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

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Abstract:

Background:
The effects of vitamin D on fracture, falls and bone mineral density (BMD) are uncertain, particularly for higher vitamin D doses.

Methods:
Random-effects meta-analyses and trial sequential analyses (TSA) of randomised controlled trials (RCTs) of vitamin D (in which treatment arms only differ by vitamin D) in adults with total fracture, hip fracture, falls, or BMD at the lumbar spine, total hip, femoral neck, total body or forearm as outcomes identified from Pubmed, Embase, Cochrane CENTRAL, and two clinical trial databases, last search Feb 2018.

Findings:
81 RCTs reported fracture (n=42), falls (n=37), or BMD (n=41). In pooled analyses, vitamin D had no effect on total fracture [36 trials, n=44790, RR 1.00 (95%CI 0.94-1.07)], hip fracture [(20 trials, n=36655, RR 1.11 (0.97-1.26)], or falls [37 trials, n=34144, RR 0.97 (0.93-1.02)]. Results were similar in RCTs of higher vs lower dose vitamin D and in subgroup analyses of RCTs using doses >800 IU/d. In pooled analyses, there were no clinically relevant between-group differences in BMD at any site (range -0.16% to 0.76% over 1-5y).

The effect estimate in the TSAs lay within the futility boundary at a threshold of 7.5% risk reduction for total fracture and falls, lay between the futility boundary and the inferior boundary at a 15% risk reduction for hip fracture, and lay within the futility boundary at thresholds of 0.5% for total hip, forearm, and total body BMD, and 1.0% for lumbar spine and femoral neck, providing reliable evidence that vitamin D does not alter these outcomes by these amounts.

Interpretation
Vitamin D supplementation does not prevent fractures or falls, or have meaningful effects on BMD. There were no differences between the effects of higher and lower doses of vitamin D.

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Background:

Vitamin D supplements have long been recommended for older people to treat or prevent osteoporosis,[1] with some early evidence suggesting benefits for musculoskeletal health, including increasing bone mineral density (BMD), and preventing falls and fractures.[2] However, later systematic reviews have reported no effect of vitamin D supplementation on BMD,[3] falls,[4-7] or fractures.[7-10] Trial sequential analyses for the hypothesis of a 15% relative risk reduction in falls or fractures showed that conducting further trials of vitamin D with or without calcium supplementation that are similar to the existing trials is unlikely to alter the conclusion of the recent systematic reviews.[6,9] However, correspondents questioned the utility of this efficacy threshold and also suggested that inadequate vitamin D doses might explain these null results,[11,12] although some randomised controlled trials (RCTs) 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 on musculoskeletal health were published in 2012-14, [3-10] 45 RCTs of vitamin D monotherapy (n=20,131) have reported on BMD, falls and fractures, increasing the number of trial participants with these outcomes by 40-85%. Most newer trials have also used substantially higher doses of vitamin D than earlier trials. Consequently, the currently available set of RCTs 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 higher and lower doses of vitamin D. Therefore, a comprehensive update of previous systematic reviews, meta-analyses, and trial-sequential analyses, that includes the important clinical and major surrogate endpoints, is warranted. An advantage of assessing these outcomes concurrently is that it is possible that an effect may be found for some endpoints whereas no effect is found for others, which might have clinical and biological relevance. Trial-sequential analyses of vitamin D and BMD have also not been previously 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, with or without vitamin D, in preventing fractures is only weak and inconsistent,[10,16] with any effect on BMD or fracture likely very small and of doubtful clinical relevance.[10,16,17] In addition, uncommon but important side-effects of calcium supplements[18-21] have been identified contributing 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 therefore have undertaken a systematic review, meta-analyses and trial sequential analyses of RCTs in adults of vitamin D supplements on the clinical musculoskeletal outcomes of fractures and falls and the commonly used surrogate endpoint of BMD. To align with the recent findings on calcium supplements, and the recent design of vitamin D RCTs, we have focused on RCTs that have used vitamin D as monotherapy, and included RCTs that compared higher doses of vitamin D with lower doses.

Methods:

Literature search

The PRISMA guidelines for development of protocols[22] and reporting of systematic reviews and meta-analyses were followed.[23] We used our literature searches for previous meta-analyses[3,6,8,9,16,17] as the starting point. For the most recent of these searches, we searched Pubmed in December 2015 for RCTs and recent systematic reviews of vitamin D in adults. We identified all studies from this search and our previous meta-analyses with fracture, falls, or bone density as an outcome. We then searched Pubmed, Embase, and Cochrane

CENTRAL in Sept 2017 and Feb 2018 using the term "vitamin D" and keywords shown in Appendix e1 for publications since 2015. 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 Appendix e1.

Study selection

We included RCTs in adults (>18y) 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 arms differed only by the use of vitamin D. We included quasi-randomized and open-label trials but excluded trials of hydroxylated vitamin D analogues. RCTs in cohorts with conditions likely to impact on bone turnover or cohorts selected for specific diseases (for example: primary hyperparathyroidism, renal or hepatic disease) were included but analysed separately in the initial analyses. We included RCTs with outcome data on total or hip fracture, falls, or BMD measured using dual energy x-ray absorptiometry (DXA) at the lumbar spine, total hip, femoral neck, total body, or forearm. Trials reporting BMD using other techniques were excluded. Cluster RCTs were included. One author (MB) screened titles and abstracts, two authors (MB, 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 Appendix e2. The flow of articles is shown in Appendix e3.

Data Extraction:

Data on participant characteristics, study design, interventions, outcomes, funding sources and conflicts of interest were extracted by one author (MB) and checked by a second author (AG). Where data were presented only in figures, we used digital callipers to extract data. Where data for falls but not fractures were reported, we emailed the authors requesting any data on fractures (Appendix e2). The risk of bias of eligible RCTs was independently assessed by two authors (MB, AG) following the approach in the Cochrane handbook.[24] Discrepancies in author assessments were resolved by discussion.

Outcomes:

The co-primary endpoints were participants with ≥1 fracture, ≥1 hip fracture, or ≥1 fall. Where 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 BMD from baseline at lumbar spine, total hip, femoral neck, total body, and forearm.

Data Analysis and Statistics:

We grouped RCTs comparing vitamin D supplementation with controls together with RCTs comparing vitamin D plus agent with the agent alone (termed vitamin D vs controls). Several trials had multiple vitamin D treatment arms. If there was a control group, we pooled the vitamin D treatment arms and compared the pooled results with the controls. If there was no control group, we pooled treatment arms in which the vitamin D dose was ≥800IU/d ('higher' dose), and compared the results to the pooled result of treatment arms where the dose was <800IU/d ('lower' dose). In subgroup analyses, we used relevant individual treatment arms for each trial.

For fractures and falls, we initially analysed RCTs conducted in unselected populations and selected populations separately, and also analysed RCTs comparing vitamin D with controls

and RCTs comparing different doses of vitamin D separately. If the results from the different groups of trials were similar, then the RCTs were pooled in subsequent analyses. For BMD, the same approach was undertaken, but the further variable of study duration was also analysed. BMD RCTs were categorised into 3 groups by duration: '1 year'- duration <1.5 years; '2 years'- duration ≥1.5 years and ≤2.5 years; and '3+ years'.

Data for fractures and falls were compared using relative risks with an intention-to-treat analysis using all available data and the number of participants randomised to the treatment for each group. BMD data were compared using the weighted difference in means. For all analyses, data were pooled using random-effects models, heterogeneity was evaluated using the I^2 statistic (I^2 >50% was considered significant heterogeneity), and systematic bias was assessed using Funnel Plots and Egger's test (Comprehensive Meta-Analysis, version 2, Biostat, Englewood New Jersey, USA). All tests were two-tailed and p-values <0.05 were considered statistically significant. The sample size of cluster RCTs was adjusted in accordance with the Cochrane Handbook.[24] Raw BMD and absolute change from baseline were converted to percentage change using the methods described in the Cochrane Handbook.[24] For studies that reported mean BMD but not a measure of spread, we imputed the standard deviation using the median site-, duration-, and treatment group-specific standard deviation from other included studies, and separately analysed these studies to determine the impact of this approach.

Trial sequential analysis[25,26] was carried out for each outcome (TSA Viewer, version 0.9.5.10 Beta; www.ctu.dk/tsa). 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.[25,26] For fractures and falls, we initially used a 15% relative risk reduction threshold, as in our previous publications,[6,9] and in further analyses used progressively smaller thresholds until the optimum sample size exceeded the actual sample size. For BMD, we initially used a threshold of a 3% increase, representing the approximate average BMD loss of a late post-menopausal women 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 RCTs in the trial sequential analysis.

Prespecified subgroup analyses were undertaken testing for interactions between the effects of vitamin D supplementation on fractures, falls, and BMD for the following factors, each of which is frequently invoked as a possible modifier of the effects of vitamin D: age <65 vs ≥65y, BMI <30 vs ≥30 kg/m^2, baseline 25-hydroxyvitamin D (25OHD) <25 vs ≥25 nmol/L, <50 vs ≥50 nmol/L, <75 vs ≥75 nmol/L; achieved 25OHD ≥50 vs <50 nmol/L, ≥75 vs <75 nmol/L, dose of vitamin D ≤800 IU/day vs >800 IU/day; intermittent vs daily dosing; trials at overall low risk of bias vs trials at moderate or high risk of bias; trial duration ≤1y vs >1y; trial size ≤200 vs >200 participants; use of co-administered calcium vs no calcium; and location- residential care vs community-dwelling. For intermittent doses where the daily equivalent dose is approximately 800 IU/day (eg 300,000 IU/year), we included these trials in the ≤800 IU/day group. All such trials had an equivalent daily dose of <1000 IU.

Role of the funding source
The funders had no role in the study design; collection, analysis, and interpretation of the data; writing of the report; and in the decision to submit the paper for publication. All authors

had access to raw data, which are provided in the Appendix. The corresponding author had the final responsibility to submit for publication.

Results:

Baseline characteristics and outcome data

We identified 81 eligible RCTs of vitamin D supplements[13-15,27-107] that reported fracture (n=42), falls (n=37), or BMD (n=41) as an outcome (Appendix e3). The study design and selected baseline characteristics of the RCTs are shown in Appendix e4 and e5 and summarised in Table 1. The majority of RCTs studied vitamin D as monotherapy, in unselected populations of community-dwelling women aged >65 years, using daily doses of >800 IU/day and had a duration of ≤1 year. The majority of trials (57%) were carried out in populations with mean 25OHD <50 nmol/L but only 4 were carried out in populations with mean 25OHD <25 nmol/L. 91% of trials reported achieved 25OHD ≥50 nmol/L and 58% achieved 25OHD ≥75 nmol/L. Appendix e6 shows our assessment of risk of bias, and e7 conflicts of interest and funding source. Nine (21%) RCTs were considered at low risk of bias for fractures, 22 (59%) low risk for falls, and 29 (71%) low risk for BMD.

Appendix e8 shows the outcome data for each study for each endpoint.

Co-primary endpoints: fractures and falls

Figures 1-3 show the results of the meta-analyses for total fracture, hip fracture, and falls by study design and population. For all 3 outcomes, there was no statistically significant interaction for results between RCTs with different study designs (vitamin D vs controls, higher vs lower dose vitamin D) in unselected populations, or between trials in selected and unselected populations. Therefore, we pooled all the RCTs, finding no effect of vitamin D supplementation on total fracture [36 trials, n=44790, RR 1.00 (95%CI 0.93-1.07)], hip fracture [(20 trials, n=36655, RR 1.11 (0.97-1.26)], or falls [37 trials, n=34144, RR 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 3 outcomes, largely due to an excess of small-medium size studies with positive effects on the outcomes.

Figures 1-3 and Table 2 show the results of the trial sequential analyses. For total fracture and falls, the effect estimate lay within the futility boundary for risk reductions 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. For hip fracture, at a 15% risk reduction, 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.

Secondary endpoints: bone density

Figures 4-6, Appendix e9-e11 show the results of the meta-analyses for BMD by site. First, we compared the results of trials with missing measures of spread and imputed standard deviations to the other trials, by duration, design and population. Appendix e9 shows that generally there was little difference between results, and therefore we included the trials with imputed standard deviations in subsequent analyses. Next, we compared the results of trials by duration, study design, and population type. Appendix e9 shows that for all combinations of these factors, there was very little difference in results between the subgroups, and therefore we pooled the trials with differing study designs (vitamin D vs controls, higher vs

lower dose vitamin D) and those in selected and unselected populations. Because there were only small differences by trial duration, we also pooled all the trials using the final time point data only for each trial. Figures 4-6, Appendix e10-11 show the between-group differences in BMD by site, by trial duration, and the pooled analyses using the final time point. Between-group differences in BMD did not consistently increase with increasing trial duration at any site, and in the pooled analyses using the final time point the between-group differences were 0.25%, 0.34%, 1.12%, -0.16%, and 0.13% at the lumbar spine, total hip, femoral neck, forearm, and total body. Of note, at the femoral neck one RCT[107] reported a between-group difference of 10.6% (95%CI 9.0-12.3) after 1y which was a clear outlier and had a disproportionate effect on the pooled result. We excluded this trial[107]from subsequent analyses, and after its exclusion, the between-group difference at the femoral neck was 0.76% (Figure 6). Using Egger's regression model and visual inspection of funnel plots, data appeared skewed toward increased BMD with vitamin D supplementation for all sites except the forearm, again largely due to an excess of small studies with positive effects on BMD. All subsequent trial sequential analyses and subgroup analyses were performed using the final time point data only for each trial.

