### Summary of findings

Vitamin D supplementation for prevention of mortality in adults

#### Patient or population: adults

#### Settings: any

#### Intervention: Vitamin D

#### Comparison: placebo or no intervention

<table>
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<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
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<td>Placebo or no intervention</td>
<td>Vitamin D</td>
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<td>All-cause mortality in trials using vitamin D3 (cholecalciferol)</td>
<td>RR 0.94 (0.91 to 0.98)</td>
<td>74789 (32 studies)</td>
<td>high</td>
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<td>Cardiovascular mortality</td>
<td>RR 1.01 (0.91 to 1.13)</td>
<td>42589 (10 studies)</td>
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<td>Cancer mortality</td>
<td>RR 0.89 (0.78 to 1.02)</td>
<td>39200 (3 studies)</td>
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<td>Adverse events - Nephrolithiasis in trials using vitamin D3 combined with calcium</td>
<td>RR 1.17 (1.02 to 1.34)</td>
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<td>Insufficient information as only one included study reported on health economics.</td>
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</table>
Vitamin D supplementation for prevention of mortality in adults

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

Types of participants

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

Adverse effects of the intervention

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

Why it is important to do this review

The available evidence on vitamin D and mortality is intriguing but inconclusive. Most observational studies have suggested that vitamin D is effective for prevention of malignant, cardiovascular, autoimmune, and infectious diseases (Holick 2007a; Njohaham 2008; Rosen 2011; Souberbielle 2010). An opposing hypothesis that vitamin D insufficiency is a consequence of disease but not the cause has been postulated by Marshall et al (Marshall 2008).

Objectives

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

Methods

Criteria for considering studies for this review

Types of studies

Randomised clinical trials, irrespective of binding, publication status, or language, that assessed supplemental vitamin D (vitamin D2 (cholecalciferol) or vitamin D3 (ergocalciferol)) or an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol)) or 1,25-dihydroxyvitamin D (calcitriol). We included primary prevention trials (defined as trials that deal with prevention of disease before it occurs) and secondary prevention trials (defined as trials that deal with prevention of recurrences or exacerbations of a disease that already has been diagnosed) (Bischoff-Ferrar 2005).

Types of participants

We included adult participants (aged 18 years or over) who were:
diagnosed with vitamin D deficiency (secondary prevention).

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

Types of interventions

Intervention
Vitamin D at any dose, for any duration, and by any route of administration. Vitamin D could have been administered as supplemental vitamin D (vitamin D₃ (cholecalciferol) or vitamin D₂ (ergocalciferol)) or an active form of vitamin D (1α-hydroxyvitamin D (alfacalcidol) or 1,25-dihydroxyvitamin D (calcitriol)).

Vitamin D could have been administered:
- as monotherapy; or
- in combination with calcium.

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

Types of outcome measures

Primary outcomes
- All-cause mortality
- Adverse events

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

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

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

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

Search methods for identification of studies

Electronic searches
We used the following sources for the identification of trials:
- The Cochrane Library (Issue 1, January 2011);
- MEDLINE (until January 2011);
- EMBASE (until January 2011);
- LILACS (until January 2011);
- Science Citation Index Expanded (until January 2011);
- Conference Proceedings Citation Index-Science (until January 2011).

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

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

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

Data collection and analysis

Selection of studies
One author (GB) performed the electronic searches. Six authors (GB, LLG, DN, KW, RGS, MB) participated in the manual searches, identified trials eligible for inclusion from the search results, and extracted data from included trials. GB listed the excluded studies with the reason for exclusion. When a discrepancy occurred in the trial selection or data extraction, CG was consulted in order to reach consensus. We contacted authors of the trials for missing information. Inter-rater agreement for trial selection was measured using the kappa statistic (Cohen 1960). Agreement between authors was very good (kappa statistic 0.85). An adapted PRISMA flow diagram of study selection is included in the review (Moher 2009).
Data extraction and management
For studies that fulfilled the inclusion criteria, six authors (GB, LLG, DN, KWW, RGS, MB) independently extracted the relevant population, intervention characteristics, and risk of bias components using standard data extraction templates. We looked out for duplicate publications. Disagreements were resolved by discussion or, when required, by CG.

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

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

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

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

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

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

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

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

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

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

Assessment of heterogeneity
We identified heterogeneity by visual inspection of the forest plots by using a standard $\chi^2$ test and a significance level of $\alpha = 0.1$. In view of the low power of such tests, we also examined heterogeneity with the I² statistic (Higgins 2002), where I² values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity was found, we attempted to determine potential reasons for it by examining individual trial characteristics and subgroups of the main body of evidence.

Assessment of reporting biases
Funnel plots were used to assess the potential existence of bias (Lau 2006). There is a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect, with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We performed adjusted rank correlation (Begg 1994) and a regression asymmetry test for detection of bias (Egger 1997).
Data synthesis
We performed this review and meta-analyses according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

For the statistical analyses we used Review Manager 5 (RevMan 2008), Trial Sequential Analysis version 0.8 (TSA 2008), STATA 8.2 (STATA Corp, College Station, Tex), and Sigma Stat 3.0 (SPSS Inc, Chicago, IL). For dichotomous outcomes, we calculated the Mantel-Haenszel risk ratios (RR); for all association measures, 95% confidence intervals (CI) were used. We analysed the data with both fixed-effect (DerSimonian 1986) and random-effects (Bauernfeind 1998) model meta-analyses. In case there was no difference in statistical significance between these models, we presented the results of the random-effects model analyses. Otherwise, we presented the results of both analyses.

