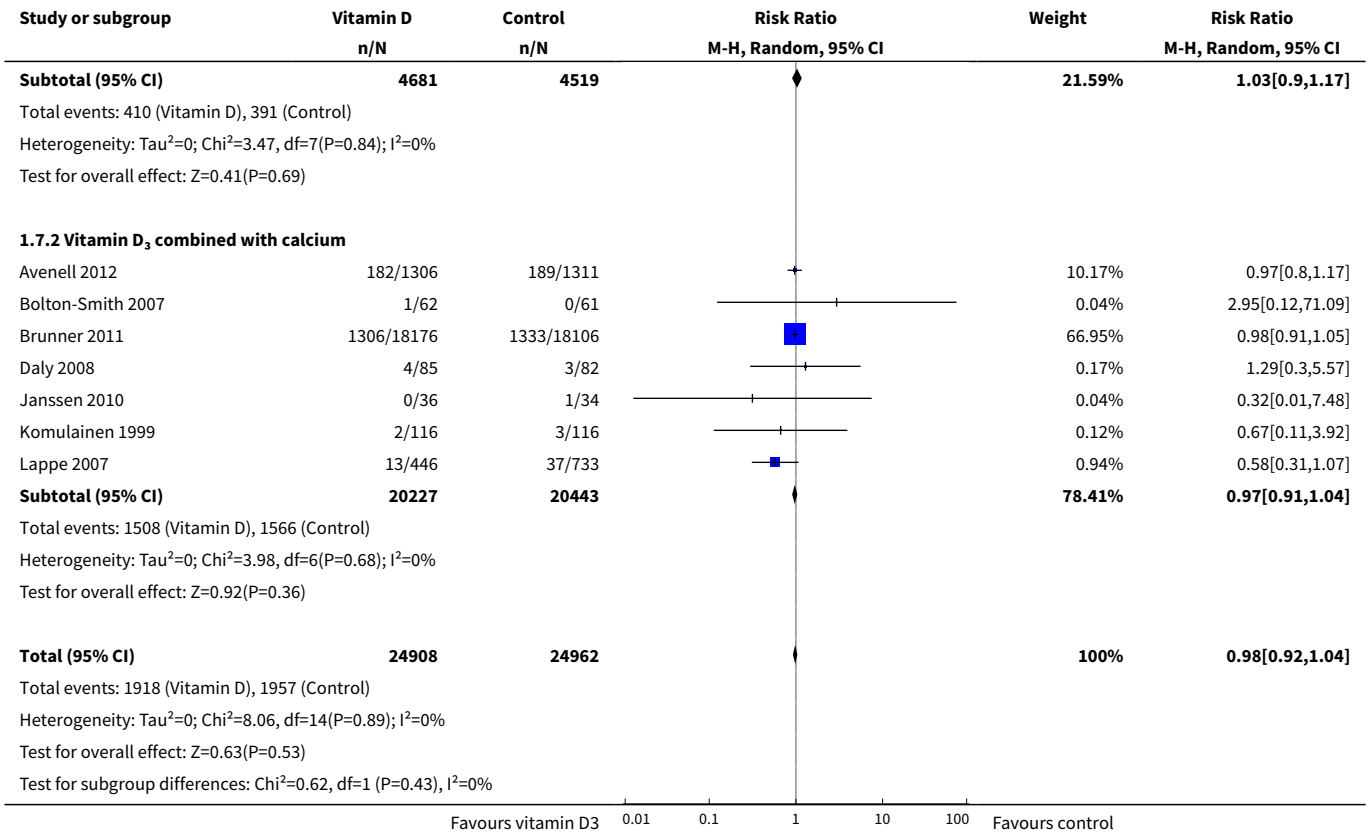
Favours vitamin D — Favours control

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

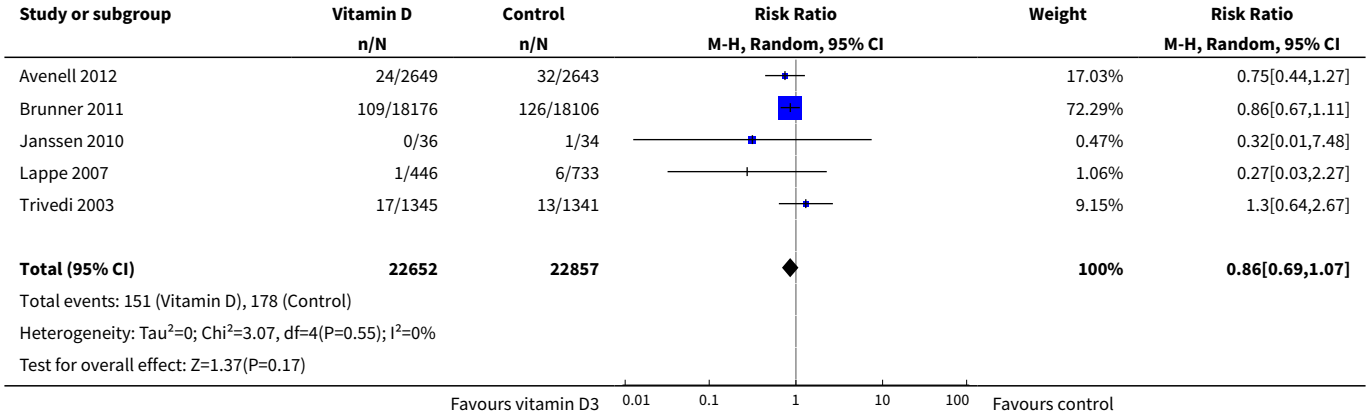
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Vitamin D_3 singly					
Avenell 2012	187/1343	189/1311		10.31%	0.97[0.8,1.16]
Glendenning 2012	19/353	15/333		0.83%	1.19[0.62,2.31]
Larsen 2012	1/65	0/65		0.04%	3[0.12,72.31]
Murdoch 2012	4/161	1/161		0.08%	4[0.45,35.4]
Sanders 2010	7/1131	10/1127		0.39%	0.7[0.27,1.83]
Trivedi 2003	188/1345	173/1341		9.79%	1.08[0.89,1.31]
Witham 2013	2/80	2/79		0.1%	0.99[0.14,6.84]
Wood 2012	2/203	1/102		0.06%	1[0.09,10.95]



Favours vitamin D3 — Favours control



Analysis 1.8. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 8 Lung cancer occurrence in trials using vitamin D_3 (cholecalciferol).



