

Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis



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Summary

Background The effects of vitamin D on fractures, falls, and bone mineral density are uncertain, particularly for high vitamin D doses. We aimed to determine the effect of vitamin D supplementation on fractures, falls, and bone density.

Methods In this systematic review, random-effects meta-analysis, and trial sequential analysis, we used findings from literature searches in previously published meta-analyses. We updated these findings by searching PubMed, Embase, and Cochrane Central on Sept 14, 2017, and Feb 26, 2018, using the search term “vitamin D” and additional keywords, without any language restrictions. We assessed randomised controlled trials of adults (>18 years) that compared vitamin D with untreated controls, placebo, or lower-dose vitamin D supplements. Trials with multiple interventions (eg, co-administered calcium and vitamin D) were eligible if the study groups differed only by use of vitamin D. We excluded trials of hydroxylated vitamin D analogues. Eligible studies included outcome data for total or hip fractures, falls, or bone mineral density measured at the lumbar spine, total hip, femoral neck, total body, or forearm. We extracted data about participant characteristics, study design, interventions, outcomes, funding sources, and conflicts of interest. The co-primary endpoints were participants with at least one fracture, at least one hip fracture, or at least one fall; we compared data for fractures and falls using relative risks with an intention-to-treat analysis using all available data. The secondary endpoints were the percentage change in bone mineral density from baseline at lumbar spine, total hip, femoral neck, total body, and forearm.

Findings We identified 81 randomised controlled trials ($n=53\,537$ participants) that reported fracture ($n=42$), falls ($n=37$), or bone mineral density ($n=41$). In pooled analyses, vitamin D had no effect on total fracture (36 trials; $n=44\,790$, relative risk 1.00, 95% CI 0.93–1.07), hip fracture (20 trials; $n=36\,655$, 1.11, 0.97–1.26), or falls (37 trials; $n=34\,144$, 0.97, 0.93–1.02). Results were similar in randomised controlled trials of high-dose versus low-dose vitamin D and in subgroup analyses of randomised controlled trials using doses greater than 800 IU per day. In pooled analyses, there were no clinically relevant between-group differences in bone mineral density at any site (range –0.16% to 0.76% over 1–5 years). For total fracture and falls, the effect estimate lay within the futility boundary for relative risks of 15%, 10%, 7.5%, and 5% (total fracture only), suggesting that vitamin D supplementation does not reduce fractures or falls by these amounts. For hip fracture, at a 15% relative risk, the effect estimate lay between the futility boundary and the inferior boundary, meaning there is reliable evidence that vitamin D supplementation does not reduce hip fractures by this amount, but uncertainty remains as to whether it might increase hip fractures. The effect estimate lay within the futility boundary at thresholds of 0.5% for total hip, forearm, and total body bone mineral density, and 1.0% for lumbar spine and femoral neck, providing reliable evidence that vitamin D does not alter these outcomes by these amounts.

Interpretation Our findings suggest that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. There were no differences between the effects of higher and lower doses of vitamin D. There is little justification to use vitamin D supplements to maintain or improve musculoskeletal health. This conclusion should be reflected in clinical guidelines.

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Introduction

Vitamin D supplements have long been recommended for older people (>65 years) to treat or prevent osteoporosis,¹ with some early evidence suggesting benefits for musculoskeletal health, including increasing bone mineral density and preventing falls and fractures.² However, more recent systematic reviews have reported

no effect of vitamin D supplementation on bone mineral density,³ falls,^{4–7} or fractures.^{7–10} Findings from our trial sequential analyses^{6,9} testing the hypothesis of a 15% relative risk reduction in falls or fractures showed that doing further trials of vitamin D, with or without calcium supplementation, which are similar to existing trials, are unlikely to alter the conclusion of these recent

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Research in context**Evidence before this study**

We used findings from literature searches in previously published meta-analyses, which we updated by searching PubMed, Embase, and Cochrane Central on Sept 14, 2017, and Feb 26, 2018, using the search term “vitamin D”, without any language restrictions. A full list of keywords is shown in the appendix. Evidence from older systematic reviews suggested vitamin D supplements might have benefits for musculoskeletal health, but more recent systematic reviews have reported no effect of vitamin D supplementation on fractures, falls, or bone mineral density. Some authors have suggested that inadequate vitamin D doses might explain these null results. At least 30 trials of vitamin D have been published since these systematic reviews, which nearly doubles the available trial results for vitamin D for these outcomes.

Added value of this study

Our meta-analyses and trial sequential analyses show that in a large number of clinical trials, vitamin D supplementation does not have clinically relevant effects on fractures, falls, and bone mineral density, and this conclusion is unlikely to be altered by future trials with similar designs. Effects of high doses of vitamin D were similar to effects of low doses, and none of the other potential modifiers of vitamin D effects were found to influence efficacy for any outcome.

Implications of all the available evidence

There is little justification for the use of vitamin D supplements to maintain or improve musculoskeletal health (except for the prevention or treatment of rickets and osteomalacia in high-risk groups), and clinical guidelines should reflect these conclusions.

systematic reviews. However, correspondents questioned the use of this efficacy threshold and also suggested that inadequate vitamin D doses might explain these null results,^{11,12} although some randomised controlled trials have reported increased risk of falls or fractures with high-dose intermittent vitamin D.^{13–15} Since the last major systematic reviews of vitamin D and musculoskeletal health were published in 2012–17,^{3–10} 45 randomised controlled trials of vitamin D monotherapy (n=20131) have reported on bone mineral density, falls, and fractures, increasing the number of trial participants with these outcomes by 40–85%. Most new trials have also used substantially higher doses of vitamin D than earlier trials. Consequently, the currently available set of randomised controlled trials has much greater power for meta-analysis and trial sequential analysis, and allows a detailed exploration of potentially important clinical factors in subgroup analyses, including comparisons of high and low doses of vitamin D. A comprehensive update of previous systematic reviews, meta-analyses, and trial sequential analyses, which includes the key clinical and major surrogate endpoints, is warranted. An advantage of assessing these outcomes concurrently is that an effect might be found for some endpoints whereas no effect is found for others, which could have clinical and biological relevance. Trial sequential analyses of vitamin D and bone mineral density have also not been reported previously.