The analyses were performed using the ITT principle, including all randomised participants irrespective of completeness of data. Patients with missing data were included in the analyses using a carry forward of the last observed response. Accordingly, patients who had been lost to follow-up were counted as being alive.

Review Manager 5.0 (RevMan 2008) does not include trials with zero events in both arms when calculating RR. To account for trials with zero events, meta-analyses of dichotomous data were repeated using risk differences (RD) (Friedrich 2007; Kius 2009). The influence of trials with zero events in the treatment, control, or both groups was also assessed by re-calculating the random-effects model meta-analyses with 0.5 and 0.01 continuity corrections (Bradburn 2007; Tweedie 2004) using Trial Sequential Analysis version 0.8 (TSA 2008).

For trials using a factorial design that tested vitamin D parallel to any other intervention (that is, hormone replacement therapy, other vitamins, etc.), we used 'inside the table' analysis in which we compared only the vitamin D intervention group with the placebo or no intervention group. Otherwise, we used 'at margins' analysis (McAlister 2001). In the trials with parallel group design with more than two intervention groups and additional therapy, we compared the vitamin D only group with the placebo or no intervention group.

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

We compared the intervention effects in subgroups of trials with the test of interaction in the fixed-effect model meta-analysis (Altman 2003).

Trial sequential analyses
We conducted trial sequential analyses to reduce the risk of random error and prevent premature statements of superiority of the experimental or control intervention (Wettrekel 2008). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986). We performed a trial sequential analysis for all-cause mortality with a type I error of 5%, type II error of 20% (80% power), and diversity-adjusted required information size (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity
We performed subgroup analyses mainly if one of the primary outcome measures demonstrated statistically significant differences between the intervention groups.

We performed the following subgroup analyses:

- trials with a low risk of bias compared to trials with a high risk of bias;
- placebo-controlled trials compared to trials with no intervention in the control group;
- individually randomised trials compared to cluster-randomised trials;
- primary prevention trials compared to secondary prevention trials;
- vitamin D3 compared to placebo or no intervention;
- trials that applied vitamin D3 singly compared to trials that applied vitamin D3 combined with calcium;
- trials that applied low-dose vitamin D3 compared to trials that applied high-dose vitamin D3;
- trials that applied vitamin D2 daily compared to trials that applied vitamin D2 intermittently;
- trials that applied vitamin D3 in vitamin D sufficient participants compared to trials that applied vitamin D3 in vitamin D insufficient participants;
- vitamin D2 compared to placebo or no intervention;
- trials that applied vitamin D2 singly compared to trials that applied vitamin D2 combined with calcium;
- trials that applied low-dose vitamin D2 compared to trials that applied high-dose vitamin D2;
- trials that applied vitamin D2 daily compared to trials that applied vitamin D2 intermittently;
- trials that applied vitamin D3 in vitamin D sufficient participants compared to trials that applied vitamin D2 in vitamin D insufficient participants;
- alfalcacidol compared to placebo or no intervention;
- trials that applied alfalcacidol in vitamin D sufficient participants compared to trials that applied alfalcacidol in vitamin D insufficient participants;
- calcitriol compared to placebo or no intervention;
- trials that applied calcitriol in vitamin D sufficient participants compared to trials that applied calcitriol in vitamin D insufficient participants.

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

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

Results
Description of studies
See Characteristics of included studies (table#CD007470-se2-0017) Characteristics of excluded studies (table#CD007470-se2-0018);
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Results of the search
We identified a total of 5295 references of possible interest through searching The Cochrane Library (n = 1054), MEDLINE (n = 1049), EMBASE (n = 1623), LILACS (n = 478), Science Citation Index Expanded (n = 1051), Conference Proceedings Citation Index-Science (n = 14), and reference lists (n = 17). We excluded 4134 duplicates and 822 clearly irrelevant references through reading the abstracts. Accordingly, 339 references were retrieved for further assessment. Of these, we excluded 86 references describing 73 studies because they were not randomised trials or did not fulfill our inclusion criteria. Reasons for exclusion are listed in the table Characteristics of excluded studies (tableID:CD007470-sec-2-0018).

In total, 144 randomised trials described in 294 references fulfilled our inclusion criteria (Figure 2). They included a total of 108,496 participants. In total, 84 trials reported no deaths. All participants of five trials completed the follow-up period. We contacted the authors of the remaining 79 trials and the authors of 48 trials confirmed that mortality was indeed zero. For 31 trials we did not obtain such confirmation. In 10 trials there were deaths reported (n = 50), but the authors did not report in which group of the trial. The authors of these trials did not respond to our requests for additional information (Cashman 2009; Chopey 1987; Doonan 2009; Flicker 2005; Flicker et al. 2006; Flicker et al. 2007; Gluud 2006; Jones 2007; Meier 2004; Ott 1989; Peacock 2002; Sato 1999b; Sato 2000; Smith 2007; Witham 2010; Witham et al. 2010; Law 2009; Sato 2000; Sanders 2010; Sanders et al. 2010; Witham et al. 2010). All 50 trials came from high-income countries.

We included 127 authors for the missing information and received answer from authors of 87 trials (68%).

We identified an additional 20 ongoing trials through searching databases of ongoing trials. Data from these trials will be included in future updates of this review.

Included studies
The included trials are described in detail in the table Characteristics of included studies (tableID:CD007470-sec-2-0017), in Table 1 (tableID:CD007470-bi-0005), Table 2 (tableID:CD007470-bi-0004), Table 3 (tableID:CD007470-bi-0005), and Appendix 2.