Table 2, Figures 4-6, Appendix e10-11, show the results of the trial sequential analyses. For the total hip, forearm, and total body sites the effect estimate 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%.

Subgroup analyses

Reported analyses in individual trials based on baseline 25OHD

18 RCTs reported the results of a subgroup analysis using various thresholds for baseline 25OHD (Appendix e12). Three RCTs reported no effects of vitamin D on fracture in subgroups, and six reported no effects in subgroups or no interactions with baseline 25OHD, and one mixed effects of vitamin D on falls in subgroups. The subgroup results in all RCTs were similar to the primary analyses. For BMD, one RCT reported positive effects in subgroups, five RCTs mixed effects, and eight RCTs no effects in subgroups or no interactions with baseline 25OHD. In 3/14 RCTs, some subgroup results were different to the primary analysis, and in the remaining 11 RCTs the subgroups results were similar to the primary analysis.

Subgroup analyses in pooled trial datasets

Appendix e13-14 shows the results of the pre-specified subgroup analyses for the meta-analyses. For fractures and falls, there was only 1 significant interaction between vitamin D supplementation and a factor (trial size for total fracture, effect greater in smaller studies) in the 12 subgroup analyses for each of the 3 outcomes (36 total analyses). For BMD, of the 64 subgroup analyses, there were 8 significant interactions, although in 4 there was only 1 trial in one of the subgroups. The remaining 4 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 5 statistically significant interactions would be expected by chance. In post-hoc analyses, we compared high daily versus low daily dose RCTs, and intermittent high dose versus intermittent low dose RCTs and there were no significant interactions between subgroups for any outcome.

Discussion

In meta-analyses of 81 RCTs, vitamin D supplementation did not affect incident fractures or falls, and did not have consistent clinically relevant effects on BMD. There were no statistically significant differences in results of trials comparing vitamin D with controls and trials comparing higher vs lower 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 higher dose vitamin D or trials with higher achieved 25OHD. 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 BMD 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 the 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 RCT will have only a small effect on the pooled result, and is unlikely to alter the conclusions of the current 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 reviews, which means the analyses have greater power, the effect estimates have greater precision, the trial sequential analyses are able to examine efficacy at lower risk reduction 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 changing 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 BMD as an outcome allowed an examination of the effects of vitamin D supplementation in trials of differing durations, which showed no evidence that between-group differences in BMD increased as trial duration increased.

The analyses also have limitations. We included studies with methodological limitations, although there was no evidence that RCTs at low risk of bias reported substantially different effects. Several meta-analyses had moderate heterogeneity in trial results, generally because a few small-moderate sized studies reported positive results that were not observed in larger RCTs. 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, as they may not be replicated in larger, longer studies. Heterogeneity of populations, study designs and results is also an issue for trial sequential analyses. While the heterogeneity in the existing RCT 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 amongst existing trial results, particularly amongst the existing large RCTs. Data were collected differently for falls in different RCTs which may affect trials results, although the 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 falls[108] or fractures[109] 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.[110,111] This might explain why some clinical guidelines continue to recommend vitamin D supplementation for musculoskeletal indications[112,113] which seems inconsistent with the available evidence.

Previous explanations for the failure of vitamin D to have meaningful effects on musculoskeletal outcomes have included that the baseline 25OHD of trial participants have been too high, the doses of vitamin D supplements too low, or that trials have been inadequately designed, underpowered, or conducted in the wrong populations. None of those explanations seems likely to account for the current findings. The trials include a broad range of study designs and populations but there are consistently neutral results for all endpoints, including the surrogate endpoint of BMD. RCTs of higher doses of vitamin D and RCTs that achieved higher 25OHD did not have different results. More than half of trials reported mean baseline 25OHD of <50 nmol/L, a cut-off often considered to indicate vitamin D insufficiency, and almost all <75 nmol/L. It is possible that trials of populations with much lower baseline 25OHD might produce different results because only 4 trials involving 831 participants reported mean baseline 25OHD <25 nmol/L.

In summary, vitamin D supplementation did not have meaningful effects on fracture, falls, or BMD 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 and/or treatment of the rare conditions of rickets and osteomalacia, which can occur after a prolonged lack of sunshine exposure when 25OHD <25 nmol/L. There is also 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 the existing trials.

Research in Context:

Evidence before this study

Early evidence 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 the previous systematic reviews, which nearly doubles the available trial results for vitamin D for these outcomes.

Added value of this study

The meta-analyses and trial sequential analyses show that in a very large body 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 higher doses of vitamin D were similar to effects of lower 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.

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Declaration of interest: AG is a shareholder in Auckland Bone Density, a company that provides bone mineral density measurements. All authors have co-authored publications on the efficacy of vitamin D supplementation.

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Author Contributions:
MB- study design; literature searches; data extraction; data analysis; interpretation of data; drafted manuscript
AG- study design; data extraction; interpretation of data; critical review of manuscript;
AA- study design; literature searches; data extraction; interpretation of data; critical review of manuscript.

MB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and the final responsibility for the decision to submit for publication.

Data availability
All data are included in the Appendix.

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147. Maity A, Chauhan K. Efficacy of calcium and vitamin D doses in relation to bone health of elderly people. *Annals of Nutrition and Metabolism* 2015; **67**:434-5.
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Table 1: Summary of selected characteristics of eligible trials

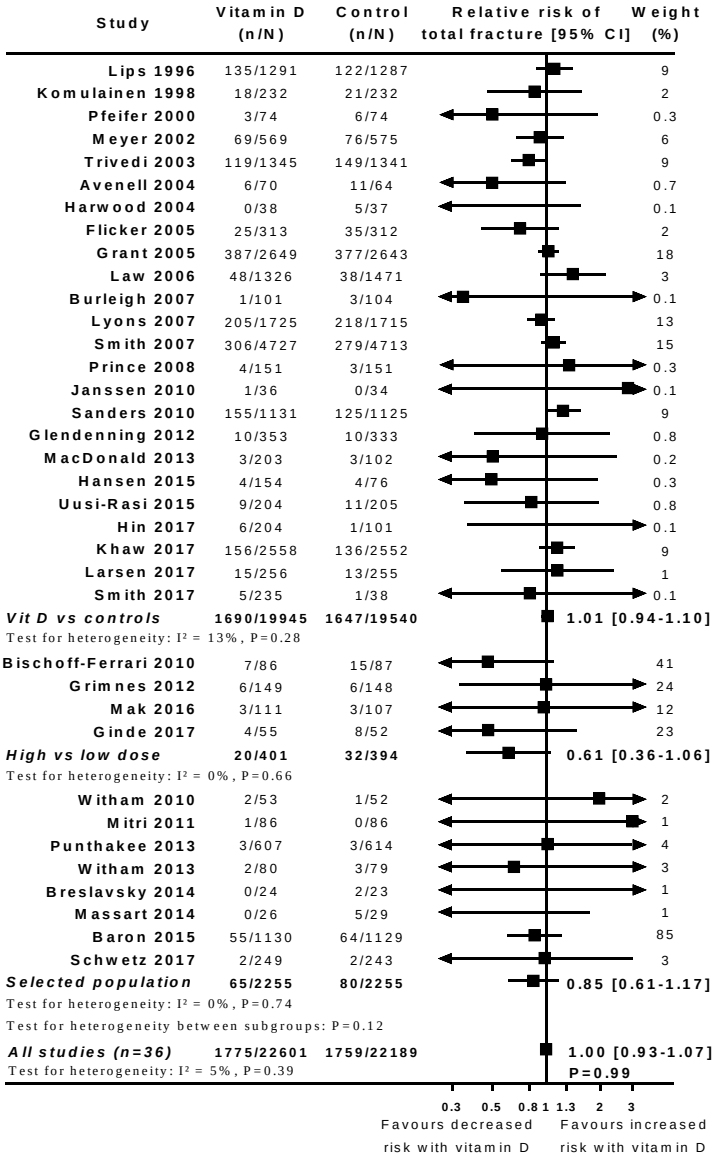
Characteristics of randomised controlled trials	All trials (n=81)
Population unselected for illness	61 (75%)
Treatment studied	
Vitamin D vs controls	39 (48)
Vitamin D with agent vs agent	26 (32)
Calcium	20
Exercise	2
Calcium/Exercise	1
Other	3
High vs low dose vitamin D	16 (20)
Vitamin D dose >800 IU/d	55 (68)
Frequency of vitamin D dose	
Daily	44 (54)
Intermittent	36 (44)
Mixed	1 (1)
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 Body Mass Index <30 kg/m^2	58 (72)
Baseline 25-hydroxyvitamin D	
<25 nmol/L	4 (6)
<50 nmol/L	41 (57)
<75 nmol/L	71 (99)
Achieved 25-hydroxyvitamin D	
50+ nmol/L	69 (91)
75+ nmol/L	44 (58)
Outcome data	
Fracture	42 (52)
Falls	37 (46)
Bone mineral density	41 (51)

Data are number of trials (%).

Table 2: Results of trial sequential analyses

Outcome	Incidence/ Heterogeneity	Effect size	Optimum sample size	Result
Total fracture	10%/18%	15% RR	14364	Futile
36 studies, n=44790		10% RR	33100	Futile
		7.5% RR	59536	Futile
		5% RR	135507	Futile
Hip fracture	2.5%/15%	20% RR	32495	Futile
20 studies, n=36655		15% RR	57722	Uncertain[a]
Falls	40%/76%	15% RR	8638	Futile
37 studies, n=34144		10% RR	19643	Futile
		7.5% RR	35098	Futile
		5% RR	79344	Uncertain[b]
Lumbar spine BMD	-/50%	3% difference	144	Not assessible
33 studies, n=5198		2% difference	327	Futile
		1% difference	1304	Futile
		0.5% difference	5212	Benefit
Total hip BMD		3% difference	46	Not assessible
28 studies, n=4572	-/64%	2% difference	104	Not assessible
		1% difference	409	Futile
		0.5% difference	1627	Futile
Femoral neck BMD		3% difference	128	Not assessible
26 studies, n=4311	-/73%	2% difference	285	Benefit
		1% difference	1140	Futile
		0.5% difference	4561	Benefit
Forearm BMD		3% difference	27	Not assessible
10 studies, n=1096	-/15%	2% difference	60	Not assessible
		1% difference	237	Futile
		0.5% difference	947	Futile
Total Body BMD	-/82%	3% difference	59	Not assessible
15 studies, n=2793		2% difference	135	Not assessible
		1% difference	535	Futile
		0.5% difference	2138	Futile

BMD- bone mineral density, RR- risk reduction. Not assessable- analyses were not possible because the optimum sample size was smaller than the sample size for the first trial.
[a] effect size lay between the futility and inferior boundaries
[b] effect size lay between the futility and superior boundaries


Study
Vitamin D (n/N)
Control (n/N)
Relative risk of total fracture [95% CI]
Weight (%)
Lips 1996 135/1291 122/1287 9
Komulainen 1998 18/232 21/232 2
Pfeifer 2000 3/74 6/74 0.3
Meyer 2002 69/569 76/575 6
Trivedi 2003 119/1345 149/1341 9
Avenell 2004 6/70 11/64 0.7
Harwood 2004 0/38 5/37 0.1
Flicker 2005 25/313 35/312 2
Grant 2005 387/2649 377/2643 18
Law 2006 48/1326 38/1471 3
Burleigh 2007 1/101 3/104 0.1
Lyons 2007 205/1725 218/1715 13
Smith 2007 306/4727 279/4713 15
Prince 2008 4/151 3/151 0.3
Janssen 2010 1/36 0/34 0.1
Sanders 2010 155/1131 125/1125 9
Glendenning 2012 10/353 10/333 0.8
MacDonald 2013 3/203 3/102 0.2
Hansen 2015 4/154 4/76 0.3
Uusi-Rasi 2015 9/204 11/205 0.8
Hin 2017 6/204 1/101 0.1
Khaw 2017 156/2558 136/2552 9
Larsen 2017 15/256 13/255 1
Smith 2017 5/235 1/38 0.1
Vit D vs controls 1690/19945 1647/19540 1.01 [0.94-1.10]
Test for heterogeneity: I² = 13%, P=0.28
Bischoff-Ferrari 2010 7/86 15/87 41
Grimnes 2012 6/149 6/148 24
Mak 2016 3/111 3/107 12
Ginde 2017 4/55 8/52 23
High vs low dose 20/401 32/394 0.61 [0.36-1.06]
Test for heterogeneity: I² = 0%, P=0.66
Witham 2010 2/53 1/52 2
Mitri 2011 1/86 0/86 1
Punthakee 2013 3/607 3/614 4
Witham 2013 2/80 3/79 3
Breslavsky 2014 0/24 2/23 1
Massart 2014 0/26 5/29 1
Baron 2015 55/1130 64/1129 85
Schwetz 2017 2/249 2/243 3
Selected population 65/2255 80/2255 0.85 [0.61-1.17]
Test for heterogeneity: I² = 0%, P=0.74
Test for heterogeneity between subgroups: P=0.12
All studies (n=36) 1775/22601 1759/22189 1.00 [0.93-1.07]
Test for heterogeneity: I² = 5%, P=0.39
P=0.99
0.3 0.5 0.8 1 1.3 2 3
Favours decreased risk with vitamin D
Favours increased risk with vitamin D