Analysis 1.9. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 9 Breast cancer occurrence 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
Avenell 2012	43/2649	37/2643		6.95%	1.16[0.75,1.79]
Brunner 2011	505/18176	523/18106		91.06%	0.96[0.85,1.09]
Lappe 2007	5/446	14/733		1.29%	0.59[0.21,1.62]
Larsen 2012	1/65	0/65		0.13%	3[0.12,72.31]
Murdoch 2012	3/161	1/161		0.26%	3[0.32,28.54]
Witham 2013	0/80	1/79		0.13%	0.33[0.01,7.96]
Wood 2012	1/203	1/102		0.17%	0.5[0.03,7.95]
Total (95% CI)	**21780**	**21889**		**100%**	**0.97[0.86,1.09]**
Total events: 558 (Vitamin D), 577 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.71, df=6(P=0.72); I^2=0%					
Test for overall effect: Z=0.52(P=0.61)					

Analysis 1.10. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 10 Colorectal cancer occurrence 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
Avenell 2012	41/2649	30/2643		16.04%	1.36[0.85,2.18]
Brunner 2011	158/18176	147/18106		70.15%	1.07[0.86,1.34]
Lappe 2007	1/446	2/733		0.61%	0.82[0.07,9.04]
Trivedi 2003	28/1345	27/1341		12.82%	1.03[0.61,1.74]
Witham 2013	2/80	0/79		0.38%	4.94[0.24,101.25]
Total (95% CI)	**22696**	**22902**		**100%**	**1.11[0.92,1.34]**
Total events: 230 (Vitamin D), 206 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.91, df=4(P=0.75); I^2=0%					
Test for overall effect: Z=1.12(P=0.26)					

Analysis 1.11. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 11 Pancreatic cancer occurrence in trials using vitamin D_3 (cholecalciferol).

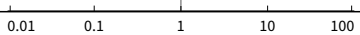
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bolton-Smith 2007	1/62	0/61		2.19%	2.95[0.12,71.09]
Brunner 2011	32/18176	36/18106		97.81%	0.89[0.55,1.42]
Total (95% CI)	**18238**	**18167**		**100%**	**0.91[0.57,1.46]**
Total events: 33 (Vitamin D), 36 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					

Analysis 1.12. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 12 Prostate cancer occurrence 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
Avenell 2012	17/2649	12/2643		0%	1.41[0.68,2.95]

Analysis 1.13. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 13 Uterine cancer occurrence 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
Lappe 2007	1/446	2/733		0%	0.82[0.07,9.04]



Analysis 1.14. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 14 Ovarian cancer occurrence in trials using vitamin D_3 (cholecalciferol).

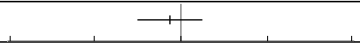
Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Wood 2012	1/203	0/102		0%	1.51[0.06,36.86]

Analysis 1.15. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 15 Oesophageal cancer occurrence 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
Brunner 2011	6/18176	12/18106		0%	0.5[0.19,1.33]

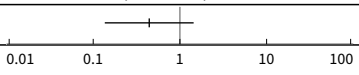
Analysis 1.16. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 16 Stomach cancer occurrence in trials using vitamin D_3 (cholecalciferol).

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
Brunner 2011	9/18176	12/18106		0%	0.75[0.31,1.77]



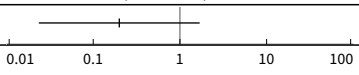
Analysis 1.17. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 17 Liver cancer occurrence in trials using vitamin D_3 (cholecalciferol).

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
Brunner 2011	4/18176	9/18106		0%	0.44[0.14,1.44]



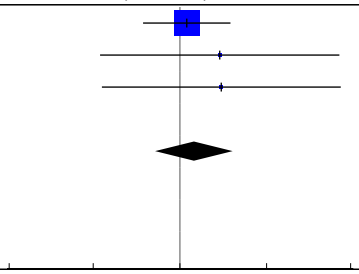
Analysis 1.18. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 18 Cancer occurrence in trials using vitamin D_2 (ergocalciferol).

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Prince 2008	1/151	5/151		0%	0.2[0.02,1.69]



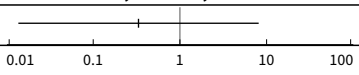
Analysis 1.19. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 19 Cancer occurrence in trials using calcitriol.

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	6/123	5/123		78.92%	1.2[0.38,3.83]
Grady 1991	1/50	0/48		10.53%	2.88[0.12,69.07]
Ott 1989	1/43	0/43		10.55%	3[0.13,71.65]
Total (95% CI)	**216**	**214**		**100%**	**1.45[0.52,4.06]**
Total events: 8 (Vitamin D), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.49, df=2(P=0.78); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					



Analysis 1.20. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 20 Breast cancer occurrence in trials using calcitriol.

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	0/123	1/123		0%	0.33[0.01,8.1]



Analysis 1.21. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 21 Uterine cancer occurrence in trials using calcitriol.

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	0/123		0%	5[0.24,103.09]

Favours calcitriol 0.005 0.1 1 10 200 Favours control

Analysis 1.22. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 22 Stomach cancer occurrence in trials using calcitriol.

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	0/123	1/123		0%	0.33[0.01,8.1]

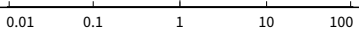
Favours calcitriol 0.01 0.1 1 10 100 Favours control

Analysis 1.23. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 23 All-cause mortality in trials with a low or high risk of bias.

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.23.1 Trials with low risk of bias					
Trivedi 2003	224/1345	247/1341		11.75%	0.9[0.77,1.07]
Subtotal (95% CI)	**1345**	**1341**		**11.75%**	**0.9[0.77,1.07]**
Total events: 224 (Vitamin D), 247 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					
1.23.2 Trials with high risk of bias					
Avenell 2012	836/2649	881/2643		52.4%	0.95[0.88,1.02]
Bolton-Smith 2007	0/62	1/61		0.03%	0.33[0.01,7.9]
Brunner 2011	744/18176	807/18106		33.38%	0.92[0.83,1.01]
Daly 2008	1/85	0/82		0.03%	2.9[0.12,70.07]
Gallagher 2001	2/123	1/123		0.06%	2[0.18,21.77]
Glendenning 2012	2/353	0/333		0.03%	4.72[0.23,97.9]
Grady 1991	1/50	0/48		0.03%	2.88[0.12,69.07]
Janssen 2010	0/36	1/34		0.03%	0.32[0.01,7.48]
Komulainen 1999	0/116	1/116		0.03%	0.33[0.01,8.1]
Lappe 2007	4/446	18/733		0.27%	0.37[0.12,1.07]
Ott 1989	0/43	1/43		0.03%	0.33[0.01,7.96]
Prince 2008	0/151	1/151		0.03%	0.33[0.01,8.12]
Sanders 2010	40/1131	47/1127		1.85%	0.85[0.56,1.28]
Witham 2013	0/80	1/79		0.03%	0.33[0.01,7.96]
Subtotal (95% CI)	**23501**	**23679**		**88.25%**	**0.93[0.88,0.99]**
Total events: 1630 (Vitamin D), 1760 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.31, df=13(P=0.82); I^2=0%					
Test for overall effect: Z=2.35(P=0.02)					
Total (95% CI)	**24846**	**25020**		**100%**	**0.93[0.88,0.98]**

Favours vitamin D 0.01 0.1 1 10 100 Favours control

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: 1854 (Vitamin D), 2007 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.41, df=14(P=0.87); I^2=0%					
Test for overall effect: Z=2.62(P=0.01)					
Test for subgroup differences: Chi^2=0.1, df=1 (P=0.75), I^2=0%					