Trial characteristics
Out of the 50 trials reporting mortality, 48 trials randomised participants individually, and two were cluster-randomised (Larsen 2004; Larsen 2005). Forty-two trials used a parallel-group design, and eight trials (Avenell 2004; Butland 1997; Campbell 2005; Gallagher 2001; Grant 2005; Komulainen 1998; Larsen 2004; Litham 2003) used the 2 x 2 factorial design (Brocks 2004). The trials were published from 1980 to 2010.

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

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

The 53 trials reporting no mortality included a total of 10,292 participants. These trials were mostly phase I or phase II short-term clinical trials assessing the pharmacokinetic or pharmacodynamic properties of vitamin D. These trials had typical outcome measures and thus were not included in our analyses of mortality (1). A further 53 trials with zero mortality in both the experimental and the control groups were included in our sensitivity analyses.

We contacted 127 authors for the missing information and received answer from authors of 87 trials (68%).

We identified an additional 20 ongoing trials through searching databases of ongoing trials. Data from these trials will be included in future updates of this review.

Characteristics of ongoing studies (tableID:CD007470-sec-2-0019)
Vitamin D supplementation for prevention of mortality in adults

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

Complete summary table

Methods

Included studies

Effects of interventions

Risk of bias in included studies

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

http://onlinelibrary.wiley.com

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

http://onlinelibrary.wiley.com

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

http://onlinelibrary.wiley.com

Effects of interventions

See: Summary of findings for the main comparison Vitamin D supplementation for prevention of mortality in adults (tablest](CD007470-tbl-0005).

All-cause mortality in all trials
Intervention effects according to bias risk of trials (Analysis 1.1)

In trials with low risk of bias, mortality was significantly decreased in the vitamin D group (RR 0.95, 95% CI 0.91 to 0.99, P = 0.03, I² = 0%). In trials with a high risk of bias, mortality was not significantly changed (RR 0.96, 95% CI 0.91 to 1.06, P = 0.71, I² = 14%). The difference between the effect estimate of vitamin D on mortality in low- and high-bias risk trials was not statistically significant by the test of interaction (Z = 0.98, P = 0.33).

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

Vitamin D significantly decreased mortality in the placebo-controlled trials (RR 0.96, 95% CI 0.92 to 0.99, P = 0.01, I² = 0%). Vitamin D had no significant effect on mortality in trials with no intervention in the control group (1.05, 95% CI 0.91 to 1.21, P = 0.51, I² = 29%). The difference between the effect estimate of vitamin D on mortality in placebo-controlled trials and trials with no intervention in the control group was not statistically significant by the test of interaction (Z = 1.53, P = 0.13).

Sensitivity analyses taking attrition into consideration

Out of 50 trials reporting mortality, 47 trials reported the exact number of participants with missing outcomes in the intervention and the control groups. Two trials did not report losses to follow-up (Larsen 2004; Saito 1997), and one trial did not report losses to follow-up for each intervention group separately (Lips 2010). There were 3688 out of 46,893 participants (7.7%) with missing outcomes in the vitamin D group and 3473 out of 47,255 participants (7.3%) with missing outcomes in the control group.

Overall, vitamin D significantly decreased all-cause mortality (RR 0.97, 95% CI 0.94 to 1.00, P = 0.03, I² = 0%). A total of 5275 of 46,893 participants (11.2%) randomised to the vitamin D group and 5410 of 47,255 participants (11.4%) randomised to the placebo or no intervention group died. A sensitivity analysis excluding cluster-randomised trials had no noticeable effect on the result (RR 0.96, 95% CI 0.92 to 0.99, P = 0.02, I² = 0%) (Analysis 1.1) (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470- CMR-01.png). The cumulative Z-curve crossed the trial sequential monitoring boundary in 2006 during the inclusion of the last trial (Figure 5).

Trial sequential analysis of all vitamin D3 trials was constructed based on a mortality of 10% in the control group, a relative risk reduction of 5% with vitamin D3, a type I error of 5%, and a type II error of 20% (80% power). There was no diversity. The required information size was calculated to be 3588 participants in the intervention group and 3473 in the control group. Subsequently, 11 trials have been published (Scholeman 2007; Bolton-Smith 2007; Chel 2008; Daly 2006; Jackson 2006; Kärkkäinen 2010; Lappe 2007; Les 2010; Messerova 2008; Sanders 2010) (Figure 6a).
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Vitamin D and calcium (Analysis 1.7)
Vitamin D3 administered singly versus placebo or no intervention had no statistically significant effect on mortality (RR 0.91, 95% CI 0.82 to 1.02, P = 0.19, I² = 19%). Vitamin D2 combined with calcium versus placebo or no intervention significantly decreased mortality (RR 0.95, 95% CI 0.91 to 0.99, P = 0.02, I² = 0%). The difference between the estimate of vitamin D3 on mortality in trials using vitamin D2 singly and trials using vitamin D3 combined with calcium was not significant (Z = 0.43, P = 0.67). The trial sequential analysis on mortality in the 23 trials that administered vitamin D3 combined with calcium revealed that the cumulative Z-curve did not cross the monitoring boundary after the 24th trial (Figure 7).

Dose of vitamin D3 (Analysis 1.8)
A dose of vitamin D3 below 800 IU a day significantly decreased mortality (RR 0.92, 95% CI 0.87 to 0.97, P = 0.009, I² = 0%). A dose of vitamin D3 2,800 IU a day had no significant effect on mortality (RR 0.98, 95% CI 0.92 to 1.05, P = 0.13, I² = 0%). The difference between the estimates of vitamin D3 on mortality in trials using a low dose of vitamin D3 and trials using a high dose of vitamin D3 was not significant (Z = 1.11, P = 0.27). The trial sequential analysis on mortality in the 12 trials that administered a low dose of vitamin D3 revealed that the cumulative Z-curve did not cross the monitoring boundary after the 12th trial (Figure 8).