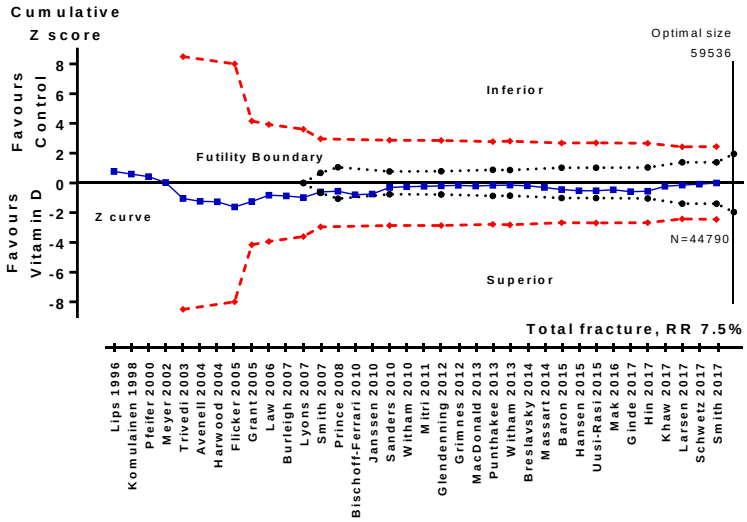

Cumulative Z score
Optimal size
59536
Favours Control
Favours Vitamin D
Inferior
Futility Boundary
Z curve
N=44790
Superior
Total fracture, RR 7.5%
8 6 4 2 0 -2 -4 -6 -8
Lips 1996
Komulainen 1998
Pfeifer 2000
Meyer 2002
Trivedi 2003
Avenell 2004
Harwood 2004
Flicker 2005
Grant 2005
Law 2006
Burleigh 2007
Lyons 2007
Smith 2007
Prince 2008
Bischoff-Ferrari 2010
Janssen 2010
Sanders 2010
Witham 2010
Mitri 2011
Glendenning 2012
Grimnes 2012
MacDonald 2013
Punthakee 2013
Witham 2013
Breslavsky 2014
Massart 2014
Baron 2015
Hansen 2015
Uusi-Rasi 2015
Mak 2016
Ginde 2017
Hin 2017
Khaw 2017
Larsen 2017
Schwetz 2017
Smith 2017

Figure 1: The top panel shows random effects meta-analyses of vitamin D supplementation on total fracture. Vit D vs controls refers to trials of vitamin D with controls in unselected populations, High vs Low dose to trials of higher and lower dose vitamin D in unselected populations, and Selected Population to trials of vitamin D with controls in populations with an underlying illness. The bottom panel shows trial sequential analysis of all trials of vitamin D on total fracture for a relative risk (RR) 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.

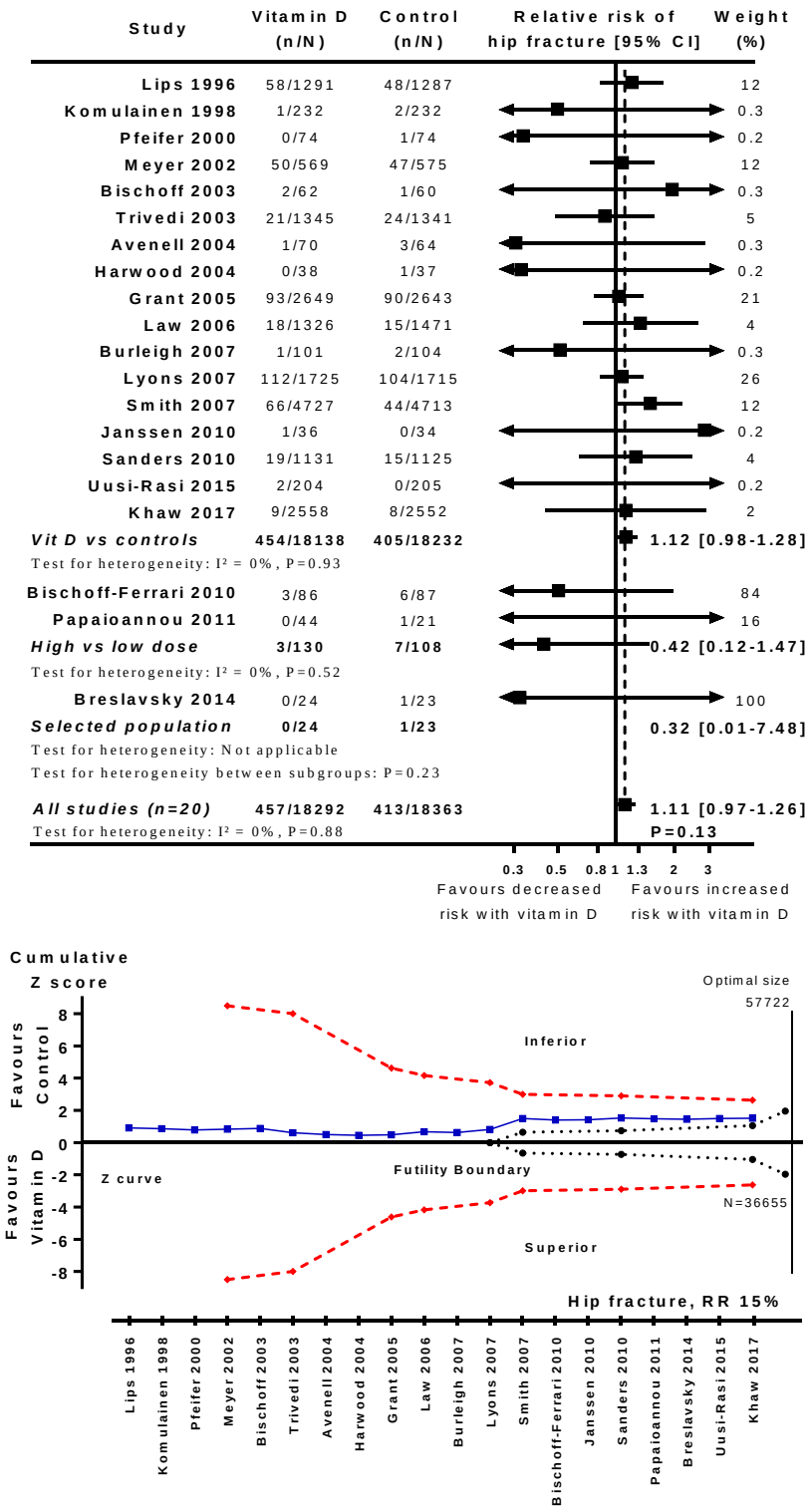
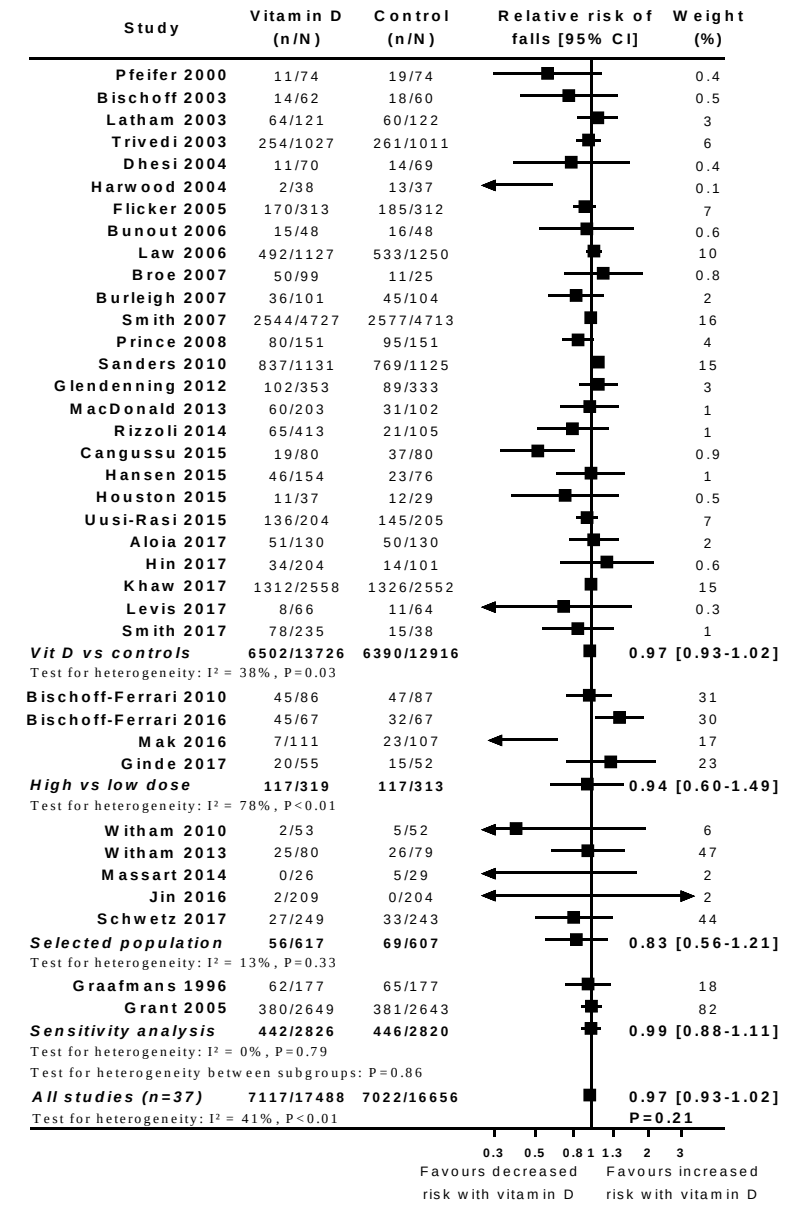


Figure 2: The top panel shows random effects meta-analyses of vitamin D supplementation on hip fracture. Vit D vs controls refers to trials of vitamin D with controls in unselected populations, High vs Low dose to trials of higher and lower dose vitamin D in unselected populations, and Selected Population to trials of vitamin D with controls in populations with an underlying illness. The bottom panel shows trial sequential analysis of all trials of vitamin D on hip fracture for a relative risk (RR) of 15% (see Figure 1 for detailed description).


Study
Vitamin D (n/N)
Control (n/N)
Relative risk of falls [95% CI]
Weight (%)
Pfeifer 2000 11/74 19/74 0.4
Bischoff 2003 14/62 18/60 0.5
Latham 2003 64/121 60/122 3
Trivedi 2003 254/1027 261/1011 6
Dhesi 2004 11/70 14/69 0.4
Harwood 2004 2/38 13/37 0.1
Flicker 2005 170/313 185/312 7
Bunout 2006 15/48 16/48 0.6
Law 2006 492/1127 533/1250 10
Broe 2007 50/99 11/25 0.8
Burleigh 2007 36/101 45/104 2
Smith 2007 2544/4727 2577/4713 16
Prince 2008 80/151 95/151 4
Sanders 2010 837/1131 769/1125 15
Glendenning 2012 102/353 89/333 3
MacDonald 2013 60/203 31/102 1
Rizzoli 2014 65/413 21/105 1
Cangussu 2015 19/80 37/80 0.9
Hansen 2015 46/154 23/76 1
Houston 2015 11/37 12/29 0.5
Uusi-Rasi 2015 136/204 145/205 7
Aloia 2017 51/130 50/130 2
Hin 2017 34/204 14/101 0.6
Khaw 2017 1312/2558 1326/2552 15
Levis 2017 8/66 11/64 0.3
Smith 2017 78/235 15/38 1
Vit D vs controls 6502/13726 6390/12916 0.97 [0.93-1.02]
Test for heterogeneity: I² = 38%, P=0.03
Bischoff-Ferrari 2010 45/86 47/87 31
Bischoff-Ferrari 2016 45/67 32/67 30
Mak 2016 7/111 23/107 17
Ginde 2017 20/55 15/52 23
High vs low dose 117/319 117/313 0.94 [0.60-1.49]
Test for heterogeneity: I² = 78%, P<0.01
Witham 2010 2/53 5/52 6
Witham 2013 25/80 26/79 47
Massart 2014 0/26 5/29 2
Jin 2016 2/209 0/204 2
Schwetz 2017 27/249 33/243 44
Selected population 56/617 69/607 0.83 [0.56-1.21]
Test for heterogeneity: I² = 13%, P=0.33
Graafmans 1996 62/177 65/177 18
Grant 2005 380/2649 381/2643 82
Sensitivity analysis 442/2826 446/2820 0.99 [0.88-1.11]
Test for heterogeneity: I² = 0%, P=0.79
Test for heterogeneity between subgroups: P=0.86
All studies (n=37) 7117/17488 7022/16656 0.97 [0.93-1.02]
Test for heterogeneity: I² = 41%, P<0.01 P=0.21
0.3 0.5 0.8 1 1.3 2 3
Favours decreased risk with vitamin D
Favours increased risk with vitamin D