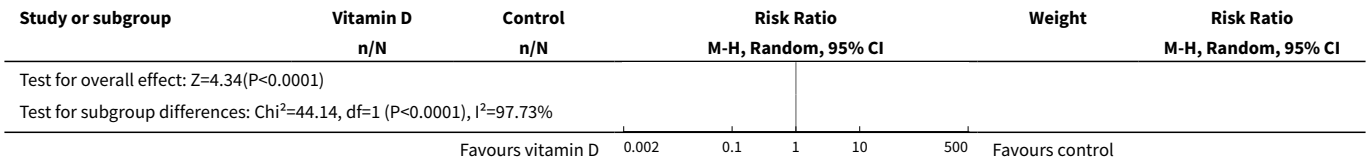


Favours vitamin D — Favours control

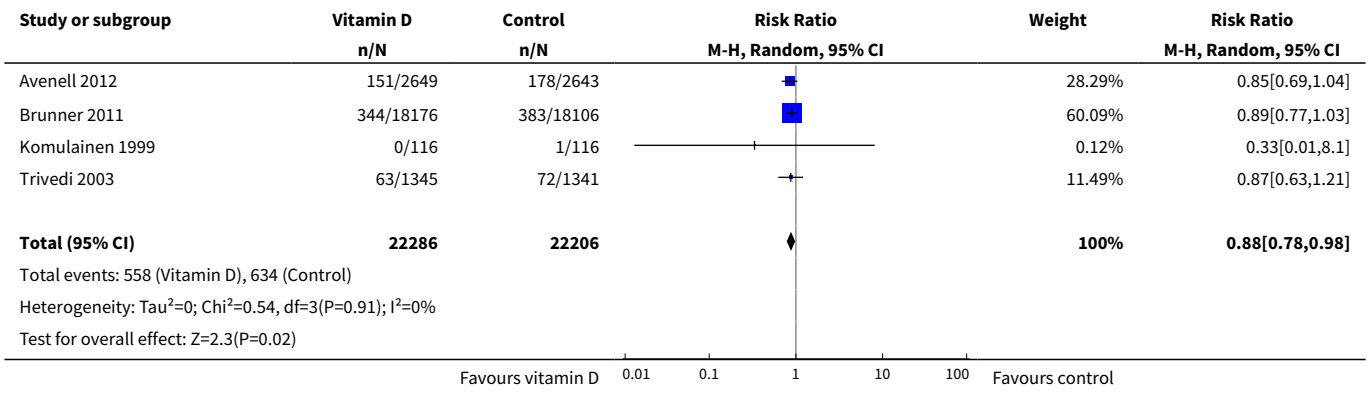
Analysis 1.24. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 24 All-cause mortality ('best-worst case' and 'worst-best case' scenario).

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
1.24.1 'Best-worst' case scenario					
Avenell 2012	836/2649	917/2643		21.45%	0.91[0.84,0.98]
Bolton-Smith 2007	0/62	5/61		1.21%	0.09[0.01,1.58]
Brunner 2011	744/18176	1291/18106		21.37%	0.57[0.53,0.63]
Daly 2008	1/85	28/82		2.42%	0.03[0,0.25]
Gallagher 2001	2/123	11/123		3.92%	0.18[0.04,0.8]
Glendenning 2012	2/353	26/333		4.17%	0.07[0.02,0.3]
Grady 1991	1/50	1/48		1.32%	0.96[0.06,14.92]
Janssen 2010	0/36	4/34		1.2%	0.11[0.01,1.88]
Komulainen 1999	0/116	4/116		1.18%	0.11[0.01,2.04]
Ott 1989	0/43	7/43		1.24%	0.07[0,1.13]
Prince 2008	0/151	7/151		1.22%	0.07[0,1.16]
Sanders 2010	40/1131	110/1127		17.3%	0.36[0.25,0.52]
Trivedi 2003	224/1345	324/1341		20.72%	0.69[0.59,0.8]
Witham 2013	0/80	11/79		1.26%	0.04[0,0.72]
Subtotal (95% CI)	**24400**	**24287**		**100%**	**0.43[0.31,0.6]**
Total events: 1850 (Vitamin D), 2746 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=118.99, df=13(P<0.0001); I^2=89.08%					
Test for overall effect: Z=5.05(P<0.0001)					
1.24.2 'Worst-best' case scenario					
Avenell 2012	867/2649	881/2643		21.5%	0.98[0.91,1.06]
Bolton-Smith 2007	8/62	1/61		2.2%	7.87[1.01,61.05]
Brunner 2011	1240/18176	807/18106		21.43%	1.53[1.4,1.67]
Daly 2008	30/85	0/82		1.25%	58.87[3.66,947.17]
Gallagher 2001	22/123	1/123		2.32%	22[3.01,160.68]
Glendenning 2012	24/353	0/333		1.24%	46.23[2.82,757.19]
Grady 1991	1/50	0/48		0.97%	2.88[0.12,69.07]
Janssen 2010	8/36	1/34		2.24%	7.56[1,57.26]
Komulainen 1999	3/116	1/116		1.86%	3[0.32,28.42]
Ott 1989	7/43	1/43		2.19%	7[0.9,54.5]
Prince 2008	7/151	1/151		2.13%	7[0.87,56.21]
Sanders 2010	116/1131	47/1127		17.71%	2.46[1.77,3.42]
Trivedi 2003	307/1345	247/1341		20.79%	1.24[1.07,1.44]
Witham 2013	7/80	1/79		2.15%	6.91[0.87,54.9]
Subtotal (95% CI)	**24400**	**24287**		**100%**	**2.03[1.47,2.8]**
Total events: 2647 (Vitamin D), 1989 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=118.77, df=13(P<0.0001); I^2=89.05%					