Vitamin D supplements have often been co-administered with calcium supplements. Recent systematic reviews have suggested that the evidence for benefits of calcium supplements in preventing fractures, with or without vitamin D, is weak and inconsistent,^{10,16} with any effect on bone mineral density or fracture likely to be small and of doubtful clinical relevance.^{10,16,17} Additionally, uncommon but important side-effects of calcium supplements^{18–21} have been identified, which contribute

to an unfavourable risk–benefit profile. No large trials of co-administered calcium and vitamin D supplements have become available with fracture or falls as the primary endpoint since the previous systematic reviews.

We did this systematic review, meta-analyses, and trial sequential analyses of randomised controlled trials in adults to study the effect of vitamin D supplements on the clinical musculoskeletal outcomes of fractures and falls, and the commonly used surrogate endpoint of bone mineral density. To align with recent findings on calcium supplements, and the recent design of vitamin D randomised controlled trials, we focused on randomised controlled trials that used vitamin D as monotherapy, and included randomised controlled trials that compared high doses of vitamin D with low doses.

Methods**Search strategy and selection criteria**

In this systematic review, meta-analysis, and trial sequential analysis, we followed PRISMA guidelines for development of protocols²² and reporting of systematic reviews and meta-analyses.²³ We used our literature searches from previously published meta-analyses^{3,6,8,9,16,17} as a starting point. We searched PubMed in December, 2015, for randomised controlled trials and recent systematic reviews of vitamin D in adults. We identified all studies from this search and our previous meta-analyses with fractures, falls, or bone density as an outcome. We then searched PubMed, Embase, and Cochrane Central on Sept 14, 2017, and Feb 26, 2018, using the term “vitamin D” and keywords shown in the appendix (p 1) for publications since 2015 (June 1, for PubMed and Embase; Jan 1, for Cochrane Central). We also searched two clinical trials databases (ClinicalTrials.gov and the WHO clinical trials portal) for completed and ongoing trials, using vitamin D as the search term. The full text of the search is described in the appendix (p 1).

See Online for appendix

We included randomised controlled trials in adults (>18 years) comparing vitamin D supplements with untreated controls, placebo, or lower-dose vitamin D supplements. Trials with multiple interventions (eg, co-administered calcium and vitamin D) were eligible, provided that the study groups differed only by the use of vitamin D. We included quasi-randomised and open-label trials but excluded trials of hydroxylated vitamin D analogues. We included randomised controlled trials in cohorts with conditions likely to affect bone turnover or cohorts selected for specific diseases (eg, primary hyperparathyroidism, renal or hepatic disease), but analysed them separately in the initial analyses (termed selected population). We included randomised controlled trials with outcome data for total or hip fractures, falls, or bone mineral density measured with dual-energy x-ray absorptiometry at the lumbar spine, total hip, femoral neck, total body, or forearm. We excluded trials reporting bone mineral density using other techniques. We included cluster-randomised controlled trials. One author (MJB) screened titles and abstracts, two authors (MJB, AA) reviewed listings on trial registries, and two authors independently (MB, AG) reviewed the full text of potentially relevant studies. Studies included in previous meta-analyses but excluded from these meta-analyses are shown in the appendix (pp 2, 3).

Data analysis

Data about participant characteristics, study design, interventions, outcomes, funding sources and conflicts of interest were extracted by one author (MJB) and checked by a second author (AG). When data were presented only in figures, we used digital calipers to extract data. When data were reported for falls but not for fractures, we emailed the authors to request any data about fractures (appendix p 2). The risk of bias of eligible randomised controlled trials was independently assessed by two authors (MJB, AG) following the approach in the Cochrane Handbook for Systematic Reviews of Interventions. Discrepancies in author assessments were resolved by discussion.

The co-primary endpoints were participants with at least one fracture, at least one hip fracture, or at least one fall. When multiple classifications of total fracture were reported, we used the largest number of participants with any fracture, non-vertebral fracture, or osteoporotic fracture. The secondary endpoints were the percentage change in bone mineral density from baseline at lumbar spine, total hip, femoral neck, total body, and forearm.

We grouped randomised controlled trials comparing vitamin D supplementation with controls, together with randomised controlled trials comparing vitamin D plus