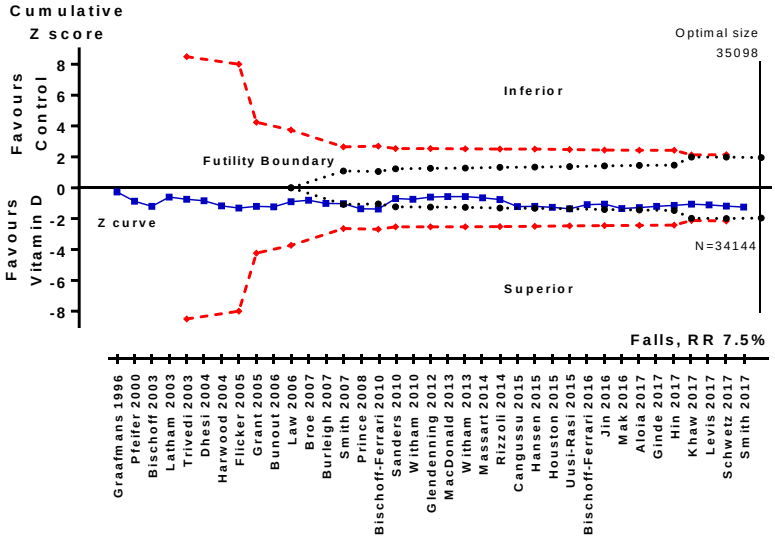
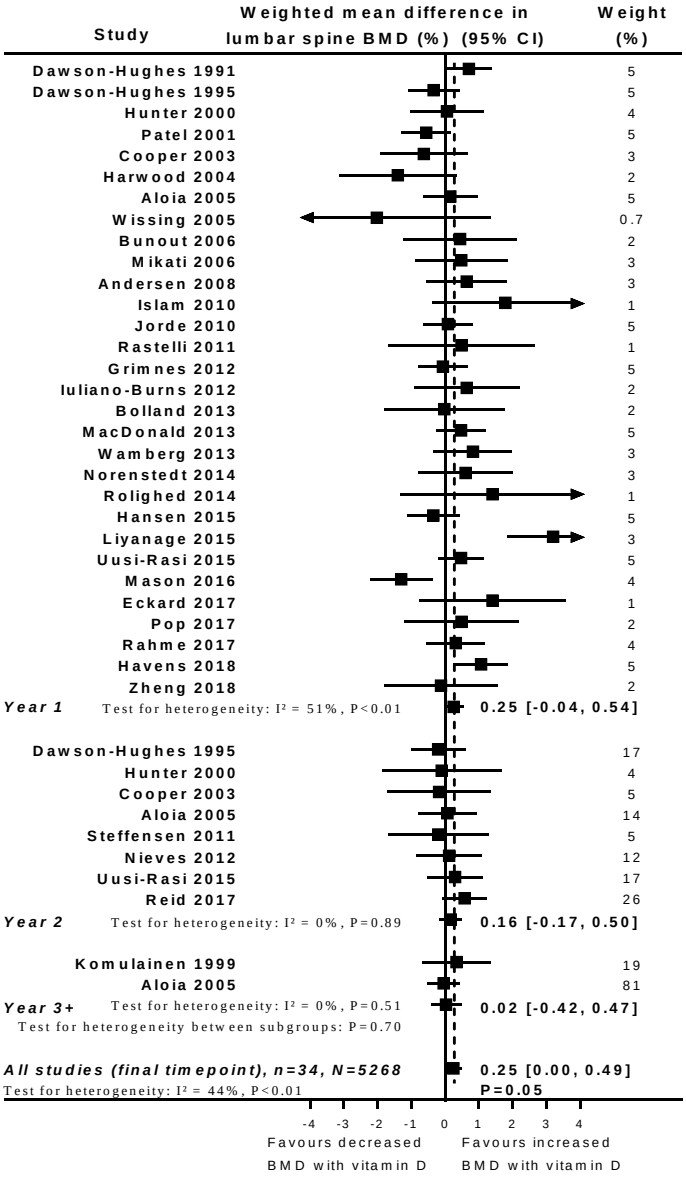

Cumulative Z score
Optimal size 35098
Favours Control
Favours Vitamin D
Inferior
Futility Boundary
Z curve
N=34144
Superior
Falls, RR 7.5%
Graafmans 1996
Pfeifer 2000
Bischoff 2003
Latham 2003
Trivedi 2003
Dhesi 2004
Harwood 2004
Flicker 2005
Grant 2005
Bunout 2006
Law 2006
Broe 2007
Burleigh 2007
Smith 2007
Prince 2008
Bischoff-Ferrari 2010
Sanders 2010
Witham 2010
Glendenning 2012
MacDonald 2013
Witham 2013
Massart 2014
Rizzoli 2014
Cangussu 2015
Hansen 2015
Houston 2015
Uusi-Rasi 2015
Bischoff-Ferrari 2016
Jin 2016
Mak 2016
Aloia 2017
Ginde 2017
Hin 2017
Khaw 2017
Levis 2017
Schwetz 2017
Smith 2017

Figure 3: The top panel shows random effects meta-analyses of vitamin D supplementation on falls. Vit D vs controls refers to trials of vitamin D with controls, High vs Low dose to trials of higher and lower dose vitamin D, sensitivity analysis to trials where falls data were gathered only in a subset of participants or for only part of the trial duration. Trials in all 3 categories were conducted in unselected populations. Selected Population refers to trials of vitamin D with controls in populations with an underlying illness. The bottom panel shows trial sequential analysis of all trials of vitamin D on falls for a relative risk (RR) of 7.5% (see Figure 1 for detailed description).


Study
Weighted mean difference in lumbar spine BMD (%) (95% CI)
Weight (%)
Dawson-Hughes 1991 5
Dawson-Hughes 1995 5
Hunter 2000 4
Patel 2001 5
Cooper 2003 3
Harwood 2004 2
Aloia 2005 5
Wissing 2005 0.7
Bunout 2006 2
Mikati 2006 3
Andersen 2008 3
Islam 2010 1
Jorde 2010 5
Rastelli 2011 1
Grimnes 2012 5
Iuliano-Burns 2012 2
Bolland 2013 2
MacDonald 2013 5
Wamberg 2013 3
Norenstedt 2014 3
Rolighed 2014 1
Hansen 2015 5
Liyanage 2015 3
Uusi-Rasi 2015 5
Mason 2016 4
Eckard 2017 1
Pop 2017 2
Rahme 2017 4
Havens 2018 5
Zheng 2018 2
Year 1 Test for heterogeneity: I² = 51%, P<0.01 0.25 [-0.04, 0.54]
Dawson-Hughes 1995 17
Hunter 2000 4
Cooper 2003 5
Aloia 2005 14
Steffensen 2011 5
Nieves 2012 12
Uusi-Rasi 2015 17
Reid 2017 26
Year 2 Test for heterogeneity: I² = 0%, P=0.89 0.16 [-0.17, 0.50]
Komulainen 1999 19
Aloia 2005 81
Year 3+ Test for heterogeneity: I² = 0%, P=0.51 0.02 [-0.42, 0.47]
Test for heterogeneity between subgroups: P=0.70
All studies (final timepoint), n=34, N=5268 0.25 [0.00, 0.49]
Test for heterogeneity: I² = 44%, P<0.01 P=0.05
-4 -3 -2 -1 0 1 2 3 4
Favours decreased BMD with vitamin D
Favours increased BMD with vitamin D

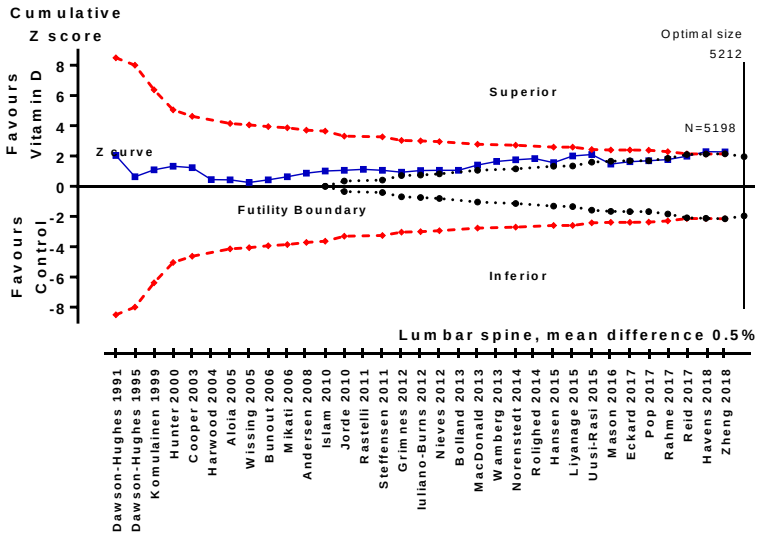
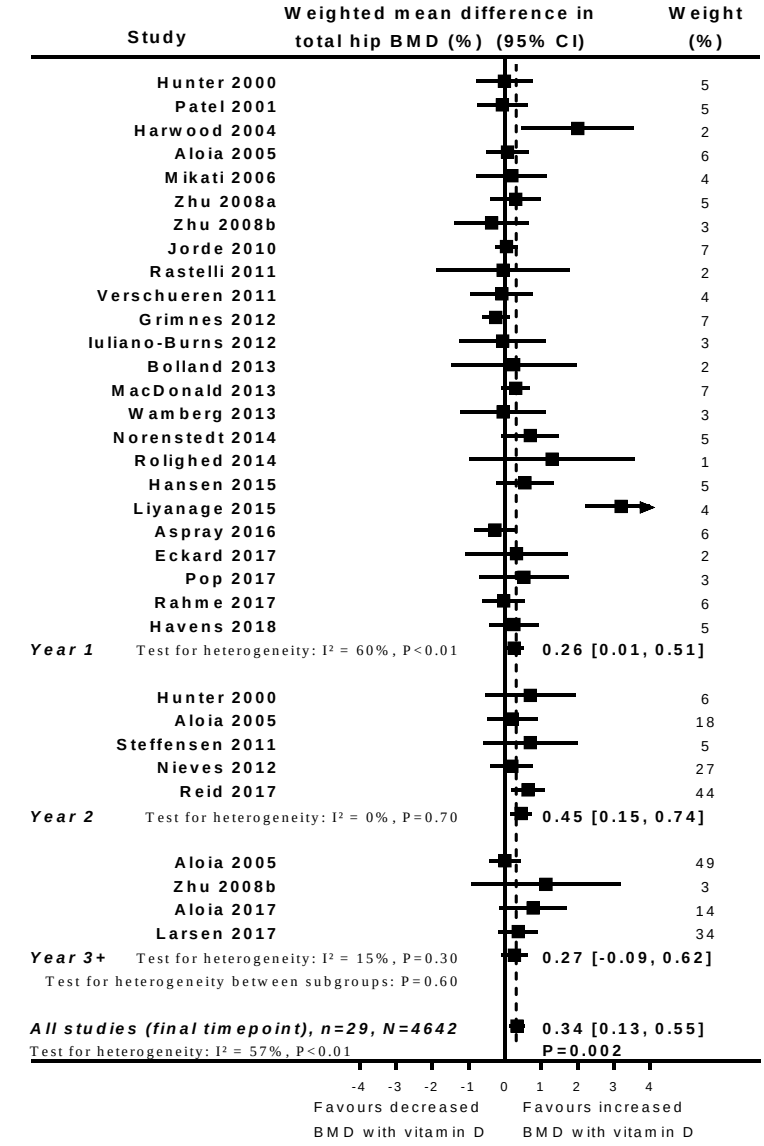

Cumulative Z score
Optimal size 5212
Favours Vitamin D
Superior
N=5198
Z curve
Futility Boundary
Favours Control
Inferior
8 6 4 2 0 -2 -4 -6 -8
Lumbar spine, mean difference 0.5%
Dawson-Hughes 1991
Dawson-Hughes 1995
Komulainen 1999
Hunter 2000
Cooper 2003
Harwood 2004
Aloia 2005
Wissing 2005
Bunout 2006
Mikati 2006
Andersen 2008
Islam 2010
Jorde 2010
Rastelli 2011
Steffensen 2011
Grimnes 2012
Iuliano-Burns 2012
Nieves 2012
Bolland 2013
MacDonald 2013
Wamberg 2013
Norenstedt 2014
Rolighed 2014
Hansen 2015
Liyanage 2015
Uusi-Rasi 2015
Mason 2016
Eckard 2017
Pop 2017
Rahme 2017
Reid 2017
Havens 2018
Zheng 2018

Figure 4: The top panel shows random effects meta-analyses of vitamin D supplementation on lumbar spine bone mineral density (BMD) by trial duration and the pooled analysis of all trials using the final time point. The bottom panel shows trial sequential analysis of all trials of vitamin D on lumbar spine BMD for a mean difference of 0.5% (see Figure 1 for detailed description).