Dosing schedule of vitamin D3 (Analysis 1.9)
Vitamin D3 administered daily significantly decreased mortality (RR 0.95, 95% CI 0.91 to 0.99, P = 0.007, I² = 0%). Vitamin D3 administered intermittently had no significant effect on mortality (RR 0.88, 95% CI 0.78 to 1.02, P = 0.08, I² = 0%). The difference between the estimate of vitamin D3 on mortality in trials that administered vitamin D3 daily and trials that administered vitamin D3 intermittently was not significant (Z = -0.87, P = 0.38).

Intervention effect of vitamin D3 according to vitamin D status (Analysis 1.10)
Vitamin D3 significantly decreased mortality in trials including participants with vitamin D insufficiency (RR 0.94, 95% CI 0.90 to 0.99, P = 0.02, I² = 3%). Vitamin D3 had no significant effect on mortality in trials including participants with vitamin D adequacy (RR 0.92, 95% CI 0.79 to 1.07, P = 0.27, I² = 0%). The difference between the estimate of vitamin D3 on mortality in trials including participants with vitamin D insufficiency and trials including participants with vitamin D adequacy was not statistically significant (Z = 0.28, P = 0.78).

Vitamin D2 (ergocalciferol) (Analysis 1.11)
Vitamin D2 was tested in 12 trials (18,349 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 9). The adjusted-rank correlation test (P = 0.60) and regression asymmetry test (P = 0.55) found no significant evidence of bias. Overall, vitamin D2 had no significant effect on mortality (RR 1.02, 95% CI 0.97 to 1.05, P = 0.42, I² = 0%). Vitamin D2 had no significant effect on mortality in trials with a low risk of bias (RR 0.99, 95% CI 0.92 to 1.05, P = 0.68, I² = 0%). Vitamin D2 significantly increased mortality in trials with a high risk of bias (RR 1.28, 95% CI 1.05 to 1.53, P = 0.007, I² = 0%). The difference between the estimate of vitamin D2 on mortality in trials with a low risk of bias and trials with a high risk of bias was significant (Z = 2.62, P = 0.009).

Trial sequential analysis of all vitamin D2 trials suggests that we reached the futility area after the eighth trial (Figure 9) allowing us to conclude that any possible intervention effect is lower than a 5% relative risk reduction or that the number needed to treat (NNT) is greater than 200. The required information size was 26993 participants. The cumulative Z-curve (blue line) crossed the futility boundary (red line) after the 8th trial.
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Dose of vitamin D2 (Analysis 1.13)

A dose of vitamin D2 below 800 IU a day, tested in one trial, had no significant effect on mortality (RR 0.82, 95% CI 0.17 to 3.98). A dose of vitamin D2 ≥ 800 IU a day had no significant effect on mortality (RR 1.03, 95% CI 0.96 to 1.10, P = 0.42, I² = 4%). The difference between the estimates of vitamin D2 on mortality in trials using vitamin D2 singly and trials using vitamin D2 combined with calcium was not significant (Z = 0.76, P = 0.45).

Dosing schedule of vitamin D3 (Analysis 1.14)

Vitamin D3 administered daily had no significant effect on mortality (RR 0.88, 95% CI 0.68 to 1.12, P = 0.30, I² = 0%). Vitamin D3 administered intermittently had no significant effect on mortality (RR 0.96, 95% CI 0.95 to 1.18, P = 0.30, I² = 39%). The difference between the estimates of vitamin D3 on mortality in trials that administered vitamin D3 daily and trials that administered vitamin D3 intermittently was not significant (Z = 0.38, P = 0.17).

Intervention effect of vitamin D2 according to vitamin D status (Analysis 1.15)

Vitamin D2 significantly increased mortality in trials including participants with vitamin D insufficiency (RR 1.30, 95% CI 1.05 to 1.67, P = 0.008, I² = 9%). Vitamin D2 had no statistically significant effect on mortality in trials including participants with vitamin D adequacy (RR 0.97, 95% CI 0.86 to 1.10, P = 0.62, I² = 0%). The difference between the estimates of vitamin D2 on mortality in trials including participants with vitamin D insufficiency and trials including participants with vitamin D adequacy was statistically significant (Z = 2.30, P = 0.02).

Aflacalcidol (1α-hydroxyvitamin D) (Analysis 1.16)

Aflacalcidol was tested in four trials (617 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 11). The adjusted-rank correlation test (P = 1.00) found no significant evidence of bias. Aflacalcidol had no significant effect on mortality (RR 0.96, 95% CI 0.23 to 4.15, P = 0.95, I² = 0%). The effect of aflacalcidol on mortality was not dependent on vitamin D status (Analysis 1.17).

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

Calcitriol was tested in three trials (430 participants). Inspection of the funnel plot does not suggest potential bias (asymmetry) (Figure 12). Calcitriol had no significant effect on mortality (RR 1.37, 95% CI 0.27 to 7.03, P = 0.71, I² = 0%). The effect of calcitriol on mortality was not dependent on vitamin D status (Analysis 1.19).