For more on digital calipers see <https://automeris.io/WebPlotDigitizer/>

For the Cochrane handbook, see <http://handbook-5-1.cochrane.org/>

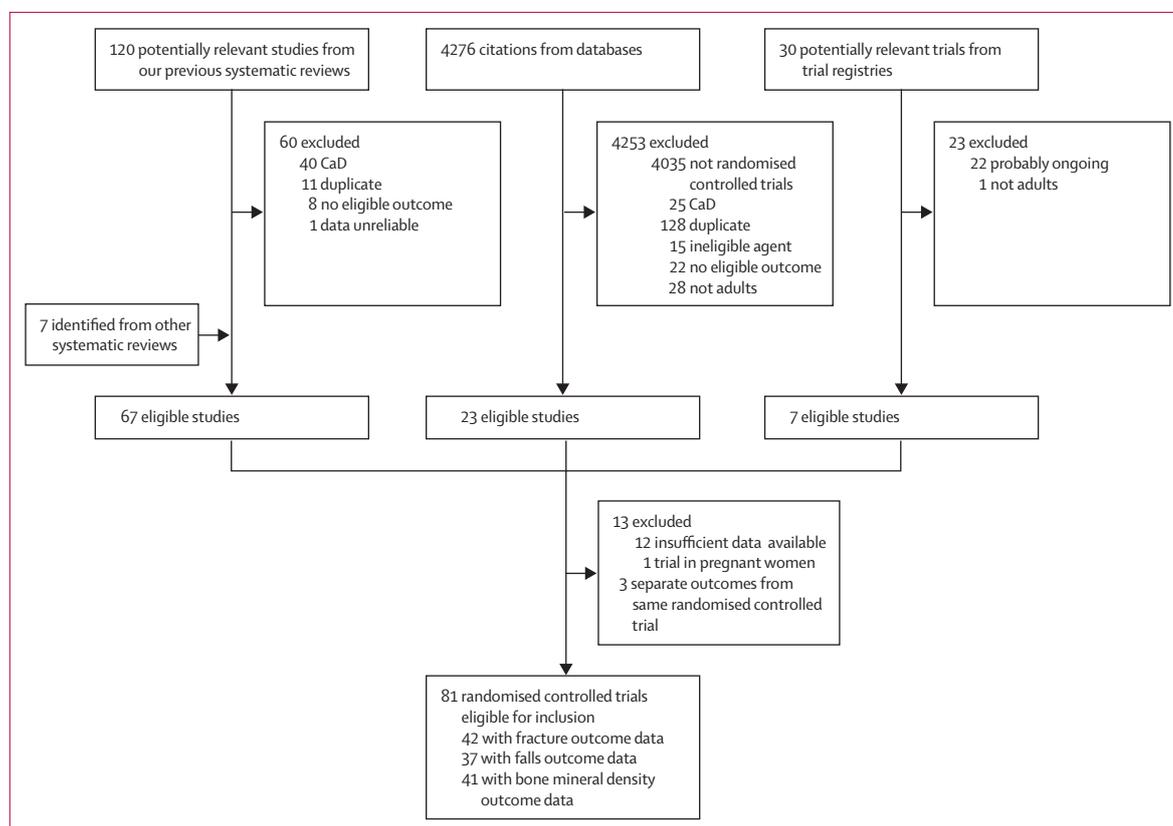


Figure 1: Study selection

CaD=co-administered calcium and vitamin D.

	All trials (n=81)
Population unselected for underlying illness	61 (75%)
Treatment studied	
Vitamin D vs controls	39 (48%)
Vitamin D with agent vs agent	26 (32%)
Calcium	20 (25%)
Exercise	2 (2%)
Calcium and exercise	1 (1%)
Other	3 (4%)
High-dose vs low-dose vitamin D	16 (20%)
Vitamin D dose >800 IU per day	55 (68%)
Frequency of vitamin D dose	
Daily	44 (54%)
Intermittent	36 (44%)
Mixed	1 (1%)
Trial duration ≤1 year	55 (68%)
>200 participants	39 (48%)
Community-dwelling participants	69 (85%)
Majority of participants female	62 (77%)
Baseline mean age <65 years	33 (41%)
Baseline mean BMI <30 kg/m ²	58 (72%)
Baseline 25-hydroxyvitamin D concentration	
<25 nmol/L	4/72 (6%)
<50 nmol/L	41/72 (57%)
<75 nmol/L	71/72 (99%)
Achieved 25-hydroxyvitamin D concentration	
≥50 nmol/L	69/76 (91%)
≥75 nmol/L	44/76 (58%)
Outcome data	
Fracture	42 (52%)
Falls	37 (46%)
Bone mineral density	41 (51%)

Data are n (%) or n/N (%), since some characteristics were not reported in all trials. See appendix (pp 4–9) for full details of trial characteristics.

Table 1: Selected trial characteristics

agent with the agent alone (termed vitamin D vs controls). Several trials had multiple vitamin D treatment groups. If there was a control group, we pooled the vitamin D treatment groups and compared the pooled results with the controls. If there was no control group, we pooled treatment groups in which the vitamin D dose was 800 IU/day or more (high dose), and compared the results with the pooled result of treatment groups in which the dose was less than 800 IU/day (low dose). In subgroup analyses, we used relevant individual treatment groups for each trial.

For fractures and falls, we initially analysed randomised controlled trials done in unselected populations and selected populations separately, and also separately analysed trials comparing vitamin D with controls and trials comparing different doses of vitamin D. If the results from the different groups of trials were similar, we pooled the trials in subsequent

analyses. For bone mineral density, we used the same approach, but we also analysed the additional variable of study duration. We categorised randomised controlled trials of bone mineral density into three groups, by duration: 1 year (<1.5 years), 2 years (≥1.5 years and ≤2.5 years), and longer than 2.5 years.

We compared data for fractures and falls using relative risks with an intention-to-treat analysis using all available data and the number of participants randomly assigned to the treatment for each group. We compared bone mineral density data using the weighted difference in means. For all analyses, we pooled data using random-effects models, assessed heterogeneity using the I^2 statistic ($I^2 >50%$ was considered significant heterogeneity), and assessed systematic bias using funnel plots and Egger's test (Comprehensive Meta-Analysis, version 2). All tests were two-tailed and p values less than 0.05 were considered to be significant. We adjusted the sample size of cluster-randomised controlled trials in accordance with the Cochrane handbook. Raw bone mineral density and absolute change from baseline were converted to percentage change using the methods described in the Cochrane handbook. For studies that reported mean bone mineral density but not a measure of spread, we imputed the SD using the median site-specific, duration-specific, and treatment-group-specific SD from other included studies, and separately analysed these studies to determine the effect of this approach.

We did a trial sequential analysis^{24,25} for each outcome (TSA Viewer, version 0.9.5.10 beta). This is a type of cumulative meta-analysis that reduces the risk of false-positive results from repetitive statistical testing and reports the information size, an estimate of the optimum sample size for statistical inference, and estimates of treatment effects and thresholds for statistical significance and futility, taking into account multiple statistical tests.^{24,25} For fractures and falls, we initially used a 15% relative risk reduction threshold, similar to our previous publications,^{6,9} and in further analyses we used progressively smaller thresholds until the optimum sample size exceeded the actual sample size. For bone mineral density, we initially used a threshold of a 3% increase, representing the approximate average bone mineral density loss of a late post-menopausal woman over 2–4 years, and then progressively smaller thresholds. To accommodate heterogeneity between trial results, we used the larger of 15% or the calculated heterogeneity from the meta-analysis of included randomised controlled trials in the trial sequential analysis.