Study
Weighted mean difference in total hip BMD (%) (95% CI)
Weight (%)
Hunter 2000 5
Patel 2001 5
Harwood 2004 2
Aloia 2005 6
Mikati 2006 4
Zhu 2008a 5
Zhu 2008b 3
Jorde 2010 7
Rastelli 2011 2
Verschueren 2011 4
Grimnes 2012 7
Iuliano-Burns 2012 3
Bolland 2013 2
MacDonald 2013 7
Wamberg 2013 3
Norenstedt 2014 5
Rolighed 2014 1
Hansen 2015 5
Liyanage 2015 4
Aspray 2016 6
Eckard 2017 2
Pop 2017 3
Rahme 2017 6
Havens 2018 5
Year 1 Test for heterogeneity: I² = 60%, P<0.01 0.26 [0.01, 0.51]
Hunter 2000 6
Aloia 2005 18
Steffensen 2011 5
Nieves 2012 27
Reid 2017 44
Year 2 Test for heterogeneity: I² = 0%, P=0.70 0.45 [0.15, 0.74]
Aloia 2005 49
Zhu 2008b 3
Aloia 2017 14
Larsen 2017 34
Year 3+ Test for heterogeneity: I² = 15%, P=0.30 0.27 [-0.09, 0.62]
Test for heterogeneity between subgroups: P=0.60
All studies (final timepoint), n=29, N=4642 0.34 [0.13, 0.55]
Test for heterogeneity: I² = 57%, P<0.01 P=0.002
-4 -3 -2 -1 0 1 2 3 4
Favours decreased BMD with vitamin D
Favours increased BMD with vitamin D

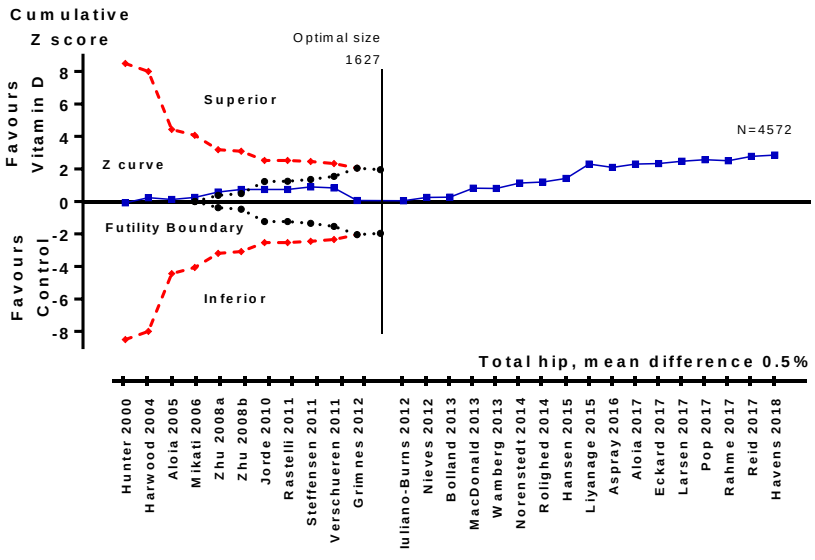
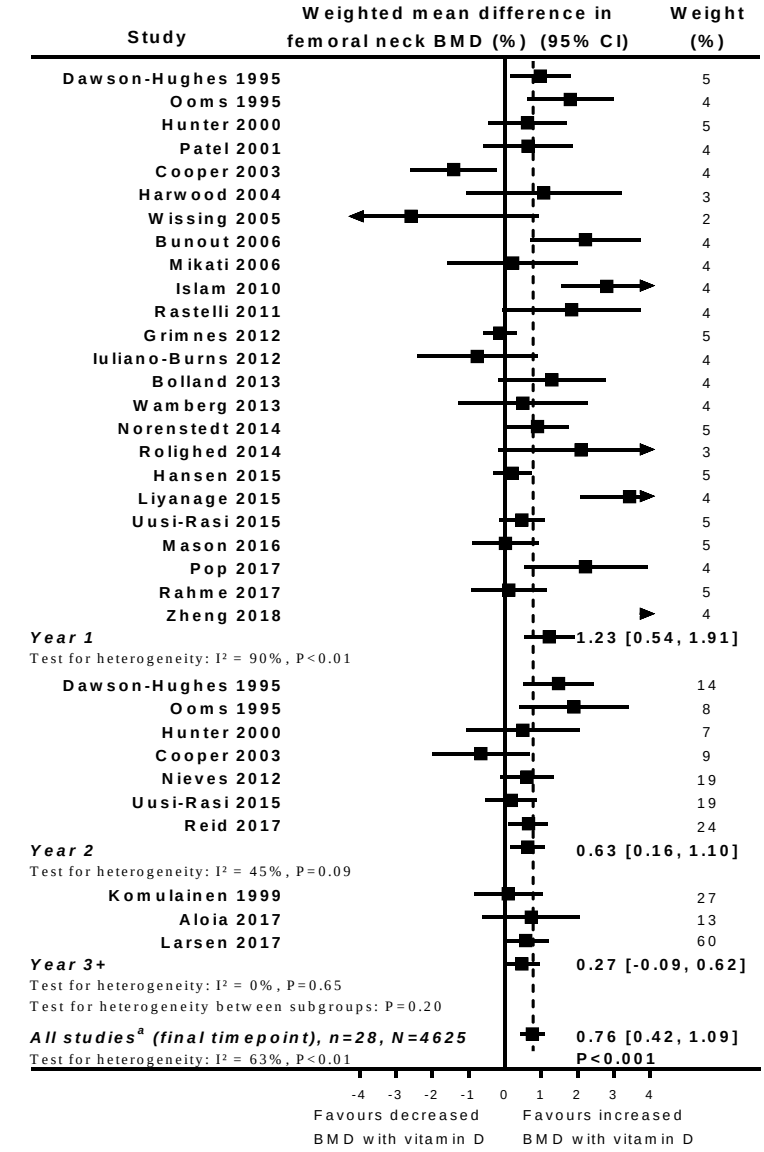

Cumulative Z score
Optimal size 1627
Favours Vitamin D
Favours Control
Superior
Z curve
Futility Boundary
Inferior
N=4572
8 6 4 2 0 -2 -4 -6 -8
Total hip, mean difference 0.5%
Hunter 2000
Harwood 2004
Aloia 2005
Mikati 2006
Zhu 2008a
Zhu 2008b
Jorde 2010
Rastelli 2011
Steffensen 2011
Verschueren 2011
Grimnes 2012
Iuliano-Burns 2012
Nieves 2012
Bolland 2013
MacDonald 2013
Wamberg 2013
Norenstedt 2014
Rolighed 2014
Hansen 2015
Liyanage 2015
Aspray 2016
Aloia 2017
Eckard 2017
Larsen 2017
Pop 2017
Rahme 2017
Reid 2017
Havens 2018

Figure 5: The top panel shows random effects meta-analyses of vitamin D supplementation on total hip bone mineral density (BMD) by trial duration and the pooled analysis of all trials using the final time point. The bottom panel shows trial sequential analysis of all trials of vitamin D on total hip BMD for a mean difference of 0.5% (see Figure 1 for detailed description).


Study
Weighted mean difference in femoral neck BMD (%) (95% CI)
Weight (%)
Dawson-Hughes 1995 5
Ooms 1995 4
Hunter 2000 5
Patel 2001 4
Cooper 2003 4
Harwood 2004 3
Wissing 2005 2
Bunout 2006 4
Mikati 2006 4
Islam 2010 4
Rastelli 2011 4
Grimnes 2012 5
Iuliano-Burns 2012 4
Bolland 2013 4
Wamberg 2013 4
Norenstedt 2014 5
Rolighed 2014 3
Hansen 2015 5
Liyanage 2015 4
Uusi-Rasi 2015 5
Mason 2016 5
Pop 2017 4
Rahme 2017 5
Zheng 2018 4
Year 1 1.23 [0.54, 1.91]
Test for heterogeneity: I² = 90%, P<0.01
Dawson-Hughes 1995 14
Ooms 1995 8
Hunter 2000 7
Cooper 2003 9
Nieves 2012 19
Uusi-Rasi 2015 19
Reid 2017 24
Year 2 0.63 [0.16, 1.10]
Test for heterogeneity: I² = 45%, P=0.09
Komulainen 1999 27
Aloia 2017 13
Larsen 2017 60
Year 3+ 0.27 [-0.09, 0.62]
Test for heterogeneity: I² = 0%, P=0.65
Test for heterogeneity between subgroups: P=0.20
All studies[a] (final timepoint), n=28, N=4625 0.76 [0.42, 1.09]
Test for heterogeneity: I² = 63%, P<0.01 P<0.001
-4 -3 -2 -1 0 1 2 3 4
Favours decreased BMD with vitamin D
Favours increased BMD with vitamin D

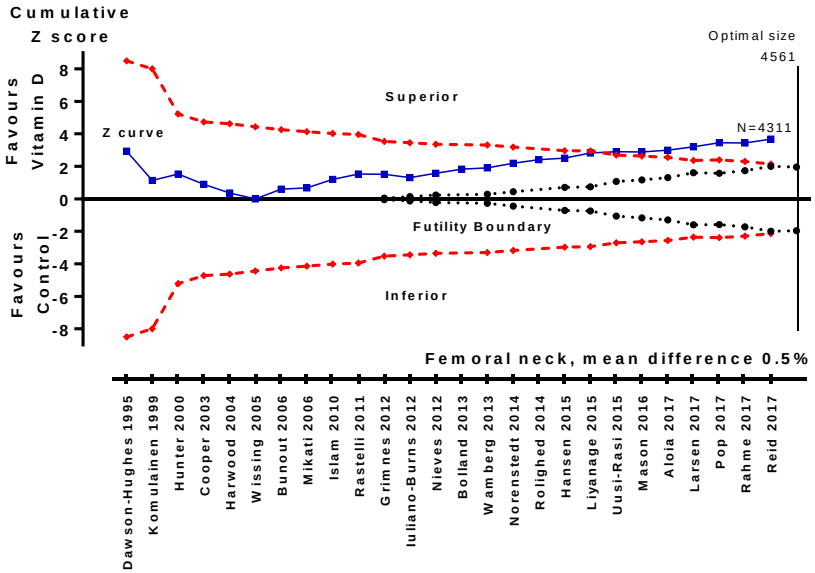

Cumulative Z score
Optimal size 4561
Favours Vitamin D
Favours Control
Superior
Z curve
N=4311
Futility Boundary
Inferior
8 6 4 2 0 -2 -4 -6 -8
Femoral neck, mean difference 0.5%
Dawson-Hughes 1995
Komulainen 1999
Hunter 2000
Cooper 2003
Harwood 2004
Wissing 2005
Bunout 2006
Mikati 2006
Islam 2010
Rastelli 2011
Grimnes 2012
Iuliano-Burns 2012
Nieves 2012
Bolland 2013
Wamberg 2013
Norenstedt 2014
Rolighed 2014
Hansen 2015
Liyanage 2015
Uusi-Rasi 2015
Mason 2016
Aloia 2017
Larsen 2017
Pop 2017
Rahme 2017
Reid 2017

Figure 6: The top panel shows random effects meta-analyses of vitamin D supplementation on femoral neck bone mineral density (BMD) by trial duration and the pooled analysis of all trials using the final time point. One study (Zheng 2018) has clearly outlying results – difference 10.6% (95%CI 9.0-12.3). Excluding this trial, reduces the effect size at 1y to 0.81% (0.37-1.25). Because of its disproportionate effect, this result was excluded from further analyses. The bottom panel shows trial sequential analysis of all trials of vitamin D on femoral neck BMD for a mean difference of 0.5% (see Figure 1 for detailed description).

Appendix:

e1. Table: Literature Searches

Database	Search Terms	Citations
December 2015		
Pubmed	Vitamin D with clinical trials filter	4018
Pubmed	Within title: (“Vitamin D” or “cholecalciferol” or “colecalciferol” or “ergocalciferol” or “calciferol”) and (random* or “trial”)	631
Pubmed	Vitamin D, publication date after 1/1/2015	634
Pubmed	Systematic reviews or Meta-analyses of randomized controlled trials of vitamin D with clinical endpoints	38
September 2017		
Pubmed	vitamin D AND (falls or fracture or ("bone density") or ("bone mineral") or ("bone mass")); June 2015- on	1575
Embase	1. vitamin D/	64209
	2. falling/	33692
	3. fracture/	80482
	4. bone density.mp. or bone density/	82944
	5. bone mineral.mp. or bone mineral/	63614
	6. bone mass.mp. or bone mass/	32201
	7. 4 or 5 or 6	111659
	8. 2 or 3 or 7	206968
	9. 1 and 8	14680
	10. limit 9 to yr="2015 -Current"	2555
Cochrane	#1 "vitamin D" Publication Year from 2015 to 2017 (Word variations have been searched)	1776
	#2 "falls" or "fracture" or "bone mineral" or "bone density" or "bone mass" Publication Year from 2015 to 2017 (Word variations have been searched)	5945
	#3 #1 and #2	420
February 2018		
Pubmed	vitamin D AND (falls or fracture or ("bone density") or ("bone mineral") or ("bone mass")) June 2017- on	476
Embase	1. vitamin D/	65390
	2. falling/	34199
	3. fracture/	81571
	4. bone density.mp. or bone density/	84341
	5. bone mineral.mp. or bone mineral/	64576
	6. bone mass.mp. or bone mass/	32585
	7. 4 or 5 or 6	113405
	8. 2 or 3 or 7	210079
	9. 1 and 8	14871
	10. limit 9 to yr="2017 -Current"	853
Cochrane	#1 "vitamin D" Publication Year from 2017 to 2018 (Word variations have been searched)	643
	#2 "falls" or "fracture" or "bone mineral" or "bone density" or "bone mass" Publication Year from 2017 to 2018 (Word variations have been searched)	2742
	#3 #1 and #2	137
Clinical trials. gov	24 new potentially relevant trials- 20 ongoing/recently completed; 4 new citations	4
WHO portal	5 new potentially relevant trials- 2 ongoing/recently completed; 3 new citations	3