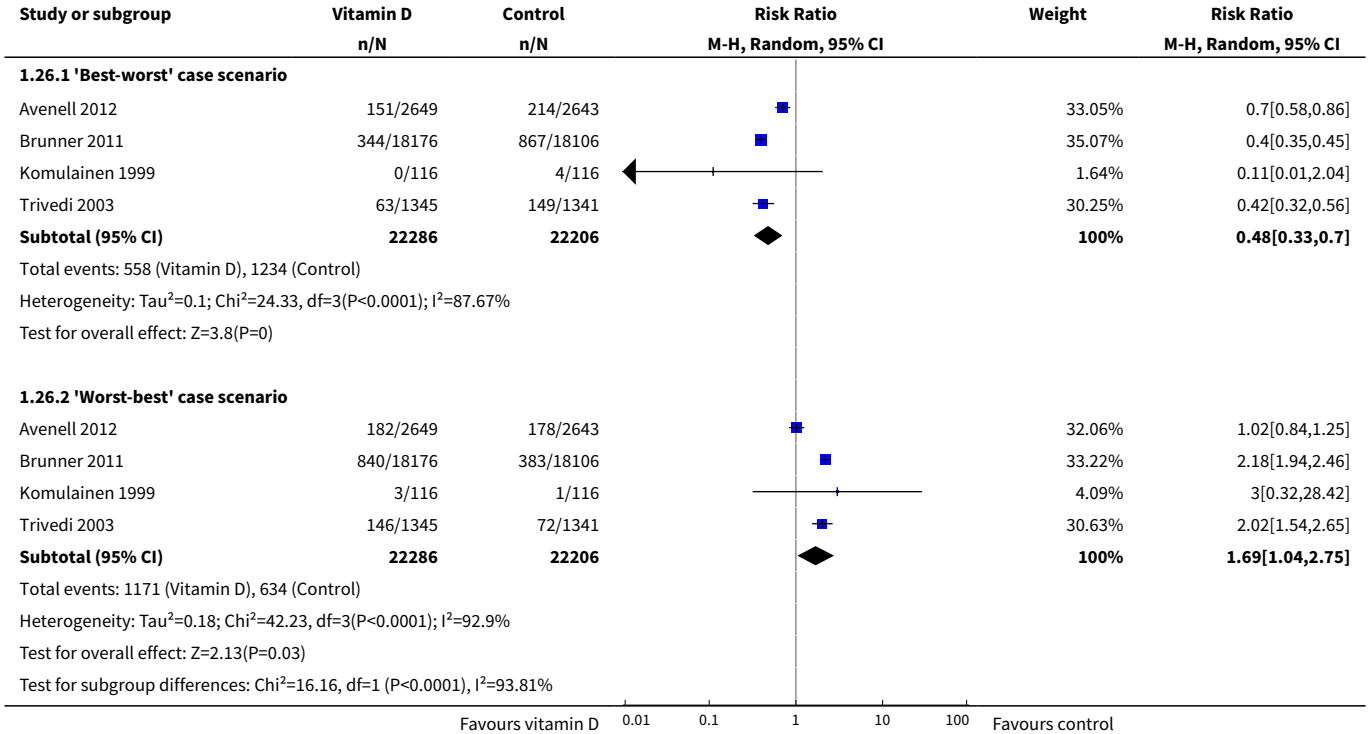
Favours vitamin D — Favours control



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

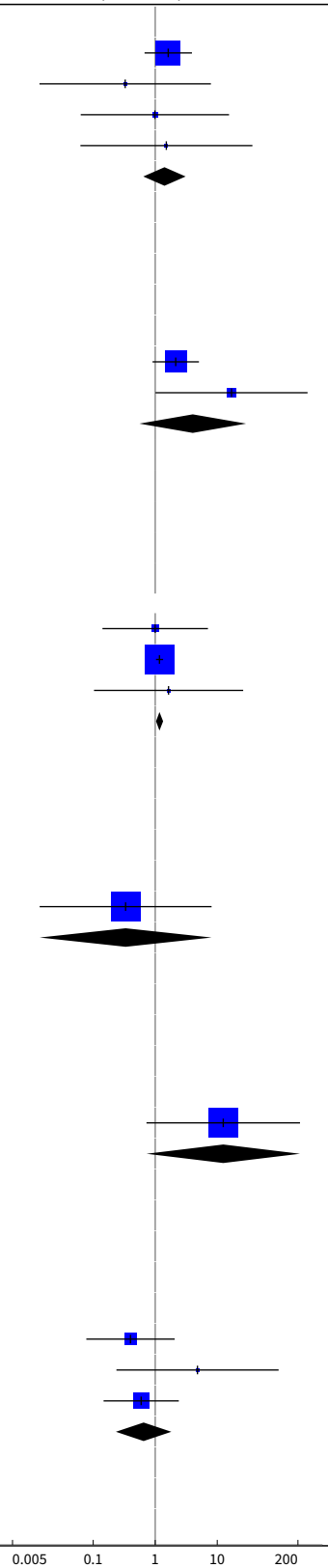


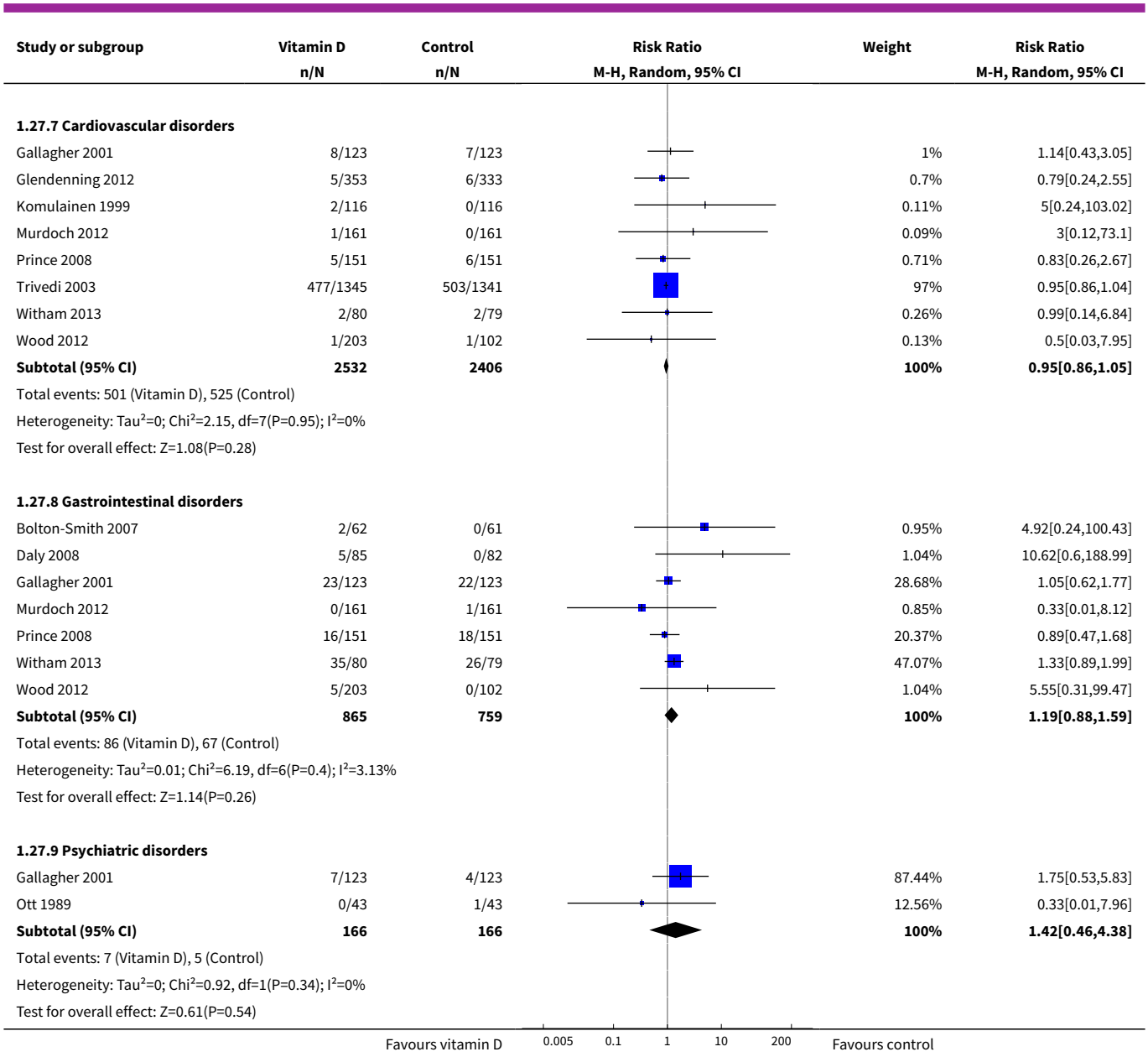
Analysis 1.26. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 26 Cancer mortality ('best-worst case' and 'worst-best case' scenario).



