Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials

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CRD summary
This review evaluated the effect of vitamin D supplementation on reducing mortality from any cause. The authors concluded that ordinary doses of vitamin D supplements have a positive association with reduced total mortality rates. Poor reporting of the review methodology and the lack of a validity assessment mean that the reliability of the authors' conclusions is unclear.

Authors' objectives
To assess the effect of vitamin D supplementation on reducing mortality from any health condition.

Searching
PubMed, ISI Web of Science, EMBASE and the Cochrane Library were searched to November 2006; the search terms were reported. In addition, manual searches of references from included studies and selected reviews and books were undertaken. No language or time restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Cluster randomised trials were excluded from the review.

Specific interventions included in the review
Studies assessing supplementation with vitamin D2 or vitamin D3, with placebo or without (open trial), were eligible for inclusion. The included studies used vitamin D supplements administered orally (on a daily, weekly or 4-monthly basis) or as a single injection. Daily doses in the included studies ranged from 300 to 2,000 IU, and study durations ranged from 6 months to 7 years. The included studies examined vitamin D, either alone or with calcium supplements. Studies that examined vitamin D analogues such as D3 (alfacalcidol) were excluded from the review.

Participants included in the review
Patients with advanced prostate cancer, chronic renal disease or end-stage renal disease, or patients undergoing renal dialysis were not eligible for inclusion. The baseline ages of participants in the included studies ranged from 33 to 106 years, with the majority being older than 60 years. The included studies used populations that included individuals who were classed as frail and elderly; had undergone a hip fracture operation; had past low-energy fracture; were insufficient in vitamin D; were at risk of hip fracture; or had congestive heart failure.

Outcomes assessed in the review
The primary review outcome was total mortality. However, studies were eligible for inclusion if they reported deaths from any cause separately for the intervention and control groups. Only one included study reported all-cause mortality; the majority of studies reported clinical fractures and/or bone mineral density as the main end point. Only studies that reported sufficient data to allow the estimation of relative risks (RRs) and 95% confidence intervals (CIs) were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they performed a validity assessment, although it appears that the statistical power of the studies was assessed.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on all-cause mortality were extracted from the trials, and RRs and 95% CIs were calculated.

Methods of synthesis
How were the studies combined?
Summary RRs were estimated by pooling the study-specific estimates in a meta-analysis, using a random-effects model. Publication bias was assessed using the sensitivity analysis of Copas and Shi and a funnel plot regression on sample size, weighted by the inverse of the pooled variance.

How were differences between studies investigated?
Statistical heterogeneity between the studies was investigated using the chi-squared test and the I-squared statistic. A subgroup analysis based on the statistical power of the studies was conducted. Further subgroup analyses were conducted on the basis of length of follow-up, dose and formulation of vitamin D, and use of concomitant supplements. Sensitivity analyses, which included a cluster randomised trial or excluded a quasi-randomised study, were also carried out.

Results of the review
Eighteen RCTs (n=57,311) were included in the review.

The authors reported that there was no evidence of publication bias (p=0.37 using the method of Copas and Shi; p=0.77 using the method of Macaskill et al.) and no indication of heterogeneity (p=0.52).

Pooled results from all trials indicated that vitamin D supplements significantly reduced the risk of all-cause mortality (RR 0.93, 95% CI: 0.87, 0.99), although none of the studies reported mortality as the main end point. Subgroup analysis showed that 9 trials with appropriate statistical power supported a significant reduction (RR 0.92, 95% CI: 0.86, 0.99), while 9 trials with low statistical power favoured the control (RR 1.15, 95% CI: 0.79, 2.73).

Authors' conclusions
There appears to be a positive association between the intake of ordinary doses of vitamin D supplements and reductions in total mortality rates.

CRD commentary
The review question was clear and appropriate inclusion criteria were reported for the interventions, outcomes and study designs. Relevant literature searches were conducted using electronic databases and manual searching. Publications were not restricted by language or date, thus reducing the possibility that some relevant studies were not included in the review. The authors also reported carrying out an analysis of possible publication bias. The authors did not report using methods designed to reduce bias and error in the selection of studies or extraction of data for the review. The absence of a validity assessment means that the reliability of the included studies and their subsequent synthesis is unclear.

It appears that appropriate methods were used to pool the results and to investigate statistical heterogeneity, although there was a considerable degree of clinical heterogeneity between the studies. The poor reporting of the review methodology, and the fact that no validity assessment was undertaken, mean that the reliability of the authors’ conclusions is unclear.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should explore the relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates. Population-based, placebo-controlled randomised trials in people 50 years or older should also be undertaken, with longer treatment duration and with total mortality as the main end point.

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