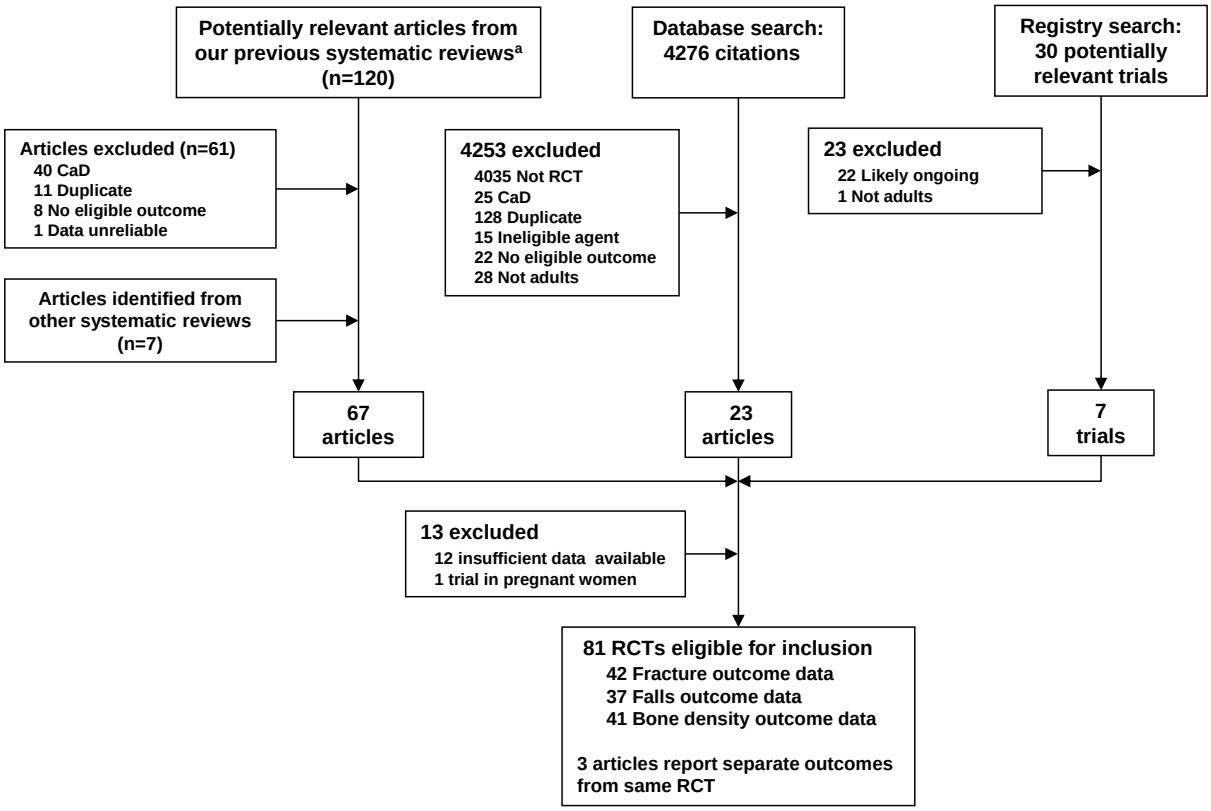
e2. Table: Ineligible potentially relevant randomised controlled trials

Reference	Reason for exclusion	Outcome
RCTs included in previous meta-analyses		
Christiansen 1980[114]	BMD not measured with DXA	BMD
Mobarhan 1984[115]	BMD not measured with DXA	BMD
Chapuy 1992[116,117]	Co-adminstered calcium and vitamin D vs placebo	Falls/Fracture/BMD
Vogelsang 1995[118]	BMD not measured with DXA	BMD
Dawson-Hughes 1997[119]	Co-adminstered calcium and vitamin D vs placebo	Fracture/BMD
Baeksgaard 1998[120]	Co-adminstered calcium and vitamin D vs placebo	BMD
Tuppurainen 1998[121]	Co-adminstered calcium and vitamin D vs placebo	BMD
Krieg 1999[122]	Co-adminstered calcium and vitamin D vs placebo	Fracture
Peichl 1999[123]	Other co-interventions in treatment but not controls	Falls
Harwood 2004[44]	Co-adminstered calcium and vitamin D vs placebo arms excluded	Fracture/Falls/BMD
Larsen 2004[124]	Co-adminstered calcium and vitamin D vs placebo	Fracture
Meier 2004[125]	Co-adminstered calcium and vitamin D vs placebo	BMD
Larsen 2005[126]	Co-adminstered calcium and vitamin D vs placebo	Falls
Porthouse 2005[127]	Co-adminstered calcium and vitamin D vs placebo	Falls/Fracture
Sato 2005[128]	Retracted	Falls/Fracture
Arden 2006[129]	Duplicate data	Falls
Bischoff-Ferrari 2006[130]	Co-adminstered calcium and vitamin D vs placebo	Falls
Jackson 2006[20]	Co-adminstered calcium and vitamin D vs placebo	Fracture/BMD
Bolton-Smith 2007[131]	Co-adminstered calcium and vitamin D vs placebo	Fracture
Berggren 2008[132]	Other co-interventions in treatment but not controls	Falls
Grieger 2009[133]	Other co-interventions in treatment but not controls	Falls
Pfeifer 2009[134]	Data inaccuracy	Falls/Fracture
Viljakainen 2009[135]	BMD not measured with DXA	
Salovaara 2010[136]	Co-adminstered calcium and vitamin D vs placebo	BMD/Fracture/Falls
Karkkainen 2010[137]	Co-adminstered calcium and vitamin D vs placebo	BMD/Fracture/Falls
Other RCTs excluded on full text review		
Takizawa 1980[138]	BMD not measured with DXA	BMD
Tjellesen 1983[139]	BMD not measured with DXA	BMD
Imaoka 2016[140]	Other co-interventions in treatment but not controls	Falls
Hin 2017[97]	BMD not measured with DXA	BMD
Mager 2017[141]	No post-baseline BMD measurement	BMD
Kruger 2017[142]	Other co-interventions in treatment but not controls	BMD
Wei 2017[143]	Pregnancy	BMD
Potential relevant RCTs but unable to obtain sufficient data		
Venkatachalam 2003[144]	Author unable to provide further data	BMD
Lappe 2007[145]	Author and co-authors didn't respond to emails	BMD/Fractures
Mieczkowski 2014[146]	Author didn't respond to emails	BMD
Maity 2015[147]	Author didn't respond to emails	BMD
Peppone 2017[148]	Author unable to provide further data	BMD
Tan 2017[149]	Author didn't respond to emails	BMD
Vos 2017[150]	Author unable to provide further data	BMD
Trials reporting falls data without complete fracture data		
Bischoff 2003[38]	Author didn't respond to emails	Falls
Latham 2003[40]	Author didn't respond to emails	Falls
Dhesi 2004[43]	Fracture data not gathered	Falls
Broe 2007[52]	Fracture data not gathered	Falls
Rizzoli 2014[82]	Fracture data not gathered	Falls
Houston 2015[87]	Fracture data not gathered	Falls
Bischoff-Ferrari 2016[15]	Author didn't respond to emails	Falls
Jin 2016[91]	Fracture data not gathered	Falls
Trials identified from registries		
Enishi	Authors replied, final data not available yet	JPRN-UMIN000008361
Wang	Authors replied, final data not available yet	ChiCTR-PRC-09000518

Hillier	Author didn't respond to emails	NCT01119131
Elliot	Author didn't respond to emails	NCT00204919
Vestergaard	Authors replied, final data not available yet	NCT01932931

Abbreviations: RCT- randomised controlled trial, BMD- bone mineral density, DXA- dual energy x-ray absorptiometry,

e3. Figure: study flow



[a] Previous systematic reviews[3,6,8,9,16,17]

Abbreviations: RCT- randomised controlled trial, CaD- co-administered calcium and vitamin D

e4. Table: Study design and selected baseline characteristics of included trials.

	Participants (Vit D/ Control)[a]	Age (y)	Gender (% F)	Duration	Treatment groups	Vit D Dose	Primary Endpoint	Secondary Endpoint
Dawson-Hughes 1991[27]	139/137	62	100	12m	CaD, Ca+Placebo	400IU/d	Bone density	
Dawson-Hughes 1995[28]	131/130	64	100	2y	CaD	100 or 700IU/d	Bone density	
Ooms 1995[29]	177/171	80	100	2y	Vit D, Placebo	400IU/d	Fracture	Bone density
Graafmans 1996[30]	177/177	83	85	28w	Vit D, Placebo	400IU/d	Fracture	Falls
Lips 1996[31]	1291/1287	80	74	4y	Vit D, Placebo	400IU/d	Fracture	Falls
Komulainen 1998/1999[32,33]	232/232	53	100	5y	2*2 factorial: Vit D, HRT, Placebo	300IU/d for 4y then 100IU/d	Bone density	Fracture
Hunter 2000[34]	79/79	59	100	2y	Vit D, Placebo	800IU/d	Bone density	
Pfeifer 2000[35]	74/74	74	100	1y	CaD, Ca	800IU/d	Body sway	Falls/Fracture
Patel 2001[36]	35/35	47	100	2y	Vit D, Placebo	800IU/d	Biochemistry	Bone density
Meyer 2002[37]	569/575	85	76	2y	Vit D, Placebo	400IU/d	Fracture	
Bischoff 2003[38]	62/60	85	100	12w	CaD, Ca	800IU/d	Falls	Fracture
Cooper 2003[39]	93/94	56	100	2y	CaD, Ca+Placebo	10,000IU/w	Bone density	
Latham 2003[40]	121/122	79	65	6m	Vit D, Placebo	300,000IU stat	Health	Falls
Trivedi 2003[41]	1345/1341	75	24	5y	Vit D, Placebo	100,000IU/3m	Fracture	Falls
Avenell 2004[42]	70/64	77	83	46m	2*2 factorial: Vit D, Ca, Control	800IU/d	Compliance	Fracture
Dhesi 2004[43]	70/69	77	78	6m	IM Vit D, Placebo	600,000IU stat	Reaction Time	Falls
Harwood 2004[44]	38/37	81	100	12m	IM Vit D, Control	300,000IU stat	Bone density	Falls/Fracture
Aloia 2005[45]	104/104	61	100	3y	CaD, Ca+Placebo	800IU/d for 24m then 2000IU/d	Bone density	
Flicker 2005[46]	313/312	83	95	2y	CaD, Ca+Placebo	10,000IU/w then 1000IU/d	Falls	Fracture
Grant 2005[47]	2649/2643	77	85	45m	2*2 factorial: Vit D, Ca, Placebo	800IU/d	Fracture	Falls
Wissing 2005[48a]	46/44	43	43	1y	CaD, Ca	25,000 IU/m	Bone density	
Bunout 2006[49a]	48/48	77	90	9m	2*2 factorial: CaD, Exercise	400IU/d	Muscle strength	Bone density/falls
Law 2006[50a]	1762/1955	85	76	10m	Vit D, Control (cluster)	100,000IU/3m	Fracture	Falls
Mikati 2006[51a]	57/49	29	54	1y	Vit D	400 or 4000IU/d	Bone density	
Broe 2007[52]	99/25	89	73	5m	Vit D, Placebo	200, 400, 600 or 800IU/d	Biochemistry	Falls
Burleigh 2007[53]	101/104	83	59	1m	CaD, Ca	800IU/d	Falls	Fracture
Lyons 2007[54]	1725/1715	84	76	3y	Vit D, Placebo	100,000IU/4m	Fracture	
Smith 2007[55]	4727/4713	79	54	3y	IM Vit D, Placebo	300,000IU/y	Fracture	Falls
Andersen 2008[56]	117/56	37	51	1y	Vit D, Placebo	400 or 800IU/d	Bone density	
Prince/Zhu 2008a[57,58]	151/151	77	100	1y	CaD, Ca+Placebo	1000IU/d	Falls	Fracture/Bone density
Zhu 2008b[59]	39/40	75	100	5y	CaD, Ca	1000IU/d	Bone density	