Cause-specific mortality (Analysis 1.20; Analysis 1.21)

Vitamin D2 had no significant effect on cardiovascular mortality (RR 1.02, 95% CI 0.91 to 1.13, I² = 0%, 7 trials) (Analysis 1.20). Vitamin D2 had no significant effect on cancer mortality (RR 0.96, 95% CI 0.78 to 1.18, I² = 27%, 3 trials) (Analysis 1.21). Vitamin D2 had no significant effect on mortality according to vitamin D status (Analysis 1.19).

Adverse events (Analysis 1.22)

Several adverse events were reported (for example, hypercalcaemia, nephrolithiasis, hypercalcinaemia, renal insufficiency, gastrointestinal disorders, cardiovascular disorders, psychiatric disorders, skin disorders, cancer). The supplemental forms of vitamin D (D2 and D3) had no significant effect on the risk of hypercalcaemia (RR 1.26, 95% CI 0.78 to 2.05, P = 0.34, I² = 0%). Active forms of vitamin D (alfacalcidol and calcitriol) significantly increased the risk of hypercalcaemia (RR 3.18, 95% CI 1.17 to 8.86, P = 0.02, I² = 77%). The difference between the estimate of vitamin D on hypercalcinaemia in trials that administered supplemental forms of vitamin D (D2 and D3) and trials that administered active forms of vitamin D (alfacalcidol or calcitriol) was not significant (Z = 1.63, P = 0.10).

Vitamin D3 combined with calcium significantly increased nephrolithiasis (RR 1.17, 95% CI 1.02 to 1.34, P = 0.02, I² = 0%). The effect of vitamin D on the other adverse events was not statistically significant (hypercalcinaemia, RR 4.64, 95% CI 0.59 to 34.76, P = 0.05, I² = 0%; renal insufficiency, RR 1.70, 95% CI 0.27 to 10.70, P = 0.57, I² = 0%; cardiovascular disorders, RR 0.95, 95% CI 0.66 to 1.35, P = 0.31, I² = 0%; gastrointestinal disorders, RR 1.35, 95% CI 0.65 to 2.14, P = 0.20, I² = 59%; psychiatric disorders, RR 1.44, 95% CI 0.96 to 3.73, P = 0.45, I² = 0%; skin disorders, RR 3.27, 95% CI 0.17 to 62.47, P = 0.43, I² = 77%; cancer, RR 1.06, 95% CI 0.89 to 1.27, P = 0.49, I² = 0%).

Health-related quality of life

One trial published data on health-related quality of life (Witham 2010). Authors reported significant worsening in disease-specific quality of life.
Vitamin D supplementation for prevention of mortality in adul...

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD0074...
Vitamin D supplementation for prevention of mortality in adult... 

We extend our gratitude to all participants and investigators in the randomised clinical trials. We are aware that by preventing fractures, especially in elderly people, vitamin D combined with calcium can indirectly decrease mortality. Our result fully concurs with the results of a recently published Cochrane review, which found that vitamin D singly could not prevent hip fracture but combined with calcium had a significant beneficial effect (Avenell 2009). However, Avenell et al (Avenell 2009) found no significant effect of vitamin D on cancer. A meta-analysis of randomised trials found that vitamin D combined with calcium could prevent falls and fractures (Bischoff-Ferrari 2009d). A recent meta-analysis of trials combining vitamin D with calcium supplementation (without co-administration of vitamin D) is associated with an increased risk of myocardial infection.

A further important finding of our review is that vitamin D3 had a beneficial effect on mortality in dosages less than 800 IU a day. The cut-off value for dividing trials was the median daily dose of vitamin D3 in the included trials (800 IU). The trial sequential analysis revealed that we may need more randomised trials assessing the influence of low doses of vitamin D3 (less than 800 IU) on mortality in order to attain the required information size. A controversy persists about the optimal dosage of vitamin D. The recommended daily intakes of vitamin D proposed by the Institute of Medicine are 600 IU per day for adults up to 70 years of age, and 800 IU per day for those aged 70 years and over (IOM 2011). Recent randomised trials and meta-analyses of randomised trials that have falls and fractures as a primary outcome measure have concluded that the reduction of risk for falls and hip and non-vertebral fractures is dose dependent (Bischoff-Ferrari 2009d; Bischoff-Ferrari 2009a; Bischoff-Ferrari 2006a). The Uppsala Longitudinal Study of Adult Men aimed to examine how vitamin D status relates to mortality (Michaels 2010). The authors found a U-shaped association between vitamin D status and all-cause mortality as well as cancer mortality. Both high and low concentrations of plasma 25-hydroxyvitamin D were associated with elevated risks of mortality (Michaels 2010). These results warn us to be very cautious about the changes of dietary reference intakes for vitamin D as suggested by some (Bischoff-Ferrari 2010).

It is still not known which route of administration and dosing schedules are optimal for vitamin D supplementation. We found that vitamin D3 applied orally and daily had a beneficial effect on mortality. Other dosing schedules and routes of administration (intermittentlly and parenterally) were without a statistically significant effect on mortality. This could be due to type II errors. Our results are in accordance with the result of the Chat et al (Chat 2009) randomised trial comparing daily, weekly, and monthly dosing of vitamin D3. They found that daily dosing is more effective than weekly and monthly dosing.

We observed that vitamin D2 may increase mortality in trials with a high risk of bias, as well as in the vitamin D insufficient participants. Those subgroup findings may be due to a random error and our trial sequential analysis supports this. Until more data become available, regulatory authorities need to consider how to handle this information.