Analysis 1.27. Comparison 1 Vitamin D versus placebo or no intervention, Outcome 27 Adverse events.

Study or subgroup	Vitamin D n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.27.1 Hypercalcaemia in trials using supplemental forms of vitamin D					
Avenell 2012	13/2649	8/2643		79.74%	1.62[0.67,3.91]
Bolton-Smith 2007	0/62	1/61		6.09%	0.33[0.01,7.9]
Witham 2013	1/80	1/79		8.12%	0.99[0.06,15.51]
Wood 2012	1/203	0/102		6.05%	1.51[0.06,36.86]
Subtotal (95% CI)	**2994**	**2885**		**100%**	**1.41[0.64,3.09]**
Total events: 15 (Vitamin D), 10 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.97, df=3(P=0.81); I^2=0%					
Test for overall effect: Z=0.85(P=0.39)					
1.27.2 Hypercalcaemia in trials using active forms of vitamin D					
Gallagher 2001	15/123	7/123		69.5%	2.14[0.91,5.07]
Ott 1989	8/43	0/43		30.5%	17[1.01,285.6]
Subtotal (95% CI)	**166**	**166**		**100%**	**4.03[0.56,29.22]**
Total events: 23 (Vitamin D), 7 (Control)					
Heterogeneity: Tau^2=1.28; Chi^2=2.13, df=1(P=0.14); I^2=52.99%					
Test for overall effect: Z=1.38(P=0.17)					
1.27.3 Nephrolithiasis in trials using vitamin D_3 combined with calcium					
Avenell 2012	2/2649	2/2643		0.47%	1[0.14,7.08]
Brunner 2011	449/18176	381/18106		99.29%	1.17[1.03,1.34]
Lappe 2007	1/446	1/733		0.24%	1.64[0.1,26.21]
Subtotal (95% CI)	**21271**	**21482**		**100%**	**1.17[1.03,1.34]**
Total events: 452 (Vitamin D), 384 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=2(P=0.96); I^2=0%					
Test for overall effect: Z=2.34(P=0.02)					
1.27.4 Nephrolithiasis in trials using calcitriol					
Gallagher 2001	0/123	1/123		100%	0.33[0.01,8.1]
Subtotal (95% CI)	**123**	**123**		**100%**	**0.33[0.01,8.1]**
Total events: 0 (Vitamin D), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
1.27.5 Hypercalciuria					
Grady 1991	6/50	0/48		100%	12.49[0.72,215.84]
Subtotal (95% CI)	**50**	**48**		**100%**	**12.49[0.72,215.84]**
Total events: 6 (Vitamin D), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.74(P=0.08)					
1.27.6 Renal insufficiency					
Avenell 2012	2/2649	5/2643		37.63%	0.4[0.08,2.06]
Grady 1991	2/50	0/48		11.56%	4.8[0.24,97.55]
Witham 2013	3/80	5/79		50.82%	0.59[0.15,2.4]
Subtotal (95% CI)	**2779**	**2770**		**100%**	**0.65[0.23,1.82]**
Total events: 7 (Vitamin D), 10 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=2.08, df=2(P=0.35); I^2=3.95%					
Test for overall effect: Z=0.82(P=0.41)					





ADDITIONAL TABLES

Table 1. Overview of study populations

Characteristic	Intervention(s) and comparator(s)	Screened/ eligible [N]	Ran-domised [N]	ITT [N]	Finishing study [N]	Ran-domised finishing study [%]
(1) Avenell 2012	I1: vitamin D_3	15,024	1343	1343	1813	68
	I2: vitamin D_3 plus calcium		1306	1306		

Table 1. Overview of study populations *(Continued)*

	C1: calcium		1311	1311	1762	67
	C2: matched placebo tablets		1332	1332		
	total:		5292	5292	3575	68
(2) Bolton-Smith 2007	I1: vitamin D_3 plus calcium	-	62	62	50	81
	C1: matched placebo		61	61	56	92
	total:		123	123	106	86
(3) Brunner 2011	I1: vitamin D_3 plus calcium	68,132	18,176	18,176	16,936	93
	C1: matched placebo		18,106	18,106	16,815	93
	total:		36,282	36,282	33,751	93
(4) Daly 2008	I1: calcium-vitamin D_3-fortified milk plus calcium	422	85	85	76	89
	C1: usual diet		82	82	73	89
	total:		167	167	149	89
(5) Gallagher 2001	I1: calcitriol	1905	123	123	101	82
	C1: matched placebo		123	123	112	91
	total:		246	246	213	87
(6) Glendenning 2012	I1: cholecalciferol	2110	353	353	331	94
	C1: placebo vitamin D		333	333	307	92
	total:		686	686	638	93
(7) Grady 1991	I1: calcitriol	98	50	50	49	98
	C1: placebo vitamin D		48	48	48	100
	total:		98	50	97	99
(8) Janssen 2010	I1: vitamin D_3 plus calcium	91	36	36	18	50
	C1:placebo vitamin D_3 plus calcium		34	34	31	91
	total:		70	70	49	70
(9) Komulainen 1999	I1: vitamin D_3 plus calcium	13,100	116	116	112	97
	C1: placebo		116	116	115	99
	total:		232	232	227	98

Table 1. Overview of study populations *(Continued)*

(10) Lappe 2007	I1: vitamin D_3 plus calcium	1180	446	446	403	90
	C1: vitamin D_3 placebo plus calcium		445	445	416	93
	C2: vitamin D_3 placebo plus calcium placebo		288	288	266	92
	total:		1179	1179	1085	92
(11) Larsen 2012	I1: vitamin D_3	136	65	65	55	85
	C1: vitamin D placebo		65	65	57	88
	total:		130	130	112	86
(12) Murdoch 2012	I1: vitamin D_3	351	161	161	148	92
	C1: vitamin D placebo		161	161	146	91
	total:		322	322	294	91
(13) Ott 1989	I1: calcitriol plus calcium	-	43	43	39	91
	C1: placebo vitamin D plus calcium		43	43	37	86
	total:		86	86	76	88
(14) Prince 2008	I1: vitamin D_2 plus calcium	827	151	151	144	95
	C1: placebo vitamin D plus calcium		151	151	145	96
	total:		302	302	289	95
(15) Sanders 2010	I1: vitamin D_3	7204	1131	1131	1015	90
	C1: vitamin D placebo		1127	1127	1017	90
	total:		2258	2258	2032	90
(16) Trivedi 2003	I1: vitamin D_3	-	1345	1345	1262	94
	C1:placebo vitamin D		1341	1341	1264	94
	total:		2686	2686	2526	94
(17) Witham 2013	I1: vitamin D_3	341	80	80	73	91
	C1: placebo vitamin D		79	79	69	87
	total:		159	159	142	89
(18) Wood 2012	I1: vitamin D_3	424	102	102	84	82
	I2: vitamin D_3		101	101	90	89
	C1: placebo vitamin D		102	102	91	89

Table 1. Overview of study populations *(Continued)*

	total:	305	305	265	87
Grand total	***All interventions***	***25,275***		***22,799***	*90*
	All controls	***25,348***		***22,827***	*90*
	All interventions and controls	***50,623***		***45,626***	*90*