Bischoff-Ferrari 2010[14a]	86/87	84	79	12m	2*2 factorial: Vit D, Physiotherapy	800, or 2000IU/d	Falls	Fracture
Islam 2010[60]	50/50	23	100	12m	Vit D, Placebo	400IU/d	Bone density	
Jorde 2010[61]	279/142	47	63	1y	CaD, Ca+Placebo	20,000 or 40,000IU/w	Biochemistry	Bone density
Janssen 2010[62a]	36/34	81	100	6m	CaD, Ca+Placebo	400IU/d	Muscle strength	Fracture
Sanders 2010[13]	1131/1125	76	100	3-5y	Vit D, Placebo	500,000IU/y	Fracture	Falls
Witham 2010[63a]	53/52	80	34	20w	Vit D, Placebo	100,000IU/10w	6 min walk	Falls/Fracture
Mitri 2011[64a]	46/46	57	51	16w	2*2 factorial: Vit D, Ca, Placebo	2000IU/d	Biochemistry	Fracture
Papaioannou 2011[65a]	44/21	78	55	3m	Vit D, Placebo	50,000 or 100,000IU stat	Biochemistry	Fracture
Rastelli 2011[66]	30/30	62	100	6m	CaD, CaD+Placebo	50,000IU/w for 8-16wk then 50,000IU/m	Pain	Bone density
Steffensen 2011[67]	35/36	40	71	96w	CaD, Ca+Placebo	20,000IU/w	Bone density	Fractures
Verschueren 2011[68]	56/57	80	100	6m	2*2 factorial: Vit D, Exercise	880 or 1600IU/d	Muscle strength	Bone density
Glendenning 2012[69]	353/333	77	100	9m	Vit D, Placebo	150,000IU/3m	Falls	Fracture
Grimnes 2012[70]	149/148	63	100	1y	CaD, CaD+Placebo	20,000IU twice/w	Bone density	
Nieves 2012[71]	64/63	62	100	2y	CaD, Ca+Placebo	1000IU/d	Bone density	
Iuliano-Burns 2012[72a]	75/35	41	17	12m	Vit D	50,000IU /m or /2m	Biochemistry	Bone density
Bolland 2013[73a]	13/14	57	70	1y	Vit D, Placebo	50,000IU/m	Biochemistry	Bone density
MacDonald 2013/Wood 2014[74,75a]	203/102	65	100	12m	Vit D, Placebo	400 or 1000 IU/d	Bone density	Falls/Fractures
Punthakee 2013[76a]	607/614	67	41	6m	3*2 factorial: Vit D, Pioglitazone, Rosiglitazone, Placebo	1000IU/d	Death or cancer	Fracture
Wamberg 2013[77a]	26/26	40	71	6m	Vit D, Placebo	7000IU/d	Biochemistry	Bone density
Witham 2013[78a]	80/79	77	48	12m	Vit D, Placebo	100,000IU/3m	Blood pressure	Falls
Breslavsky 2014[79a]	24/23	66	53	12m	Vit D, Placebo	1000 IU/d	Biochemistry	Fractures
Massart 2014[80a]	26/29	64	38	13w	Vit D, Placebo	25,000IU/w	Biochemistry	Fracture
Norenstedt 2014[81a]	75/75	60	79	1y	CaD, Ca	1600IU/d	Biochemistry	Bone density
Rizzoli 2014[82a]	413/105	67	91	6m	Vit D, control	1000IU/d	25OHD	Falls
Rolighed 2014[83a]	23/23	59	76	1y	Vit D, Placebo	2800IU/d	Biochemistry	Bone density
Baron 2015[84a]	1130/1129	58	37	3-5y	2*2 factorial: Vit D, Ca, Placebo	1000IU/d	Colorectal adenoma	Fracture
Cangussu 2015[85a]	80/80	59	100	9m	Vit D, Placebo	1000IU/d	Falls	
Hansen 2015[86a]	154/76	61	100	12m	Vit D, Placebo	800 IU/d or 50,000 IU/d for 15d then 50,000 IU/2w	Calcium absorption	Bone density/Falls/Fracture
Houston 2015[87a]	38/30	78	72	5m	Vit D, Placebo (cluster)	100,000IU/ m	Adherence	Falls
Liyanage 2015[88a]	42/43	58	55	6m	IM Vit D, Placebo	50,000IU/m	Biochemistry	Bone density
Uusi-Rasi 2015[89a]	204/205	74	100	2y	2*2 factorial: Vit D, Exercise	800 IU/d	Falls	Bone density
Aspray 2016[90a]	253/126	75	48	12m	Vit D	12,000, 24,000 or 48,000IU/m	Bone density	Falls
Bischoff-Ferrari 2016[15a]	67/67	78	67	12m	Vit D	24,000 or 60,000IU/m	Physical performance	Falls

Jin 2016[91a]	209/204	63	50	24m	Vit D, Placebo	50,000 IU/m	Cartilage volume	Falls
Mak 2016[92a]	111/107	84	77	4w	Vit D, Placebo	250,000IU stat	Gait velocity	Falls/Fractures
Mason 2016[93a]	109/109	60	100	12m	Vit D, Placebo	2000IU/d	Weight loss	Bone density
Aloia 2017[94a]	130/130	68	100	3y	CaD, Ca+Placebo	Vit D to keep 25OHD > 75nmol/L	Bone density	Falls
Eckard 2017[95a]	66/36	20	36	12m	Vit D	18,000, 60,000 or 120,000IU/m	Bone density	
Ginde 2017[96a]	55/52	81	58	12m	Vit D	12,000 or 100,000IU/m	Acute respiratory infection	Falls/Fractures
Hin 2017[97a]	204/101	72	49	12m	Vit D, Placebo	2000 or 4000IU	25OHD	Falls/Fracture
Khaw 2017[98,103a]	2558/2552	65.9	42	3.4y	Vit D, Placebo	200,000IU stat then 100,000IU/m	Cardiovascular disease	Falls/Fractures
Larsen 2017[99a]	256/255	62	39	5y	Vit D, Placebo	20,000IU/w	Incidence of diabetes	Bone density/Fractures
Levis 2017[100a]	66/64	72	0	9m	Vit D, Placebo	4000IU/d	Physical performance	Falls
Pop 2017[101a]	57/24	58	100	1y	CaD, CaD+placebo, CaD+placebo	10,000 or 25,000IU/w	Bone density	
Rahme 2017[102a]	129/128	71	55	1y	CaD, CaD+Placebo	10,000IU/w	Bone density	
Reid 2017[98,103a]	228/224	69	37	2y	Vit D, Placebo	200,000IU then 100,000IU/m	Cardiovascular disease	Bone density
Schwetz 2017[104a]	249/243	65	35	6m	Vit D, Placebo	540,000IU stat then 90,000IU/m	Hospital stay	Falls/Fractures/Bone density
Smith 2017[105a]	235/38	66	100	12m	Vit D, Placebo	400, 800, 1600, 2400, 3200, 4000, or 4800IU/d	25OHD	Falls/Fractures
Havens 2018[106a]	109/105	22	16	48w	CaD, CaD+placebo	50,000IU/q4w	Bone density	
Zheng 2018[107a]	30/30	66	45	24w	Vit D, Placebo	5000IU/d	Biochemistry	Bone density

[a] Trial not included in our previous systematic reviews[3,6,9]

Abbreviations: Vit D- vitamin D; CaD- co-administered calcium and vitamin D; Ca- calcium; HRT- hormone replacement therapy; IM-intramuscular; 25OHD- 25 hydroxyvitamin D

e5. Table: Further selected baseline characteristics of included trials.

	Country	Population	Residental status	BMI (or Weight) (kg/m^2)	Additional agent in both groups	Baseline 25OHD (nmol/L)	Achieved 25OHD (nmol/L)	Assay
Dawson-Hughes 1991	USA	White, postmenopausal	Community	68kg	Ca 380 mg/d	NS	95/71 (All)	CBP
Dawson-Hughes 1995	USA	White, postmenopausal	Community	26	Ca 500 mg/d	NS	100/66 (All)	CBP
Ooms 1995	Netherlands	Residential care , > 70y	Institution	28		26/27 (All)	62/23 (All)	HPLC
Graafmans 1996	Netherlands	Residential care, substudy of Lips	Institution	NS		NS	NS	
Lips 1996	Netherlands	>70y	Institution	NS		26/27 (270)	54/23 (96)	HPLC
Komulainen 1998/1999	Finland	Postmenopausal	Community	26	Ca 93 mg/d in Vit D/Placebo groups	26/29 (35/34)	35/26 (35/34)	HPLC
Hunter 2000	UK	Twins	Community	24		71/70 (All)	105/80 (All)	Incstar
Pfeifer 2000	Germany	>70y	Community	25	Ca 1.2 g/d	26/25 (All)	66/43 (All)	Nichols RIA
Patel 2001	UK	Healthy Females	Community	25		68/76 (All)	+25 (All)	Incstar
Meyer 2002	Norway	Residential care	Institution	22		47/51 (31/34)	64/46 (31/34)	HPLC
Bischoff 2003	Switzerland	Residential care	Institution	25	Ca 1.2 g/d	31/29 (All)	66/29 (All)	Nichols RIA
Cooper 2003	Australia	Postmenopausal	Community	67kg	Ca 1g/d	82/83 (All)	81/70 (All)	Incstar
Latham 2003	NZ	Frail and in hospital	Community	25	Exercise	38/48 (All)	60/48 (All)	Diasorin RIA
Trivedi 2003	UK	Mainly UK doctors	Community	24		NS	74/53 (124/114)	NS
Avenell 2004	UK	Previous fracture	Community	NS	Ca 1g/d in 2 groups	NS	NS	
Dhesi 2004	UK	Falls clinic	Community	27		27/25 (All)	44/32	IDS
Harwood 2004	UK	Recent hip fracture	Community	24		28/30 (All)	40/27 (25/32)	Incstar RIA
Aloia 2005	USA	African American, postmenopausal	Community	30	Ca up to 1.2-1.5 g/d	48/43 (All)	71/NS (All)	Diasorin RIA
Flicker 2005	Australia	Residential care	Institution	60kg	Ca 600 mg/d	NS	NS	
Grant 2005	UK	Previous fracture	Community	65kg	Placebo or Ca 1g/d	38 (60)	62/44 (60)	HPLC
Wissing 2005	Belgium	Renal transplant receiving steroids	Community	24	Ca up to 2g/d	61/49 (All)	67/41 (All)	Diasorin RIA
Bunout 2006	Chile	25OHD < 40	Community	29	Exercise or nil, Ca 800 mg/d	31/33 (All)	65/36 (All)	Not stated
Law 2006	UK	Residential Care	Institution	NS		59/NS (18)	99/NS (18)	IDS
Mikati 2006	Lebanon	Anticonvulsants	Community	26		34/33 (All)	66/44 (All)	Incstar
Broe 2007	US	Residential care	Institution	25		48/53 (All)	63/60 (All)	NS
Burleigh 2007	UK	Hospital ATR ward	Institution	NS	Ca 1.2 g/d	25/22 (54)	27/22 (NS)	Nichols RIA
Lyons 2007	UK	Residential care	Institution	NS		NS	80/54 (102)	Diasorin RIA
Smith 2007	UK	GP register	Community	NS		56.5 (43)	+21%/NS (NS)	Nichols RIA
Andersen 2008	Denmark	Pakistanis in Denmark	Community	27		16/16 (All)	46/15 (All)	HPLC
Prince/Zhu 2008a	Australia	Recent fall	Community	29	Ca 1 g/d	45/44 (All)	60/44 (All)	Diasorin RIA

Zhu 2008b	Australia	Postmenopausal	Community	70kg	Ca 1.2 g/d	70/67 (All)	106/64 (All)	CBP
Bischoff-Ferrari 2010	Switzerland	Post hip fracture	Community	24	Ca 1g/d, Standard/extended physiotherapy	33/31 (All)	89/112 (All)	Diasorin RIA
Islam 2010	Bangladesh	Factory workers	Community	22		37/35 (All)	69/36 (All)	IDS
Jorde 2010	Norway	Overweight	Community	35	Ca 500 mg/d	59/60 (All)	122/56 (All)	Diasorin RIA
Janssen 2010	Netherlands	>65y	Institution	26	Ca 500 mg/d	33/34 (All)	77/42 (All)	NS
Sanders 2010	Australia	>70y	Community	NS		53/45 (74/57)	55-74/~40-50 (16-57/20-49)	Diasorin RIA
Witham 2010	UK	CHF, >70y, 25OHD <50 nmol/L	Community	27		21/24 (All)	41/25 (All)	RIA
Mitri 2011	USA	Glucose intolerance/diabetes	Community	32	Placebo or 800 mg/d	61/62 (All)	77/46 (All)	HPLC
Papaioannou 2011	Canada	Post hip fracture	Community	69kg	Vit D 1000IU/d	48/47 (27/18)	79/87 (All)	Diasorin
Rastelli 2011	USA	Past breast cancer using anastrozole	Community	32	Ca 1g/d, vit D 400IU/d	58/55 (All)	74/64 (All)	Diasorin Liaison
Steffensen 2011	Norway	Multiple sclerosis	Community	26	Ca 500 mg/d	56/57 (All)	123/62 (All)	LCMS/MS
Verschueren 2011	Belgium	Residential care , > 70y	Institution	27	Vibration or nil, Calcium 1 g/d	55/52 (All)	157/138 (All)	Diasorin RIA
Glendenning 2012	Australia	>70y	Community	27		65/67 (20/20)	75/60 (20/20)	Liaison
Grimnes 2012	Norway	Low BMD	Community	25	Ca 1g/d, vit D 800IU/d	71/71 (All)	186/90 (All)	LCMS/MS
Nieves 2012	USA	African American, Postmenopausal	Community	31	Ca to 1 g/d total intake	29/29 (All)	55/32 (All)	Diasorin RIA
Iuliano-Burns 2012	Australia	Antarctic explorers	Community	85kg		58/63 (All)	66/54 (All)	Roche
Bolland 2013	New Zealand	Sarcoidosis	Community	27		40/45 (All)	79/47 (All)	LCMS/MS
MacDonald 2013/Wood 2014	UK	Postmenopausal, white	Community	25		33/36 (All)	70/32 (All)	LCMS/MS
Punthakee 2013	Multinational	Diabetes Mellitus	Community	31	Pioglitazone, rosiglitazone, or placebo	NS	NS	
Wamberg 2013	Denmark	Obese	Community	36		35/35 (All)	110/47 (All)	LCMS/MS
Witham 2013	UK	Systolic hypertension	Community	28		45/45 (All)	67/48 (All)	IDS
Breslavsky 2014	Israel	Diabetes Mellitus	Community	29		27/34 (All)	42/35 (All)	NS
Massart 2014	Belgium	Haemodialysis	Community	27		46/43 (All)	88/41 (All)	Liaison
Norenstedt 2014	Sweden	Post parathyroidectomy	Community	26	Ca 1 g/d	40/45 (All)	73/51 (All)	Diasorin Liaison
Rizzoli 2014	13 countries	Osteoporosis	Community	25	Strontium 2 g/d, Calcium 1 g/d	44/44 (All)	67/45 (All)	Diasorin RIA
Rolighed 2014	Denmark	Pre/Post parathyroidectomy	Community	81kg		50/57 (All)	105/63 (All)	LCMS/MS
Baron 2015	USA	Recent colorectal adenoma removed	Community	29	Placebo or Ca 1.2 g/d	61/61 (All)	81/NS (All)	IDS
Cangussu 2015	Brazil	Recent fall	Community	30		38/42 (All)	69/35 (All)	HPLC
Hansen 2015	USA	25OHD 35-68 nmol/L, no osteoporosis	Community	31		53/53 (All)	86/45 (All)	HPLC
Houston 2015	USA	Meals on Wheels programme	Community	NS		56/47 (All)	106/56 (All)	Liaison
Liyanage 2015	Sri Lanka	Diabetic nephropathy	Community	24		56/50 (All)	82/46 (All)	Vitros