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

We were not able to identify a specific cause of death responsible for the differences in overall mortality. Vitamin D had no significant effect on cardiovascular mortality but there was a trend towards decreased cancer mortality. There has been much debate in the literature about the possible beneficial effect of vitamin D on cardiovascular diseases (Garland 2007; Schwartz 2007; Apperly 1941). Several mechanisms have been proposed to explain how vitamin D may modify cancer risk. Experimental studies revealed that vitamin D inhibits cellular proliferation and stimulates apoptosis (Aranda 2010; Pan 2010). A large number of observational studies have provided evidence suggesting that vitamin D may have a role in cancer prevention (Gastland 2007; Gehram 2007; Schwartz 2007). The first evidence came from ecologic studies, which found an inverse relationship between exposure to sunlight and cancer risk (Epstein 1942; Gehram 1985). However, some observational studies found that high vitamin D status was associated with increased oesophageal cancer (Chen 2007), pancreatic (Blotzinger 2006), breast (Goodman 2009), and prostate cancer risks (Alm 2008). One should consider the possibility of a U-shaped relation between vitamin D status and cancer risk (Tover 2005). Our results are in accordance with the conclusions of the recently published International Agency for Research on Cancer and Institute of Health Statements that vitamin D status is not correlated with cancer incidence (IARC 2008; IOM 2011). We still lack evidence and we need more randomised trials to better understand the effect of vitamin D on cancer.

Vitamin D3 combined with calcium significantly increased nephrolithiasis. Active forms of vitamin D significantly increased hypercalcaemia.

Other adverse events, like elevated urinary calcium excretion; renal insufficiency; cardiovascular, gastrointestinal, psychiatric, or skin disorders, were not statistically significant influenced by vitamin D supplementation.

We lack sufficient evidence on the effect of vitamin D supplementation on health-related quality of life or the cost-effectiveness of vitamin D supplementation. However, vitamin D3 products and calcium are cheap, with multiple producers across the world, so these interventions are likely to be cost-effective.

Authors’ conclusions

Implications for practice

We found evidence that vitamin D3 decreases mortality in predominantly elderly women, living independently or in institutional care. Vitamin D3 combined with calcium seems to increase nephrolithiasis. Vitamin D2, alfalcacidol, and calcitriol had no statistically significant beneficial effect on mortality. Alfalcacidol and calcitriol seem to increase hypercalcaemia. Elevated urinary calcium excretion; renal insufficiency; cardiovascular, gastrointestinal, psychiatric, or skin disorders were not significantly influenced by vitamin D supplementation.

Implications for research

More randomised trials are needed on the effects of vitamin D on mortality in younger, healthy persons and in males. We need more evidence before drawing final conclusions on the effects of vitamin D on cancer, especially when we consider the different forms of vitamin D used for supplementation. More randomised trials are needed testing the efficacy of vitamin D applied singly or in combination with calcium and comparing different doses of vitamin D3. The effect of vitamin D on health-related quality of life and cost-effectiveness deserves further investigation.

Acknowledgements

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

Download statistical data ( downloadable)

### Comparison 1. Vitamin D versus placebo or no intervention

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
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<td></td>
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<td>2 All-cause mortality in individually and cluster randomised trials</td>
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<td>94148</td>
<td>Risk Ratio</td>
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<td>3 All-cause mortality in placebo controlled and no intervention trials</td>
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<td>4 All-cause mortality in primary and secondary prevention trials</td>
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</tr>
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<td>5 All-cause mortality and vitamin D status</td>
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</tbody>
</table>

### Comparison of Vitamin D supplementation for prevention of mortality in adults

#### Outcome or subgroup title
- All-cause mortality in trials with a low or high risk of bias
  - 1 All-cause mortality in trials with low risk of bias
  - 2 All-cause mortality in individually and cluster randomised trials
  - 3 All-cause mortality in placebo controlled and no intervention trials
  - 4 All-cause mortality in primary and secondary prevention trials
  - 5 All-cause mortality and vitamin D status

#### Statistical method
- Risk Ratio
- M-H
- 95% CI

#### Effect size
- [0.93, 0.99]
6.2 Vitamin D trials with high risk of bias (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-09.png?v=1&t=h142bclh&shoulderp=665001602dea7b52e6e3634cae2e2dd4ab670bb4) 16 23186 Risk Ratio (M-H, Random, 95% CI) 0.91 (0.93, 1.00)

7 All-cause mortality in trials using vitamin D singly or combined with calcium (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-07.png?v=1&n=14280122&y=af7970a34e016539c28ca99317ad2663) 32 62914 Risk Ratio (M-H, Random, 95% CI) 0.95 (0.91, 0.99)

7.1 Vitamin D singly (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-07.png?v=1&n=14280122&y=af7970a34e016539c28ca99317ad2663) 9 11587 Risk Ratio (M-H, Random, 95% CI) 0.91 (0.82, 1.02)

7.2 Vitamin D combined with calcium (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-07.png?v=1&n=14280122&y=af7970a34e016539c28ca99317ad2663) 25 62914 Risk Ratio (M-H, Random, 95% CI) 0.95 (0.91, 0.99)

8 All-cause mortality in trials using low- or high-dose of vitamin D (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-09.png?v=1&t=h142bclh&shoulderp=665001602dea7b52e6e3634cae2e2dd4ab670bb4) 32 74789 Risk Ratio (M-H, Random, 95% CI) 0.94 (0.91, 0.98)

9.1 Vitamin D daily (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-09.png?v=1&t=h142bclh&shoulderp=665001602dea7b52e6e3634cae2e2dd4ab670bb4) 28 69002 Risk Ratio (M-H, Random, 95% CI) 0.95 (0.93, 0.99)