"-" denotes not reported
ITT: intention-to-treat

APPENDICES

Appendix 1. Search strategies

Search terms and databases
Unless otherwise stated, search terms are free text terms. '$': 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.
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 colecalciferol* in All Text) 10. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) 11. MeSH descriptor Mortality explode all trees 12. (mortality in All Text or mortaliti* in All Text) 13. (#11 or #12) 14. MeSH descriptor Primary Prevention explode all trees 15. prevent* in All Text 16. MeSH descriptor Neoplasms explode all trees 17. (cancer* in All Text or neoplasm* in All Text or tumo?r* in All Text) 18. (#14 or #15 or #16 or #17) 19. (#10 and #13) 20. (#10 and #18) 21. (#19 or #20)
MEDLINE
1. exp Vitamin D/ 2. exp Cholecalciferol/ 3. exp ergocalciferols/ or exp dihydrotachysterol/ or exp 25-hydroxyvitamin d 2/ 4. exp Hydroxycholecalciferols/ 5. vitamin D?.tw,ot.

(Continued)

6. (cholecalciferol$ or calcifediol$ or calcitriol$ or dihydrotachysterol$ or hydroxyvitamin$ d?).tw,ot.
7. (alfacalcidol$ or alphacalcidol$ or colecalciferol$).tw,ot.
8. or/1-7
9. exp Mortality/
10. mortality.tw,ot.
11. mortaliti$.tw,ot.
12. or/9-11
13. exp Primary Prevention/
14. (prevention$ or prevent$).tw,ot.
15. exp Neoplasm/
16. (cancer$ or neoplasm$ or tumo?r$).tw,ot.
17. or/13-16
18. exp Randomized Controlled Trials as topic/
19. Randomized Controlled Trial.pt.
20. exp Controlled Clinical Trials as topic/
21. Controlled Clinical Trial.pt.
22. exp Random Allocation/
23. exp Double-Blind Method/
24. exp Single-Blind Method/
25. or/18-24
26. exp "Review Literature as topic"/
27. exp Technology Assessment, Biomedical/
28. exp Meta-analysis as topic/
29. Meta-analysis.pt.
30. hta.tw,ot.
31. (health technology adj6 assessment$).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/

(Continued)

19. double blind procedure/
20. single blind procedure/
21. exp randomization/
22. exp controlled clinical trial/
23. or/18-22
24. exp meta analysis/
25. (metaanaly$ or meta analy$ or meta?analy$).ab,ti,ot.
26. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systematic$)).ab,ti,ot.
27. exp Literature/
28. exp Biomedical Technology Assessment/
29. hta.tw,ot.
30. (health technology adj6 assessment$).tw,ot.
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	Intervention(s) [route, frequency, total dose/day]	Comparator(s) [route, frequency, total dose/day]
Avenell 2012	I1: vitamin D_3 (800 IU) orally, daily	C1: calcium (1000 mg) orally, daily
	I2: vitamin D_3 (800 IU) plus calcium (1000 mg) orally, daily	C2: matched placebo tablet orally, daily
Bolton-Smith 2007	I1: vitamin D_3 (400 IU) plus calcium 1000 mg orally, daily	C1: vitamin K_1 200 µg orally, daily
	I2: vitamin D_3 (400 IU) plus calcium 1000 mg plus vitamin K_1 200 µg orally, daily	C2: matched placebo tablet orally, daily

(Continued)

Brunner 2011	I: vitamin D_3 (400 IU) plus calcium (1000 mg) orally, daily	C: matched placebo tablet orally, daily
Daly 2008	I: calcium-vitamin D_3-fortified milk containing vitamin D_3 (800 IU) plus calcium (1000 mg) daily	C: usual diet
Gallagher 2001	I1: calcitriol (0.5 µg) daily	C1: calcitriol (0.5 µg daily) plus conjugated oestrogens 0.625 mg/daily plus medroxyprogesterone acetate 2.5 mg orally, daily
	I2: conjugated oestrogens 0.625 mg/daily plus medroxyprogesterone acetate 2.5 mg orally, daily	C2: matched placebo tablet orally, daily
Glendenning 2012	I: cholecalciferol 150,000 IU 3-monthly	C: placebo vitamin D 3-monthly
Grady 1991	I: calcitriol (0.5 µg) orally, daily	C: placebo vitamin D orally, daily
Janssen 2010	I: vitamin D_3 (400 IU) plus calcium (500 mg) orally, daily	C: matched placebo vitamin D_3 plus calcium (500 mg) orally, daily
Komulainen 1999	I1: sequential combination of 2 mg estradiol valerate (days 1 to 21) and 1 mg cyproterone acetate (days 12 to 21) and a treatment-free interval (days 22 to 28)	C1: sequential combination of 2 mg estradiol 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
	I2: vitamin D_3 (300 IU) plus calcium (500 mg) daily[a]	C2: placebo
Lappe 2007	I1: vitamin D_3 (1000 IU) plus calcium (1400 to 1500 mg) orally, daily	C1: vitamin D_3 placebo plus calcium placebo, orally, daily
	I2: vitamin D_3 placebo plus calcium (1400 to 1500 mg) orally, daily	
Larsen 2012	I: vitamin D_3 3000 IU orally, daily	C: matched placebo vitamin D orally
Murdoch 2012	I: vitamin D_3 an initial dose of 200,000 IU of vitamin D_3, then 200,000 IU 1 month later, then 100,000 IU monthly orally	C: matched placebo vitamin D orally
Ott 1989	I: calcitriol 0.25 to 2 µg plus calcium 1000 mg, orally, daily	C: matched placebo vitamin D plus calcium 1000 mg orally, daily
Prince 2008	I: vitamin D_2 1000 IU plus calcium 1000 mg orally, daily	C: matched placebo tablet of vitamin D plus calcium 1000 mg orally, daily
Sanders 2010	I: vitamin D_3 500,000 IU orally, yearly	C: matched placebo tablet of vitamin D orally, yearly
Trivedi 2003	I: vitamin D_3 100,000 IU every 4 months orally	C: matched placebo vitamin D every 4 months orally
Witham 2013	I: vitamin D_3 100,000 IU every 3 months orally	C: matched placebo vitamin D every 3 months orally
Wood 2012	I1: vitamin D_3 400 IU orally, daily	C: matched placebo vitamin D orally, daily
	I2: vitamin D_3 1000 IU orally, daily	

"-" denotes not reported

(Continued)

[a]No intake during June to August, the vitamin D_3 dosage was lowered to 100 IU/day after 4 years of treatment

C: comparator; I: intervention

Appendix 3. Baseline characteristics (I)