We did prespecified subgroup analyses to test for interactions between the effects of vitamin D supplementation on fractures, falls, and bone mineral density for the following factors, each of which is frequently invoked as a possible modifier of the effects of vitamin D: age (<65 years vs ≥65 years), BMI (<30 vs ≥30 kg/m²), baseline 25-hydroxyvitamin D (25OHD; <25 nmol/L vs ≥25 nmol/L, <50 nmol/L vs ≥50 nmol/L, <75 nmol/L vs

≥75 nmol/L), achieved 25OHD (<50 nmol/L vs ≥50 nmol/L, <75 nmol/L vs ≥75 nmol/L), dose of vitamin D (≤800 IU/day vs >800 IU/day, low vs high dose treatment arms within individual studies), intermittent versus daily dosing, trials at overall low risk of bias versus trials at moderate or high risk of bias, trial duration (≤1 year vs >1 year), trial size (≤200 vs >200 participants), use of co-administered treatment versus no co-administered treatment, and location (residential care vs community dwelling). For intermittent doses in which the daily equivalent dose is approximately 800 IU/day (eg, 300 000 IU per year), we included these trials in the 800 IU/day or less group. All such trials had an equivalent daily dose of less than 1000 IU.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

We identified 81 eligible randomised controlled trials of vitamin D supplements (n=53 537 participants)^{13–15,26–106} that reported fractures (n=42), falls (n=37), or bone mineral density (n=41) as an outcome (figure 1). The study design and selected baseline characteristics of the included trials are shown in the appendix (pp 4–9) and summarised in table 1. The majority of randomised controlled trials studied vitamin D as monotherapy, in unselected populations of community-dwelling women aged 65 years or older, with daily doses of more than 800 IU/day, and had a duration of 1 year or less. 41 (57%) of 72 trials were done in populations with mean baseline 25OHD concentrations less than 50 nmol/L, but only four (6%) were done in populations with mean baseline 25OHD concentrations less than 25 nmol/L. 69 (91%) of 76 trials reported achieved 25OHD concentrations of 50 nmol/L or more, and 44 (58%) reported achieved 25OHD concentrations of 75 nmol/L or higher. Our

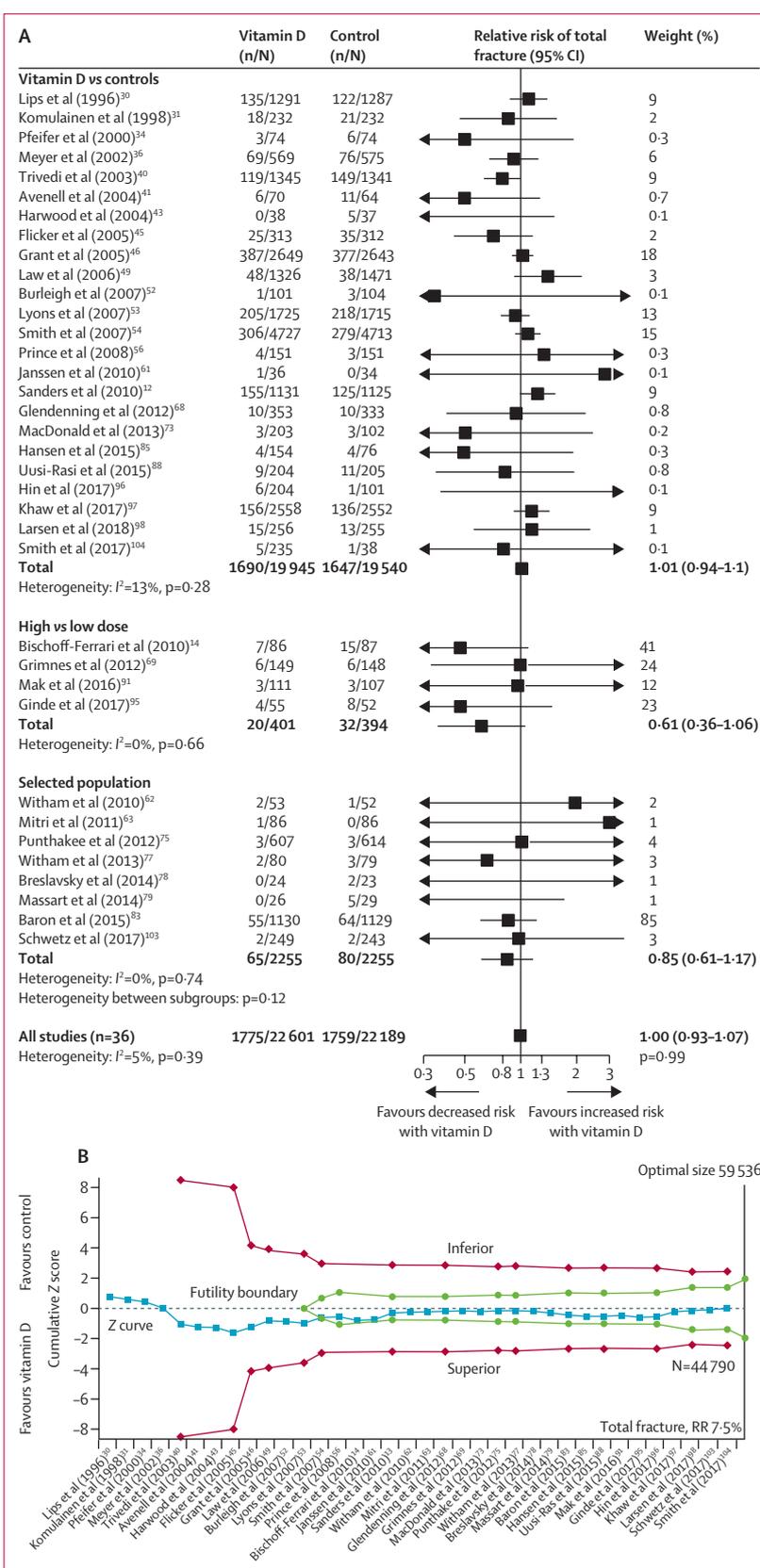
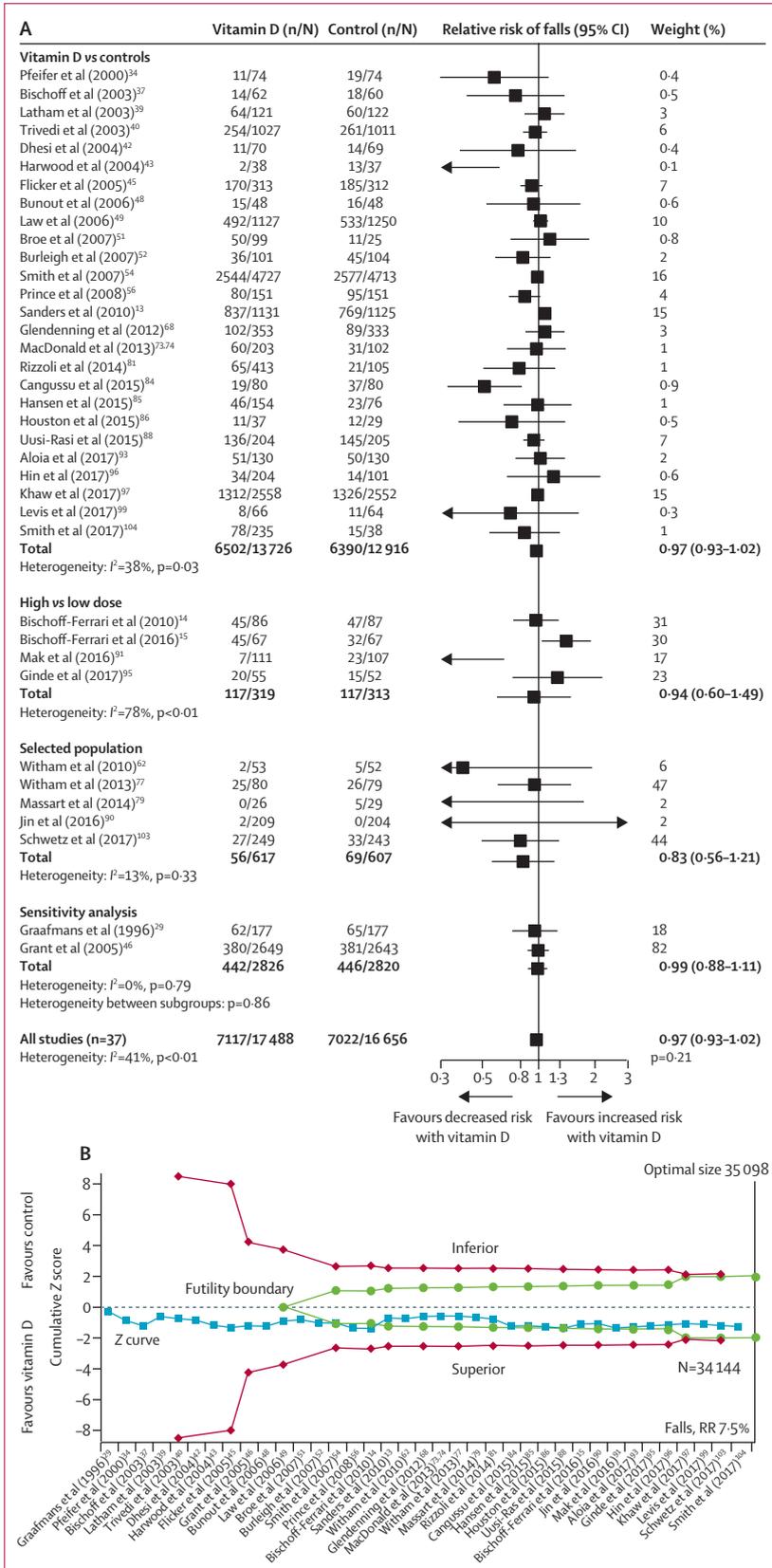