9.2 High-dose of vitamin D (≥ 800 IU a day) (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-09.png?v=1&t=h142bclh&shoulderp=665001602dea7b52e6e3634cae2e2dd4ab670bb4) 12 50367 Risk Ratio (M-H, Random, 95% CI) 0.92 (0.87, 0.97)

10.1 All-cause mortality in trials applying vitamin D daily or intermittently (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-10.png?v=1&n=14280122&y=458d6b0c3217118b7f6f2d450116f0664420) 32 74789 Risk Ratio (M-H, Random, 95% CI) 0.94 (0.91, 0.98)

10.2 All-cause mortality in trials using vitamin D1 and vitamin D status (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-10.png?v=1&n=14280122&y=458d6b0c3217118b7f6f2d450116f0664420) 32 74789 Risk Ratio (M-H, Random, 95% CI) 0.94 (0.91, 0.98)

11.1 Vitamin D insufficiency (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-11.png?v=1&n=14280122&y=44b8f6e80f9273f34a37913add6e14b3146) 16 55481 Risk Ratio (M-H, Random, 95% CI) 0.94 (0.90, 0.99)

11.2 Vitamin D adequacy (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-11.png?v=1&n=14280122&y=44b8f6e80f9273f34a37913add6e14b3146) 9 4293 Risk Ratio (M-H, Random, 95% CI) 0.92 (0.79, 1.07)

13.1 Unknown vitamin D status (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-13.png?v=1&n=14280122&y=ba65019b53da75b52e43314ace3a2dd4676b4) 7 15015 Risk Ratio (M-H, Random, 95% CI) 0.95 (0.78, 1.19)

11.3 All-cause mortality in trials using vitamin D2 (ergocalciferol) (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-11.png?v=1&n=14280122&y=af7970a34e016539c28ca99317ad2663) 12 18349 Risk Ratio (M-H, Random, 95% CI) 1.02 (0.97, 1.08)

11.4 Vitamin D trials with low risk of bias (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-11.png?v=1&n=14280122&y=af7970a34e016539c28ca99317ad2663) 9 14439 Risk Ratio (M-H, Random, 95% CI) 0.99 (0.92, 1.05)

11.5 Vitamin D trials with high risk of bias (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-11.png?v=1&n=14280122&y=af7970a34e016539c28ca99317ad2663) 3 3910 Risk Ratio (M-H, Random, 95% CI) 1.20 (1.05, 1.37)

12.1 All-cause mortality in trials using vitamin D singly or combined with calcium (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-12.png?v=1&n=14280122&y=af7970a34e016539c28ca99317ad2663) 12 18079 Risk Ratio (M-H, Random, 95% CI) 1.94 (1.24, 3.03)

12.2 Vitamin D combined with calcium (http://onlinelibrary.wiley.com/store/mrw_content/cochrane/clsysrev/articles/CD007470/image_n/nCD007470-CMP-001-12.png?v=1&n=14280122&y=af7970a34e016539c28ca99317ad2663) 5 1307 Risk Ratio (M-H, Random, 95% CI) 1.00 (0.64, 1.67)
13. All-cause mortality in trials using low- or high-dose of vitamin D:

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<th>p-value</th>
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<td>M-H</td>
<td>1.07</td>
<td>[0.99, 1.16]</td>
<td>0.09</td>
</tr>
</tbody>
</table>


- All-cause mortality in trials applying vitamin D: [0.88, 0.99]
- Vitamin D insufficiency: [0.76, 0.90]
- Vitamin D adequacy: [0.95, 1.07]

15. All-cause mortality in trials using vitamin D2 and vitamin D status:

<table>
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<td>[0.92, 1.00]</td>
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16. All-cause mortality in trials using alfalcacidol (1α-hydroxyvitamin D):

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<th>p-value</th>
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</thead>
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<td>[0.98, 1.17]</td>
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</table>

17. Vitamin D insufficiency:

- Vitamin D3 intermittently: [0.95, 1.05]
- Vitamin D inadequacy: [0.97, 1.02]

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

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

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<td>M-H</td>
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<td>[0.99, 1.16]</td>
<td>0.09</td>
</tr>
</tbody>
</table>

20. Cardiovascular mortality:

- Vitamin D supplementation for prevention of mortality in adults: [0.92, 1.07]
Vitamin D supplementation for prevention of mortality in adult...
Appendix 2. Baseline characteristics