Characteristic Study ID	Design of study	Duration of intervention [years]	Duration of follow-up [years]	Description of participants	Country	Setting
Avenell 2012	Factorial RCT	3.75	6.2	Elderly people with low-trauma, osteoporotic fracture in the previous 10 years	United Kingdom	Outpatients
Bolton-Smith 2007	Factorial RCT	2	2	Elderly nonosteoporotic women	United Kingdom	Outpatients
Brunner 2011	RCT	7	7	Postmenopausal women	United States	Outpatients
Daly 2008	RCT	2	3.5	Healthy ambulatory men	Australia	Outpatients
Gallagher 2001	Factorial RCT	3	5	Elderly women	United States	Outpatients
Glendenning 2012	RCT	0.5	0.75	Elderly women	Australia	Outpatients
Grady 1991	RCT	0.5	0.5	Elderly people	United States	Outpatients
Janssen 2010	RCT	1	1	Elderly vitamin D-insufficient women	Netherlands	Outpatients
Komulainen 1999	Factorial RCT	5	5	Postmenopausal women	Finland	Outpatients
Lappe 2007	RCT	4	4	Postmenopausal women	United States	Outpatients
Larsen 2012	RCT	0.38	0.38	Hypertensive patients	Denmark	Outpatients
Murdoch 2012	RCT	1	1	Healthy adults	New Zealand	Outpatients
Ott 1989	RCT	2	2	Postmenopausal women	United States	Outpatients
Prince 2008	RCT	1	1	Elderly women with vitamin D insufficiency	Australia	Outpatients
Sanders 2010	RCT	2.96	2.96	Elderly women	Australia	Outpatients
Trivedi 2003	RCT	5	5	Elderly people	United Kingdom	Outpatients
Witham 2013	RCT	1	1	Elderly patients with isolated systolic hypertension	United Kingdom	Outpatients

(Continued)

Wood 2012	RCT	1	1	Healthy postmenopausal white women	United Kingdom	Outpatients

Appendix 4. Baseline characteristics (II)

Characteristic Study ID	Sex [female %]	Age [mean years (range)]	Ethnic groups [%]	Co-medications / Co-interventions	Co-morbidities
Avenell 2012	85	77	-	-	Low-trauma osteoporotic fracture in the previous 10 years
Bolton-Smith 2007	100	68	-	Vitamin K_1	-
Brunner 2011	100	62.4 (50 to 79)	-	-	-
Daly 2008	0	61.9	-	-	-
Gallagher 2001	100	71 (65 to 67)	-	Conjugated oestrogens plus medroxyprogesterone acetate	-
Glendenning 2012	100	76.7	-	-	-
Grady 1991	54	79.1 (70 to 97)	-	-	-
Janssen 2010	100	80.8	-	-	-
Komulainen 1999	100	52.7 (47 to 56)	-	Oestradiol valerate and cyproterone acetate	-
Lappe 2007	100	66.7	White: 100	-	-
Larsen 2012	69	60	White: 100		Arterial hypertension
Murdoch 2012	75	47	-	-	-
Ott 1989	100	67.5 (50 to 80)	-	-	-
Prince 2008	100	77.2 (70 to 90)	-	-	-
Sanders 2010	100	76	-	-	-
Trivedi 2003	24	74.7 (65 to 85)	-	-	-
Witham 2013	48	77 (>70)	-	-	Arterial hypertension
Wood 2012	100	64 (60 to 70)	White: 100	-	-

(Continued)

"-" denotes not reported

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]
Avenell 2012	Fractures	Overall mortality, vascular disease mortality, cancer mortality, and cancer occurrence (3.75, 6.2 y)	-
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)
Brunner 2011	Fractures, cancer occurrence, mortality (3, 7 y)	-	-
Daly 2008	Bone mineral density	-	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-hidrohyvitamin 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)
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 y)	-	Adverse events (5 y), overall mortality (5 y)
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)
Larsen 2012	Systolic blood pressure	Diastolic blood pressure and heart rate, central blood pressure, central augmentation index, carotid-femoral pulse wave velocity, urinary calcium-creatinine ratio, and plasma levels of renin, angiotensin II, aldosterone, brain natriuretic peptide, 25(OH)D, intact parathyroid hormone, ionized calcium, phosphate, and fibroblast growth factor 23 at 20 weeks	Adverse events (20 wk)
Murdoch 2012	Upper respiratory tract infections	Duration and severity of upper respiratory tract infections episodes, and number of days of missed work due to upper respiratory tract infections episodes 1 yr	Adverse events (1 yr)
Ott 1989	Bone mass (0, 6, 12, 18, 24 mo)	Adverse events (24 mo)	Overall mortality (24 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)
Trivedi 2003	Fractures (5 y), cause-specific mortality (5 y)	Cancer occurrence (5 y), cardiovascular disease (5 y)	Overall mortality (5 y)
Witham 2013	Blood pressure (0, 3, 6, 9, 12 mo)	24-hour blood pressure, soluble markers of cardiovascular risk, endothelial function, pulse wave velocity, other biochemical measurements (glucose, total cholesterol, LDL and HDL cholesterol, triglycerides, serum albumin and calcium), exercise capacity and falls (3, 6, 9, 12 mo)	Adverse events (3, 6, 9, 12 mo)
Wood 2012	Markers of cardiovascular disease risk (12 mo)	Adverse events (12 mo)	-

Primary or secondary endpoint(s) refer to verbatim statements in the publication, other endpoints relate to outcomes which were not specified as 'primary' or 'secondary' outcomes in the publication

"-" denotes not reported

mo: months; wk: weeks; y: years

Appendix 6. Adverse events

Characteristic Study ID	Intervention(s) and comparator(s)	Randomised [N]	Deaths [n/N (%)]	All adverse events [n/N (%)]	Severe/serious adverse events [n/N (%)]	Discontinued study due to adverse events [n/N (%)]
Avenell 2012	I1: vitamin D_3	2649	836/2649 (31.6)	363/2649 (13.7)	-	-
	C1: matched placebo	2643	881/2643 (33.3)	386/2643 (14.6)		
	all:	5292			33 (0.6)	
Bolton-Smith 2007	I1: vitamin D_3 plus calcium	62	0/62 (0)	-	-	-
	C1: matched placebo	61	1/60 (1.7)			
	all:	123				
Brunner 2011	I1: vitamin D_3 plus calcium	18,176	744/18,176 (4.1)	449/18176 (2.5)	449/18,176 (2.5)	-
	C1: matched placebo	18,106	807/18,106 (4.5)	381/18106 (2.1)	381/18,106 (2.1)	

(Continued)