Figure 2: Total fracture meta-analysis (A) and trial sequential analysis (B)
 (A) Random-effects meta-analysis of vitamin D supplementation on total fracture. Vitamin D versus controls refers to trials of vitamin D with controls in unselected populations. High dose versus low dose refers to trials of high-dose and low-dose vitamin D in unselected populations. Selected population refers to trials of vitamin D with controls in populations with an underlying illness. Totals are relative risk (95% CI). (B) Trial sequential analysis of all trials of vitamin D on total fracture for a relative risk of 7.5%. The Z curve is a measure of treatment effect, and the boundaries are thresholds for statistical significance, adjusted for heterogeneity of trial results and multiple statistical testing. A treatment effect outside the statistical significance boundary (dashed line) indicates that there is reliable evidence of a treatment effect, and a treatment effect within the futility boundary (dotted line) indicates that there is reliable evidence of no treatment effect. Optimal size indicates the calculated optimum sample size for statistical inference, and N indicates the number of participants in the meta-analysis. n/N=number of fractures/group size.



assessment of risk of bias and conflicts of interest and funding source are shown in the appendix (pp 10–14). Ten (24%) of 42 trials were considered to be at low risk of bias for fractures, 19 (51%) of 37 were at low risk of bias for bone mineral density. The outcome data for each study for each endpoint are shown in the appendix (pp 15–19).

Figures 2 and 3 and the appendix (p 20) show the results of the meta-analyses for total fracture, hip fracture, and falls, by study design and population. For all three co-primary endpoints, there was no significant interaction for results between randomised controlled trials with different study designs (vitamin D vs controls, high dose vs low dose vitamin D) in unselected populations, or between trials in selected and unselected populations. Therefore, we pooled all the trials, and found no effect of vitamin D supplementation on total fracture (36 trials, $n=44790$; relative risk [RR] 1.00, 95% CI 0.93–1.07), hip fracture (20 trials, $n=36655$; 1.11, 0.97–1.26), or falls (37 trials, $n=34144$; 0.97, 0.93–1.02). Using Egger’s regression model and visual inspection of funnel plots, data appeared skewed toward a reduction in events with vitamin D supplementation for all primary outcomes, largely because of an excess of studies of small-to-medium size with positive effects on the outcomes (data not shown).