|----------------|------------|-------------|----------------|---------------|---------------|-----------------|--------------|-----------|--------------|---------------|------|
| Intervention 1 | Interv (I1): | | | | | | | | | | 1
| (I1) | vitamin D3 (800 IU) daily; | | | | | | | | | | 1
| Intervention 2 | (I2): | | | | | | | | | | 1
| (I2): | vitamin D3 (1200 IU) plus calcium (1500 mg) daily; | | | | | | | | | | 1
| Control 1 (C1) | | | | | | | | | | | 1
| (C1): | matched placebo plus calcium (1200 to 1500 mg) daily; | | | | | | | | | | 1
| Control 2 (C2) | | | | | | | | | | | 1
| (C2): | matched placebo plus calcium (1200 to 1500 mg) daily; | | | | | | | | | | 1
| C1: no tablets. | | | | | | | | | | | 1
| C2: | | | | | | | | | | | 1
| vitamin D3 (800 IU) plus calcium (1000 mg) daily; | | | | | | | | | | 1
| multivitamin containing retinol 800 µg; thiamine 1.4 mg; riboflavin 1.6 mg; pyridoxine 2 mg; cyanocobalamin 1 µg; folic acid 100 µg; niacin 18 mg; pantothenic acid 6 mg; biotin 150 µg; ascorbic acid 60 mg; D-alpha tocopherol 10 mg; and phylloquinone 70 µg daily; | | | | | | | | | | 1
| Control 1 (C1): | matched placebo tablets daily. | | | | | | | | | | 1
| Intervention 1 (I1): | vitamin D3 (800 IU) plus calcium (1200 mg) daily; | | | | | | | | | | 1
| Intervention 2 (I2): | vitamin D3 (400 IU) plus calcium (500 mg) daily; | | | | | | | | | | 1
| Control 1 (C1): | calcium 1200 mg daily; | | | | | | | | | | 1
| Intervention 3 (I3): | vitamin K1 200 µg daily; | | | | | | | | | | 1
| Control 1 (C1): | matched placebo tablet. | | | | | | | | | | 1
| Intervention 4 (I4): | vitamin K1 200 µg daily; | | | | | | | | | | 1
| Control 1 (C1): | matched placebo tablet. | | | | | | | | | | 1
| Intervention 5 (I5): | vitamin K1 200 µg daily; | | | | | | | | | | 1
| Control 1 (C1): | matched placebo tablet. | | | | | | | | | | 1
| Intervention 6 (I6): | vitamin K1 200 µg daily; | | | | | | | | | | 1
| Control 1 (C1): | matched placebo tablet. | | | | | | | | | | 1

Vitamin D supplementation for prevention of mortality in adults... http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD0074...
<table>
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<th>Ethnic groups [%]</th>
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<th>I1: n/a</th>
<th>I1: n/a</th>
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| Vitamin D supplementation for prevention of mortality in adul... | http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD0074...
Vitamin D supplementation for prevention of mortality in adul...

Appendix 3. Adverse events

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Vitamin D supplementation for prevention of mortality in adults.
| Event Type                  | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | C1: n/a | I2: n/a | I2: n/a | C1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | I1: n/a | C1: n/a |
|-----------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Serious adverse events     | 8/104   | 7/104   | 0/104   | 0/104   | 0/104   | 0/104   | 0/104   | 0/104   | 28/104  | 26/104  | 28/104  | 28/104  | 28/104  | 28/104  | 28/104  | 28/104  | 28/104  | 28/104  | 28/104  | 28/104  | 28/104  |
| Serious adverse events [%] | 7.7     | 6.7     | 0       | 0       | 0       | 0       | 0       | 0       | 14.7    | 13.5    | 15.8    | 17.5    | 15.8    | 17.5    | 15.8    | 17.5    | 15.8    | 17.5    | 15.8    | 17.5    |
| Hospitalisation            | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     |
| Hospitalisation [%]        | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     |
| Out-patient treatment      | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     | n/a     |
What's new

Last assessed as up-to-date: 30 January 2011.

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History

Review first published: Issue 7, 2011

Contributions of authors

Goran Bjelakovic (GB): 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.
Jørn Wetterslev (JW): revised the protocol, performed data extraction, and revised the review.
Rosa G Simonetti (RGS): joined the team of authors during the preparation of the review, performed data extraction, and revised the review.
Marija Bjelakovic (MB) joined the team of authors during the preparation of the review, performed data extraction, and revised the review.
Christian Gluud (CG): initiated the systematic review, revised the protocol, acted as arbiter for disagreements, and revised the review.

Declarations of interest

None known

Sources of support

Internal sources

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

External sources
Vitamin D supplementation for prevention of mortality in adult... 

**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 patients, which were excluded in order to be more precise: patients with secondary induced osteoporosis (for example, glucocorticoid-induced osteoporosis, thyrotoxicosis, primary hyperparathyroidism, chronic kidney disease, liver cirrhosis, Crohn's disease, and gastrointestinal by-pass surgery). All of these conditions are accompanied by an increase in bone resorption and by a decrease in bone formation.

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 this 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; risk of other bias as the guideline was updated.

5. Data collection and analysis. Data synthesis. We also planned to conduct trial sequential analyses with diversity-adjusted required information size in addition to 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 (Walter 2009).

6. Sensitivity analysis. We have now deleted the comparison: repeating the analysis taking account of trial quality and hence bias risk. The reason is that we already have that comparison under subgroup analysis. We have now added two new comparisons: repeating analysis including trials with zero mortality in both arms, and repeating analyses taking attrition bias into consideration.

7. We assessed the influence of trials with zero mortality in both arms by re-calculating the RR with 0.5, 0.01, and 0.001 as empirical continuity corrections. The reason is that we used Trial Sequential Analysis version 0.8 (TSA 2006) for those calculations. This computer program has pre-defined empirical continuity corrections of 0.5, 0.01, and 0.005.

8. Two co-authors (RGS and MB) joined the team of authors during the preparation of the review.

**Index terms**

Medical Subject Headings (MeSH)

- *Mortality
- *Calcitriol
- *Vitamins

MeSH check words

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

**References**

**References to studies included in this review**

**Alloia 2005 (published data only)**


**Avenell 2004 (published data only)**


**Baeksgaard 1998 (published data only)**


**References**

**References to studies included in this review**

**Alloia 2005 (published data only)**


**Avenell 2004 (published data only)**


**Baeksgaard 1998 (published data only)**


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Sato 1999a {published data only}

Sato 2005a (published data only)


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Lind 1989c (published data only)


Lind 1988 (published data only)


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Wetterslev 2008

Wood 2008

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Zittermann 2006

Zittermann 2009

Zittermann 2010

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