Effectiveness and safety of vitamin D in relation to bone health

CRD summary
This review assessed the efficacy and safety of interventions to increase vitamin D. The authors concluded that vitamin D3 plus calcium supplementation has beneficial effects on bone mineral density, fractures and falls without evidence of harm, although these may be limited to particular subgroups. These conclusions accurately reflected the evidence and were likely to be reliable.

Authors' objectives
A number of objectives were identified. These included: to assess whether food fortification, sun exposure and vitamin D supplementation affect the circulating concentration of 25 hydroxyvitamin D (25(OH)D); to assess the effectiveness of supplemental doses of vitamin D on bone mineral density and fracture or fall risk; and to assess whether intake of vitamin D above the current reference level results in toxicities. The report also addressed the association of 25(OH)D concentrations with specified bone health outcomes in children, reproductive age women and the elderly including postmenopausal women; and whether there is a level of sunlight exposure which maintains adequate vitamin D levels, but does not increase the risk of skin cancer; however, these lie outside the scope of this abstract.

Searching
MEDLINE, EMBASE, CINAHL, AMED, Biological Abstracts and the Cochrane Central Register of Controlled Trials were searched from 1966 to June 2006. Search terms were reported. Recent reviews were handsearched. Only studies published in English were eligible for inclusion.

Study selection
For questions addressed in this abstract, randomised controlled trials (RCTs) were eligible for inclusion in the review. For the impact of food fortification, sun exposure and vitamin D supplementation on the circulating concentration of 25(OH)D studies of D2 or D3 in children aged 0-18 years, women aged 19 to 49 years, women aged over 50 and men aged over 65 were eligible for inclusion. These criteria were also used for the effect of supplemental vitamin D with or without calcium on bone mineral density and risk of fracture or fall. RCTs assessing other osteoporosis therapies and including vitamin D plus calcium as a control therapy were excluded unless they also contained a placebo or lower dose vitamin D arm. Studies assessing vitamin D for treatment of secondary causes of osteoporosis or vitamin D-dependent rickets were also excluded. The toxicity question had primary outcomes of adverse effects including hypercalcaemia, nephrolithiasis and soft tissue calcification, which were assessed in different age groups. In all, cases studies assessing the vitamin D preparations calcitriol or alphacalcidol were excluded from the review.

Two reviewers independently selected studies for the review after initial screening by one reviewer. Disagreements were resolved through consensus or recourse to a third reviewer.

Assessment of study quality
One reviewer assessed the studies for validity using the Jadad scale, an assessment of allocation concealment for RCTs and a grading system adapted from the work of Harris et al for the observational studies. RCTs with a Jadad score of 3 or higher were considered to be higher quality. Aggregate levels of evidence were determined based on quantity, quality and consistency of results.

Data extraction
One reviewer abstracted the data using an a priori specified form, which was checked by a second reviewer. Differences were resolved by consensus or adjudication. Data abstracted included the type of 25(OH)D assay and sources of vitamin D. Mean differences were calculated for continuous outcomes and odds ratios (ORs) for dichotomous outcomes. Where possible, intention-to-treat data were extracted with other reported data used when this was not possible.
Methods of synthesis
Where possible, studies were combined in meta-analyses; where this was not possible a narrative synthesis was adopted.
Fixed-effect analyses were employed unless statistically significant heterogeneity was detected, in which case a
DerSimonian and Laird random-effects model was used. Pooled ORs were calculated for the dichotomous outcomes
and weighted mean differences for the continuous outcomes. Pre-specified sub-groupings based on oral versus injected
vitamin D, D2 versus D3, and concomitant use of calcium were employed. Statistical heterogeneity was assessed using
the $I^2$ statistic. Where statistically significant heterogeneity was detected, exploratory subgroup and sensitivity, and meta-
regression analyses were conducted as appropriate. Publication bias was assessed using a funnel plot analysis.

Results of the review
One hundred and six RCTs were included in the review questions addressed here.

Effect of fortified foods on circulating 25(OH)D concentrations (13 RCTs): there was good evidence of a positive
effect of supplementation, based on 11 trials (of which six were high quality), although the magnitude of the effect
varied (range 15-40nmol/L).

Effect of UV light on circulating 25(OH)D concentrations (eight RCTs): there was fair evidence that sun exposure or
artificial UV-B radiation increased serum 25(OH)D in participants with low or normal baseline levels (based on eight
studies, of which two were high quality).

Effect of vitamin D supplementation on circulating 25(OH)D concentrations (74 RCTs): a meta-analysis showed a dose
response effect of vitamin D3 supplementation on serum 25(OH)D when doses of less than 400 IU (two RCTs) were
compared with doses over 400 IU (14 RCTs) (11.36, 95% CI: 8.6, 14). There was a high degree of clinical and
statistical heterogeneity across all trials.

Effect of vitamin D supplementation on bone density, falls and fractures in elderly men and postmenopausal women
(17 RCTs): small increases in bone mineral density were associated with supplementation, although synthesis was
limited by heterogeneity. Fifteen RCTs showed inconsistent evidence for fracture reduction associated with
supplementation, but fair evidence for a subgroup of older individuals in institutional settings (OR 0.69, 95% CI: 0.53,
0.90, two RCTs). The evidence of 14 RCTs was inconsistent for the effect on falls with a small overall benefit (OR
0.89, 95% CI: 0.80, 0.99, 12 RCTs). However, subgroup analysis suggested that there were benefits in postmenopausal
women (OR 0.80, 95% CI: 0.66, 0.98, six RCTs) and when vitamin D3 was combined with calcium supplementation
(OR0.84, 95% CI: 0.76, 0.93, eight RCTs).

Toxicity resulting from vitamin D intake above current reference level (22 RCTs): there was little evidence that vitamin
D intake above the current reference intake was harmful.

Full details of all subgroup analyses were provided in the report.

Authors' conclusions
In most trials the effects of vitamin D and calcium supplementation could not be separated. Vitamin D3 at a dose of at
least 700 IU/day with calcium supplementation had a small beneficial effect on bone mineral density compared to
placebo and reduced the risk of fractures and falls, although the benefit may be restricted to specific subgroups. There
was no increased risk of adverse events associated with vitamin D intakes above current reference intakes, although
further research was needed to confirm this.

CRD commentary
The review questions and inclusion criteria were clear. The search was reasonably extensive, but the decision to limit
the review to published studies reported in English may have led to the exclusion of some relevant studies and the
introduction of publication or language bias. The authors reported using methods designed to reduce reviewer bias and
error at some but not all stages of the review process. Appropriate assessments of study validity were undertaken.
Decisions to employ meta-analysis were appropriate and suitable investigations of heterogeneity were undertaken.
However, the use of heterogeneity as a criterion to determine whether a fixed or random effects analysis was employed
may not have been appropriate. The authors' conclusions were an accurate reflection of the results of the review and
appeared likely to be reliable.

**Implications of the review for practice and research**

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

Research: the authors made a large number of recommendations for future research. These comprised the following: validation of laboratory assays of 25(OH)D measurement; consensus on meaningful outcome measures for vitamin D adequacy in groups of interest; the dose response relationship for vitamin D in these groups; high quality RCTs to determine bone health and safety outcomes in infants, children and adolescents; clear reporting of all outcome data, including safety data; high quality studies in minority ethnic populations in North America; research on modifiers of the effect of 25(OH)D status; development of sensitive and specific indices of the risk of vitamin D toxicity; and a systematic review of the safety and efficacy of sun exposure that provides adequate vitamin D photosynthesis.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.