In trial sequential analyses of total fracture and falls, the effect estimate lay within the futility boundary for relative risks of 15%, 10%, 7.5%, and 5% (total fracture only) providing reliable evidence that vitamin D supplementation does not reduce fractures and falls by these amounts (figures 2, 3; table 2). For hip fracture, at a 15% RR, the effect estimate lay between the futility boundary and the inferior boundary, meaning there is reliable evidence that vitamin D supplementation does not reduce hip fractures by this amount, but uncertainty remains as to whether it might increase hip fractures (table 2; appendix p 20).

Figure 4 and the appendix (pp 21–27) show the results of the meta-analysis for bone mineral density. First, we compared the results of trials with missing measures of spread and imputed SDs to the other trials, by duration, design, and population. Generally, there was little difference between results, and therefore we included the trials with imputed SDs in subsequent analyses

Figure 3: Falls meta-analysis (A) and trial sequential analysis (B)
 (A) Random-effects meta-analysis of vitamin D supplementation on falls. Vitamin D versus controls refers to trials of vitamin D with controls, high dose versus low dose refers to trials of high-dose and low-dose vitamin D, and sensitivity analysis refers to trials in which data about falls were gathered only in a subset of participants or for only part of the trial duration. Trials in all three categories were done in unselected populations. Selected population refers to trials of vitamin D with controls in populations with an underlying illness. Totals are relative risk (95% CI). (B) Trial sequential analysis of all trials of vitamin D for falls, for a relative risk of 7.5% (see figure 2 for detailed description). n/N=number of falls/group size.

(appendix p 21). Next, we compared the results of trials by duration, study design, and population type. For all combinations of these factors, there was little difference in results between the subgroups, and therefore we pooled the trials with differing study designs (vitamin D vs controls, high-dose vs low-dose vitamin D) and those in selected and unselected populations (appendix pp 21–23). Because there were only small differences by trial duration, we also pooled all the trials using only the final timepoint data for each trial. Figure 4 and the appendix (pp 24–27) show the between-group differences in bone mineral density by site and trial duration, and the pooled analyses using the final timepoint. Between-group differences in bone mineral density did not consistently increase with increasing trial duration at any site, and in the pooled analyses using the final timepoint the between-group differences were 0.25% (95% CI 0.00 to 0.49) for lumbar spine, 0.34% (0.13 to 0.55) for total hip, 1.12% (0.58–1.65) for femoral neck, –0.16% (–0.46 to 0.13) for forearm, and 0.13% for total body (–0.16 to 0.42). Notably, at the femoral neck, one study¹⁰⁶ reported a between-group difference of 10.6% (95% CI 9.0–12.3) after 1 year, which was a clear outlier and had a disproportionate effect on the pooled result. We excluded this trial¹⁰⁶ from subsequent analyses, and after its exclusion, the between-group difference at the femoral neck was 0.76% (95% CI 0.42–1.09; appendix p 25). Using Egger's regression model and visual inspection of funnel plots, data appeared skewed toward increased bone mineral density with vitamin D supplementation for all sites except the forearm, again largely due to many small studies with positive effects on bone mineral density (data not shown). We did all subsequent trial sequential analyses and subgroup analyses using only the final timepoint data for each trial.

In trial sequential analysis of bone mineral density, the effect estimates for total hip, forearm, and total body lay within the futility boundary for a between-group difference of 0.5% (or more), and at the lumbar spine and femoral neck the effect estimate lay within the futility boundary for a difference of 1.0% but above the superior boundary for a difference of 0.5% (table 2; figure 4; appendix pp 24–27).

18 randomised controlled trials reported the results of a subgroup analysis using various thresholds for baseline 25OHD (appendix p 28). Three trials reported no effects of vitamin D on fracture in subgroups, and five reported no effects in subgroups or no interactions with baseline 25OHD, and one reported mixed effects of vitamin D on falls in subgroups (appendix p 28). The subgroup results in all randomised controlled trials were similar to the primary analyses in each study. For bone mineral density, one trial reported positive effects in subgroups, five trials reported mixed effects, and eight trials reported no effects in subgroups, no difference, or no interactions with baseline 25OHD (appendix p 28). In three of 14 trials reporting subgroup analyses results for bone density,