	all:	36,282				
Daly 2008	I1: calcium-vitamin D_3-fortified milk plus calcium	85	1/85 (1.2)	9/85 (10.6)	9/85 (10.6)	9/85 (10.6)
	C1: no intervention	82	0/82 (0)	2/82 (2.4)	2/82 (2.4)	2/82 (2.4)
	all:	167				
Gallagher 2001	I1: calcitriol	123	2/123 (1.6)	87/123 (71.0)	55/123 (45.0)	-
	C1: matched placebo	123	1/123 (0.8)	(56/123 (45.5)	46/123 (37.0)	
	all:	246				
Glendenning 2012	I: cholecalciferol 150,000 3-monthly	353	2/353 (0.6)	24/353 (6.8)	19/353 (5.4)	-
	C: placebo vitamin D 3-monthly	333	0/333 (0)	21/333 (6.3)	15/333 (4.5)	
	all:	686				
Grady 1991	I: calcitriol	50	1/50 (2)	7/50 (14.0)	7/50 (14.0)	-
	C: placebo vitamin D	48	0/48 (0)	2/48 (4.2)	2/48 (4.2)	
	all:	98				
Janssen 2010	I: vitamin D_3 plus calcium	36	0/36 (0)	-	-	-
	C: matched placebo vitamin D_3 plus calcium	34	0/34 (0)			
	all:	70				
Komulainen 1999	I: vitamin D_3 plus calcium	116	0/116 (0)	-	5/116 (4.3)	-
	C: placebo	116	1/116 (0.9)		4/116 (3.4)	
	all:	232				
Lappe 2007	I1: vitamin D_3 plus calcium	446	4/446 (0.9)	1/446 (0.2)	13/446 (2.9)	-
	I2: calcium plus vitamin D placebo	733	18/733 (2.5)	4/733 (0.5	20/733 (2.7)	
	all:	1179				
Larsen 2012	I1: vitamin D_3	65	2/65 (3.1)	0/65 (0.0)	2/65 (3.1)	1/65 (1.5)
	C1: matched placebo vitamin D	65	0/65 (0.0)	0/65 (0.0)	0/65 (0.0)	0/65 (0.0)
	all:	130				
Murdoch 2012	I1: vitamin D_3	161	0/161 (0)	700/161	21/161 (13)	-
	C1: matched placebo vitamin D	161	0/161 (0)	792/161	19/161 (11.8)	

(Continued)

	all:	322				
Ott 1989	I1: vitamin D_3 plus calcium	43	0/43 (0)	11/43 (25.6)	-	-
	C1: matched placebo vitamin D plus calcium	43	1/43 (2.3)	1/43 (2.3)		
	all:	86				
Prince 2008	I1: vitamin D_{22} plus calcium	151	0/151 (0)	-	-	-
	C1: matched placebo tablet of vitamin D plus calcium	151	1/151 (0.7)			
	all:	302				
Sanders 2010	I1: vitamin D_3	1131	40/1131 (3.5)	223/1131 (19.7)	244/1131 (19.7)	-
	C1: matched placebo tablet	1127	47/1127 (4.2)	201/1127 (17.8)	207/1127 (17.8)	
	all:	2258				
Trivedi 2003	I1: vitamin D_3	1345	224/1345 (16.7)	-	-	-
	C1: matched placebo vitamin D	1341	247/1341 (18.4)			
	all:	2686				
Witham 2013	I1: vitamin D_3	80	0/80 (0)	18/80 (22.5)	11/80 (13.7)	0/80 (0)
	C1: matched placebo vitamin D	79	1/79 (1.3)	21/79 (26.6)	13/79 (16.5)	0/79 (0)
	all:	159				
Wood 2012	I1: vitamin D_3	203	0/203 (0)	32/203 (15.8)	15/203 (7.4)	11/203 (5.4)
	C1: matched placebo vitamin D	102	0/102 (0)	20/102 (19.6)	4/102 (3.9)	2/102 (2.0)
	all:	305				

"-" denotes not reported

CONTRIBUTIONS OF AUTHORS

Goran Bjelakovic (GB): initiated the review, drafted the protocol, performed the literature search, data extraction, and statistical analyses, and drafted the review.
Lise Lotte Gluud (LLG): revised the protocol, performed data extraction, and revised the review.
Dimitrinka Nikolova (DN): revised the protocol, performed data extraction, and revised the review.
Kate Whitfield (KW): developed the search strategy, revised the protocol, performed data extraction, and revised the review.
Goran Krstic (GK): joined the team of authors during the preparation of the review, performed data extraction, and revised the review.
Jørn Wetterslev (JW): revised the protocol, performed data extraction, and revised the review.
Christian Gluud (CG): revised the protocol, acted as arbiter for disagreements, and revised the review.

DECLARATIONS OF INTEREST

Goran Bjelakovic (GB): None known.
Lise Lotte Gluud (LLG): None known.
Dimitrinka Nikolova (DN): None known.
Kate Whitfield (KW): None known.
Goran Krstic (GK): None known.
Jørn Wetterslev (JW): None known.
Christian Gluud (CG): None known.

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Internal sources

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

External sources

- Ministry of Education, Science and Technological Development of the Republic of Serbia, Serbia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Methods section. Criteria for considering studies for this review. Types of participants. We have now added the following categories of participants, which were excluded in order to be more precise: people with secondary induced osteoporosis (for example, glucocorticoid-induced osteoporosis, thyroidectomy, primary hyperparathyroidism, chronic kidney disease, liver cirrhosis, Crohn's disease, and gastrointestinal bypass surgery). Firstly, all of these conditions are accompanied by deranged vitamin D metabolism, and by an increase in bone resorption and by a decrease in bone formation. Secondly, we decided to follow exclusion criteria applied in our previous Cochrane review on vitamin D supplementation for prevention of mortality (Bjelakovic 2014).
2. Methods section. Criteria for considering studies for this review. Types of interventions. We have now deleted the following types of interventions: in combination with other vitamins or trace elements; in combination with calcium and other vitamins and trace elements. Our intention was to eliminate the influence of other co-interventions on our results. We wanted to obtain results that would reflect the pure influence of vitamin D on the outcome measures.
3. We changed QUORUM (Moher 1999) into PRISMA (Moher 2009) as the guideline was updated.
4. Data collection and analysis. Assessment of risk of bias in included studies. We have now added the following risk of bias domains: incomplete outcome data; selective outcome reporting; for-profit bias; and risk of other bias as the guidelines for risk of bias were updated.
5. Data collection and analysis. Data synthesis. We also planned to conduct trial sequential analyses with diversity-adjusted required information size instead of heterogeneity-adjusted required information size. The reason is that the diversity-adjusted required information size seems to give less biased estimates of the required information size than the inconsistency-adjusted required information size (Wetterslev 2009).
6. Data collection and analysis. Dealing with missing data. Regarding the primary outcomes, we included participants with incomplete or missing data in sensitivity analyses by imputing them according to the extreme case analysis favouring the experimental intervention ('best-worst' case scenario): none of the dropouts/participants lost from the experimental arm, but all of the dropouts/participants lost from the control arm experienced the outcome, including all randomised participants in the denominator, and extreme case analysis favouring the control ('worst-best' case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomised participants in the denominator.
7. Data collection and analysis. Subgroup analysis. We have decided against performing the following subgroup analysis: "trials without risk of for-profit bias compared to trials with risk of for-profit bias", due to the introduction of this source of bias in the review.
8. Data collection and analysis. Sensitivity analysis. We have now decided against performing the following sensitivity analyses: repeating the analysis excluding unpublished trials; repeating the analysis excluding trials using the following filters: diagnostic criteria, language of publication, country. The reason is that all included trials used the same diagnostic criteria. We did not find unpublished trials. All included trials came from high-income countries and were published in the English language.
9. Goran Krstic joined the team of authors during the preparation of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Calcitriol [administration & dosage]; Cholecalciferol [administration & dosage]; Hydroxycholecalciferols [administration & dosage]; Neoplasms [epidemiology] [*prevention & control]; Randomized Controlled Trials as Topic; Vitamin D [*administration & dosage] [analogs & derivatives]; Vitamins [*administration & dosage]

MeSH check words

Aged; Female; Humans; Male; Middle Aged