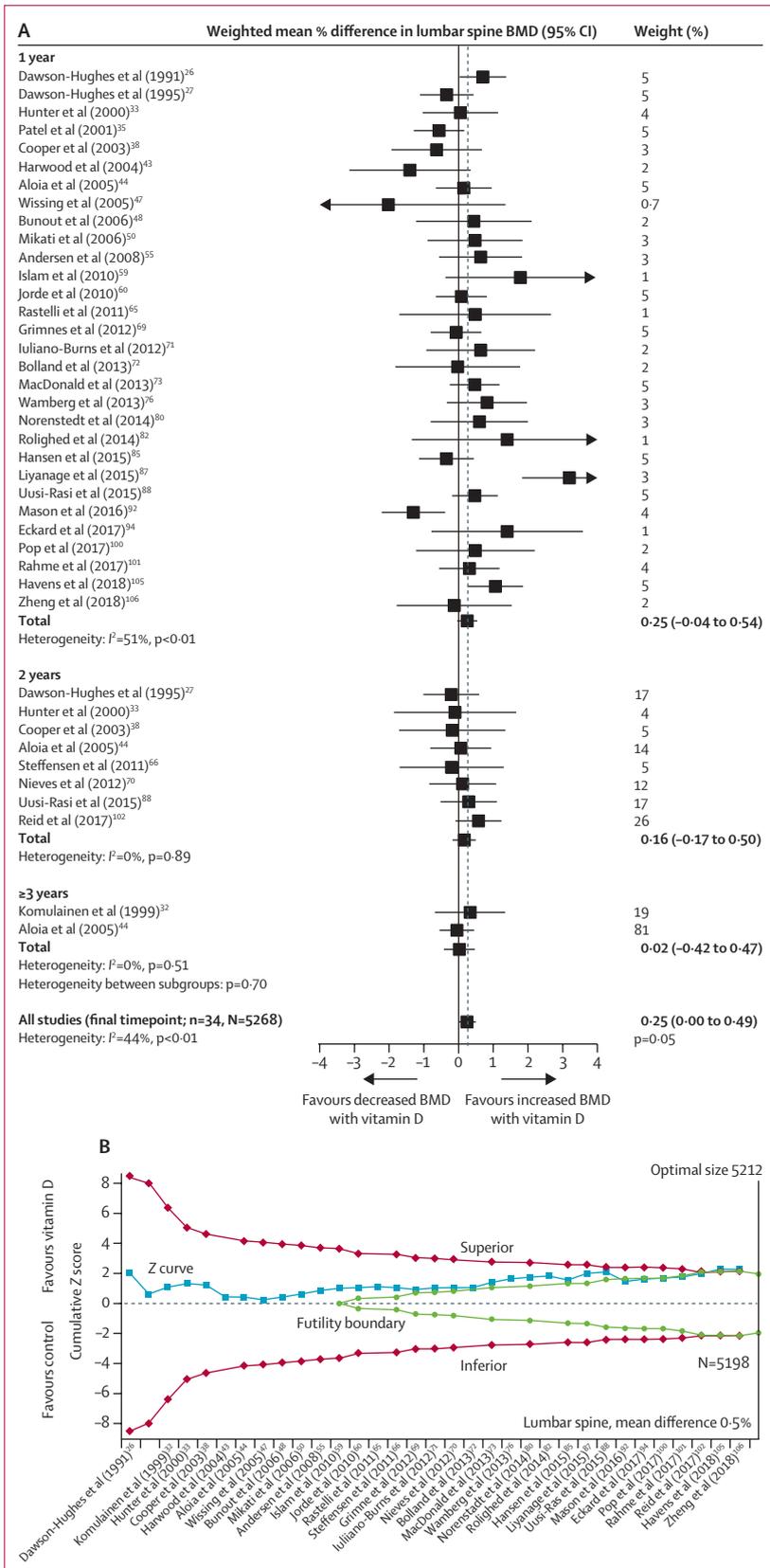
	Incidence/ heterogeneity	Optimum sample size (n)	Result
Total fracture (36 studies, n=44 790)			
15% RR	10%/18%	14 364	Futile
10% RR	10%/18%	33 100	Futile
7.5% RR	10%/18%	59 536	Futile
5% RR	10%/18%	135 507	Futile
Hip fracture (20 studies, n=36 655)			
20% RR	2.5%/15%	32 495	Futile
15% RR	2.5%/15%	57 722	Uncertain*
Falls (37 studies, n=34 144)			
15% RR	40%/76%	8638	Futile
10% RR	40%/76%	19 643	Futile
7.5% RR	40%/76%	35 098	Futile
5% RR	40%/76%	79 344	Uncertain†
Lumbar spine BMD (33 studies, n=5198)‡			
3% difference	50%	144	Not assessable§
2% difference	50%	327	Futile
1% difference	50%	1304	Futile
0.5% difference	50%	5212	Benefit
Total hip BMD (28 studies, n=4572)‡			
3% difference	64%	46	Not assessable§
2% difference	64%	104	Not assessable§
1% difference	64%	409	Futile
0.5% difference	64%	1627	Futile
Femoral neck BMD (26 studies, n=4311)‡			
3% difference	73%	128	Not assessable§
2% difference	73%	285	Benefit
1% difference	73%	1140	Futile
0.5% difference	73%	4561	Benefit
Forearm BMD (ten studies, n=1096)‡			
3% difference	15%	27	Not assessable§
2% difference	15%	60	Not assessable§
1% difference	15%	237	Futile
0.5% difference	15%	947	Futile
Total body BMD (15 studies, n=2793)‡			
3% difference	82%	59	Not assessable§
2% difference	82%	135	Not assessable§
1% difference	82%	535	Futile
0.5% difference	82%	2138	Futile

The RR and % difference are thresholds that indicate the relative risk reduction in falls or fractures, or the between-groups difference in bone mineral density assessed in the trial sequential analyses. RR=relative risk. BMD=bone mineral density. *Effect size was between the futility and inferior boundaries. †Effect size was between the futility and superior boundaries. ‡Only heterogeneity results shown. §Analyses were not possible because the optimum sample size was smaller than the sample size for the first trial.

Table 2: Results of trial sequential analyses, by effect size

some subgroup results were different to the primary analysis, and in the remaining 11 trials, the subgroup results were similar to the primary analysis.

In the 12 prespecified subgroup analyses for the primary outcome of fractures and falls, there was only one significant interaction between vitamin D supplementation and



a factor (total fracture; effect greater in studies ≤ 200 participants; 36 total analyses; appendix pp 29, 30). For bone mineral density, of the 64 subgroup analyses done, there were eight significant interactions, although in four interactions there was only one trial in one of the subgroups (appendix pp 31, 32). The other four significant interactions were for total hip (effect greater without co-administered calcium), femoral neck (effect greater in smaller studies or without co-administered treatments), and total body (effect greater with higher doses). Overall, there were 100 subgroup analyses. If all the results were independent, about five statistically significant interactions would be expected by chance. In post-hoc analyses, we compared high daily dose with low daily dose randomised controlled trials, and intermittent high-dose with intermittent low-dose randomised controlled trials, and there were no significant interactions between subgroups for any outcome (data not shown).

Discussion

In meta-analyses of 81 randomised controlled trials, vitamin D supplementation did not affect incident fractures or falls, and did not have consistent clinically relevant effects on bone mineral density. There were no significant differences in results of trials comparing vitamin D with controls and trials comparing high doses with low doses of vitamin D, although there are fewer trials with the latter study design. Likewise, there was no consistent evidence of different effects in subgroup analyses based upon potentially influential baseline variables including baseline 25OHD or study design characteristics, nor of different effects in trials of high-dose vitamin D or trials with higher achieved 25OHD concentrations. Trial sequential analyses showed that there is reliable evidence that vitamin D supplementation does not have meaningful clinical benefits: it does not reduce the relative risk of total fracture by 5% or falls by 7.5%, it does not increase bone mineral density by 0.5–1%, and uncertainty remains as to whether it might increase the risk of hip fracture. Further similar trials are unlikely to alter the conclusions of these trial sequential analyses. If a large future trial has markedly different results to the current trials, adding its results will substantially increase the heterogeneity of the trial results, which in turn will reduce the weighting the new large trial receives in the pooled analyses. Thus, adding a positive result from a large randomised controlled trial will have only a small

Figure 4: Lumbar spine BMD meta-analysis (A) and trial sequential analysis (B)

(A) Random-effects meta-analysis of vitamin D supplementation on lumbar spine bone mineral density (BMD), by trial duration, and the pooled analysis of all trials using the final timepoint. Totals are % difference (95% CI). (B) Trial sequential analysis of all trials of vitamin D on lumbar spine BMD for a mean difference of 0.5% (see figure 2 for detailed description).

effect on the pooled result, and is unlikely to alter the conclusions of these meta-analyses.

The strengths of the current analyses are that they are comprehensive, include all available data from a large number of new trials, and concomitantly assess the major clinical and surrogate endpoints for musculoskeletal health. The analyses are based on substantially more trials, more participants, and more events than previous analyses, which means they have greater power, the effect estimates have greater precision, the trial sequential analyses are able to examine efficacy at lower RR thresholds, and the subgroup analyses are more comprehensive. The trial sequential analyses are important because they provide estimates about the reliability of current evidence and the likelihood of future trials to change current conclusions. The number of studies included permitted a large number of subgroup analyses exploring the effects of potentially relevant trial and participant characteristics, some of which have been invoked as explanations for the null findings of individual trials of vitamin D. The greater number of trials with bone mineral density as an outcome allowed us to examine the effects of vitamin D supplementation in trials of differing durations, which showed no evidence that between-group differences in bone mineral density increased as trial duration increased.

These analyses also have limitations. We included studies with methodological limitations, although there was no evidence that randomised controlled trials at low risk of bias reported substantially different effects. Several meta-analyses had moderate heterogeneity in trial results, generally because a few studies of small-to-moderate size reported positive results that were not observed in larger trials. The subgroup analyses show that, for all outcomes, smaller studies of shorter duration tended to have inflated effect sizes compared with larger and longer studies, such that the results of small, short-duration studies should be interpreted very cautiously, since they might not be replicated in larger, longer studies. Heterogeneity of populations, study designs, and results is also an issue for trial sequential analyses. Although the heterogeneity in the existing results is incorporated into the trial sequential analysis calculations, assumptions about the results of future large trials are based on the expectation that they will be similar to the existing trials. For vitamin D, this seems a reasonable assumption given the consistency among existing trial results, particularly among large randomised controlled trials. Data were collected differently for falls in different trials, which might affect the study findings, although these results were independent of our assessment of the risk of bias.

The results from these meta-analyses are consistent with most of the recent systematic reviews of vitamin D supplementation on musculoskeletal outcomes,^{3,6,7,9,10} including those from the Cochrane groups,^{4,5,8} and align with the recent statements from the US Preventative Services Taskforce, which recommends against vitamin D

supplementation to prevent falls¹⁰⁷ or fractures¹⁰⁸ in community-dwelling adults. Some previous meta-analyses reached more optimistic conclusions as a result of differences in trial selection and outcome definition, and use of per-protocol rather than intention-to-treat analysis.^{109,110} The differences in meta-analyses results might explain why some clinical guidelines continue to recommend vitamin D supplementation for musculoskeletal indications,^{111,112} which seems inconsistent with the available evidence.

There have been several explanations for the absence of meaningful effects of vitamin D on musculoskeletal outcomes. These have included that the baseline 25OHD concentrations of trial participants have been too high, the doses of vitamin D supplements too low, or that trials have been inadequately designed, underpowered, or done in the wrong populations. None of those explanations seems likely to account for our findings. The trials we included have a broad range of study designs and populations, but there are consistently neutral results for all endpoints, including the surrogate endpoint of bone mineral density. Randomised controlled trials of high doses of vitamin D and trials that achieved higher 25OHD concentrations did not have different results. More than half of the trials reported a mean baseline 25OHD concentration of less than 50 nmol/L, a cutoff often considered to indicate vitamin D insufficiency, and almost all reported mean baseline concentrations less than 75 nmol/L. It is possible that trials of populations with low baseline 25OHD might produce different results, because only four trials, involving 831 participants, reported mean baseline 25OHD concentrations less than 25 nmol/L.

In summary, vitamin D supplementation did not have meaningful effects on fracture, falls, or bone mineral density, and future trials are unlikely to alter these conclusions. Therefore, there is little justification for the use of vitamin D supplements to maintain or improve musculoskeletal health, and clinical guidelines should reflect these findings. The clear exception to this is for the prevention or treatment of the rare conditions of rickets and osteomalacia, which can occur after a prolonged lack of exposure to sunshine that leads to 25OHD concentrations lower than 25 nmol/L. We believe there is no justification for more trials of vitamin D supplements with musculoskeletal outcomes because there is no longer equipoise about the effects of vitamin D on these outcomes. Trials of vitamin D supplementation in individuals with marked vitamin D deficiency, who are not at risk of osteomalacia, might produce different results, but require a strong scientific rationale before being undertaken, given the absence of effects of vitamin D seen in existing trials.

Contributors

MJB, AG, and AA designed the study. MJB and AA searched the literature. MJB, AG, and AA extracted the data. MJB analysed the data. MJB, AG, and AA interpreted the data. MJB drafted the manuscript, and AG and AA critically reviewed the manuscript.

Declaration of interests

MJB and AG report grants from the Health Research Council (HRC) of New Zealand during the conduct of the study. AG is a shareholder in Auckland Bone Density, a company that provides bone mineral density measurements. AA reports grants from the Chief Scientist Office of the Scottish Government Health and Social Care Directorates during the conduct of the study. All authors have co-authored publications about the efficacy of vitamin D supplementation.

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