Uusi-Rasi 2015	Finland	Recent fall	Community	28		63/69 (All)	93/69 (All)	IDS
Aspray 2016	UK	Older men and women	Community	27		41/43 (All)	80/61 (All)	LCMS/MS
Bischoff-Ferrari 2016	Switzerland	Recent fall	Community	26		47/52 (All)	100/76 (All)	LCMS/MS
Jin 2016	Australia	Osteoarthritis	Community	30		44/44 (All)	84/51 (All)	Liaison
Mak 2016	Australia	Hip fracture surgery	83% Community	25	Ca 500 mg/d, Vit D 800IU/d	56/50 (All)	80/72 (All)	Diasorin
Mason 2016	US	Overweight undertaking weight loss	Community	32	Weight loss programme	54/54 (All)	88/50 (All)	Diasorin Liaison
Aloia 2017	US	African American	Community	NS	Ca to 1 g/d total intake	NS/NS	94/52 (All)	NS
Eckard 2017	US	HIV	Community	23		45/43 (All)	87/74 (All)	IDS or ADVIA
Ginde 2017	USA	Residential Care	Institution	27		58/58 (All)	77/65 (All)	LCMS/MS
Hin 2017	UK	>65y	Community	27		52/47 (All)	120/53 (All)	Access 2
Khaw 2017	New Zealand	50-84y	Community	28		64/63 (All)	135/66 (171/163)	LCMS/MS
Larsen 2017	Norway	Prediabetes	Community	30		60/62 (All)	122/67 (All)	LCMS/MS
Levis 2017	USA	65-90y	Community	31		58/57 (All)	115/60 (All)	LCMS/MS
Pop 2017	US	BMI>25	Community	30	Vit D to 600IU/d, Ca to 1.2 g/d total intake, Weight loss programme	69/67 (39/19)	96/76 (39/19)	Diasorin RIA
Rahme 2017	Lebanon	BMI>25	Community	30	Ca 1 g/d, Vit D 500IU/d	52/50 (All)	90/65 (All)	LCMS/MS
Reid 2017	New Zealand	Substudy of Khaw	Community	82kg		55/56 (All)	129/60 (All)	LCMS/MS
Schwetz 2017	Austria	ICU	Community	28		33/33 (All)	115/66 (37/43)	IDS
Smith 2017	USA	25OHD 13-50 nmol/L	Community	31		36/36 (All)	NS	Diasorin
Havens 2018	US	HIV taking tenofovir	Community	24	Multivit (400IU/d vit D, Ca 162 mg/d)	39/42 (All)	92/52 (All)	IDS
Zheng 2018	Taiwan	Secondary HPT on Haemodialysis	Community	22	Cinacalcet, Calcitriol	46/48 (All)	94/59 (All)	Immundiagnostik

BMI- body mass index; 25OHD- 25 hydroxyvitamin D; CHF- congestive heart failure; ICU- intensive care unit; HPT- hyperparathyroidism; NS- not stated; Ca- calcium; Vit D- vitamin D; CBP- competitive binding protein; HPLC- high performance liquid chromatography; RIA- radioimmunoassay; LSMS/MS- liquid chromatography tandem mass spectometry

e6. Table: Assessment of risk of bias in included trials

	Random sequence generation described	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessment	Incomplete outcome data	Differential loss to follow-up	Selective reporting	Definition of falls	Duration of recall of falls (risk of bias)	Overall assessment of risk of bias falls	Overall assessment of risk of bias fracture	Overall assessment of risk of bias bone density
Dawson-Hughes 1991	Not stated	Not stated	Double-blind	Yes	Yes	No	No					Moderate
Dawson-Hughes 1995	Not stated	Not stated	Double-blind	Yes	Yes	No	No					Moderate
Ooms 1995	Yes	Yes	Double-blind	Yes	Yes	No	No					Low
Graafmans 1996	Yes	Yes	Double-blind	Yes	Yes	Not stated	No	Yes	1w (Low)	Moderate		
Lips 1996	Yes	Yes	Double-blind	Yes	No	No	No				Low	
Komulainen 1998/1999	Yes	Yes	No	No	No	No	No				Moderate	Moderate
Hunter 2000	Yes	Yes	Double-blind	Yes	Yes	No	No					Moderate
Pfeifer 2000	Not stated	Not stated	Double-blind	Yes	No	No	No	Yes	Not stated	Moderate	Moderate	
Patel 2001	Not stated	Not stated	Double-blind	Yes	No	No	No					Moderate
Meyer 2002	Pseudo (DOB)	Yes	Double-blind	Yes	No	No	No				Low	
Bischoff 2003	Not stated	Yes	Double-blind	Yes	Yes	No	No	Yes	Daily (Low)	Moderate	Moderate	
Cooper 2003	Not stated	Not stated	Double-blind	Yes	No	No	No					Low
Latham 2003	Yes	Yes	Double-blind	Yes	No	No	No	No	Daily (Low)	Low		
Trivedi 2003	Yes	Yes	Double-blind	Yes	No	No	No	No	12m (High)	Moderate	Low	
Avenell 2004	Yes	Not stated	No	Yes	No	Yes	No				High	
Dhesi 2004	Yes	Not stated	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Moderate		
Harwood 2004	Yes	Yes	No	No	No	Yes	No	No	3-6m (High)	High	High	High
Aloia 2005	Yes	Not stated	Double-blind	Yes	No	No	No					Low
Flicker 2005	Yes	Yes	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low	Low	
Grant 2005	Yes	Yes	Double-blind	Yes	No	No	No	No	1w (Low)	Moderate	Low	
Wissing 2005	Pseudo	No	Not stated	Not stated	Yes	Yes	No					High
Bunout 2006	Yes	Yes	Double-blind	Yes	No	No	No	No	1m (Low)	Low		Low
Law 2006	Yes	Not stated	No	Yes	No	No	No	No	NS	Moderate	Moderate	
Mikati 2006	Pseudo	No	Open-label	Yes	Yes	Yes	No					High
Broe 2007	Yes	Yes	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low		
Burleigh 2007	Yes	Yes	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low	Moderate	
Lyons 2007	Yes	Yes	Double-blind	Yes	No	No	No				Low	
Smith 2007	Not stated	Yes	Double-blind	Yes	No	No	No	No	6m (High)	Moderate	Low	
Andersen 2008	Yes	Yes	Double-blind	Yes	No	No	No					Low
Prince/Zhu 2008a	Yes	Yes	Double-blind	Yes	No	No	No	Yes	6w (Mod)	Low	Moderate	Low

Zhu 2008b	Yes	Yes	Double-blind	Yes	No	No	No					Low
Bischoff-Ferrari 2010	Yes	Not stated	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low	Moderate	
Islam 2010	Not stated	Yes	Double-blind	Yes	No	Yes	No					Low
Jorde 2010	Not stated	Not stated	Double-blind	Yes	No	No	No					Low
Janssen 2010	Not stated	Yes	Double-blind	Yes	No	No	No				High	
Sanders 2010	Yes	Yes	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low	Low	
Witham 2010	Yes	Yes	Double-blind	Yes	No	No	No	No	10w (Mod)	Moderate	Moderate	
Mitri 2011	Yes	Yes	Double-blind	Yes	No	No	No				Moderate	
Papaioannou 2011	Yes	Yes	Double-blind	Yes	No	No	No				High	
Rastelli 2011	Yes	Yes	Double-blind	Yes	No	No	No					Low
Steffensen 2011	Yes	Yes	Double-blind	Yes	No	No	No				High	Low
Verschueren 2011	Yes	Yes	Not stated	Yes	No	No	No					Low
Glendenning 2012	Yes	Yes	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low	Moderate	
Grimnes 2012	Yes	Yes	Double-blind	Yes	No	No	No					Low
Nieves 2012	Not stated	Not stated	Double-blind	Yes	No	Yes	No					Low
Iuliano-Burns 2012	Not stated	Not stated	Double-blind	Yes	No	No	No					Low
Bolland 2013	Yes	Yes	Double-blind	Yes	No	No	No					Moderate
MacDonald 2013/Wood 2014	Yes	Yes	Double-blind	Yes	No	No	No	No	2m (Mod)	Low	Moderate	Low
Punthakee 2013	Yes	Yes	Double-blind	Yes	No	No	No				High	
Wamberg 2013	Yes	Yes	Double-blind	Yes	No	No	No					Low
Witham 2013	Yes	Yes	Double-blind	Yes	No	No	No	No	Daily (Low)	Low	Moderate	
Breslavsky 2014	Not stated	Not stated	Not stated	Not stated	No	No	No				High	
Massart 2014	Yes	Not stated	Yes	Yes	No	No	Yes	No	Not stated	High	Moderate	
Norenstedt 2014	Not stated	Not stated	Double-blind	Yes	No	No	No					Low
Rizzoli 2014	Not stated	Yes	Double-blind	Yes	Yes	Yes	No	Yes	Daily (Low)	Moderate		
Rolighed 2014	Yes	Yes	Double-blind	Yes	No	No	No					Moderate
Baron 2015	Yes	Yes	Double-blind	Yes	No	No	No				Low	
Cangussu 2015	Yes	Yes	Double-blind	Yes	No	No	No	Yes	9m (High)	Moderate	Moderate	
Hansen 2015	Not stated	Yes	Yes	Yes	No	No	No	No	1-4m (Mod)	Low	Moderate	Low
Houston 2015	Yes	Not stated	Single	Uncertain	No	No	No	No	1m (Low)	High		
Liyanage 2015	Yes	Yes	Double-blind	Yes	No	No	No					Low
Uusi-Rasi 2015	Yes	Yes	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low	Moderate	Low
Aspray 2016	Not stated	Not stated	Double-blind	Yes	No	No	Yes					Low
Bischoff-Ferrari 2016	Yes	Yes	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low		

Jin 2016	Yes	Yes	Yes	Yes	No	Yes	No	No	NS	High		
Mak 2016	Yes	Yes	Double-blind	Yes	No	No	No	Yes	Daily (Low)	Low	Moderate	
Mason 2016	Yes	Yes	Double-blind	Yes	No	No	No					Low
Aloia 2017	Not stated	Not stated	Double-blind	Yes	No	No	No		3m (Mod)	Low		Low
Eckard 2017	Yes	Yes	Double-blind	Yes	No	No	No					Low
Ginde 2017	Yes	Yes	Double-blind	Yes	No	No	No	No	Daily (Low)	Low	Moderate	
Hin 2017	Yes	Yes	Double-blind	Yes	No	No	No	No	6m (High)	Moderate	Moderate	
Khaw 2017	Yes	Yes	Double-blind	Yes	No	No	No	Yes	1-4m (Mod)	Low	Low	
Larsen 2017	Yes	Yes	Double-blind	Yes	No	No	No				Moderate	Low
Levis 2017	Not stated	Yes	Double-blind	Yes	No	No	No	No	3m (Mod)	Moderate	Moderate	
Pop 2017	Not stated	Not stated	Double-blind	Yes	Yes	No	No					Moderate
Rahme 2017	Not stated	Yes	Double-blind	Yes	No	No	No					Low
Reid 2017	Yes	Yes	Double-blind	Yes	No	No	No					Low
Schwetz 2017	Yes	Yes	Double-blind	Yes	Yes	Yes	No	No	6m (High)	High	High	
Smith 2017	Yes	Yes	Double-blind	Yes	Yes	No	Yes	Yes	3m (Mod)	Low	Moderate	
Havens 2018	Not stated	Not stated	Double-blind	Yes	No	No	No					Low
Zheng 2018	Not stated	Not stated	Open-label	Not stated	No	No	No					Moderate

Pseudo- pseudorandomised; DOB- date of birth; Mod- moderate;

e7. Table: Reported conflicts of interest and funding sources from included trials

	Conflict of Interest statement	Conflict of Interest exists	Funding
Dawson-Hughes 1991	No	Yes	Mixed industry/ non-industry
Dawson-Hughes 1995	No	Yes	Mixed industry/ non-industry
Ooms 1995	No	Unknown	Non-industry, drugs from industry
Graafmans 1996	No	Unknown	Non industry, drugs from industry
Lips 1996	No	Unknown	Non-industry, drugs from industry
Komulainen 1998/1999	No	Yes	Mixed industry/ non-industry
Hunter 2000	No	Unknown	Non-industry
Pfeifer 2000	No	Yes	Industry funded, run, and co-authored.
Patel 2001	No	Unknown	Not stated, drugs from industry
Meyer 2002	No	Yes	Industry funded, drugs from industry
Bischoff 2003	No	Yes	Mixed industry/non-industry
Cooper 2003	Yes	No	Non-industry, drugs from industry
Latham 2003	No	Unknown	Non-industry
Trivedi 2003	Yes	No	Non-industry
Avenell 2004	No	No	Non-industry, drugs from industry
Dhesi 2004	Yes	No	Non-industry
Harwood 2004	No	Unknown	Industry
Aloia 2005	Yes	No	Non-industry
Flicker 2005	Yes	No	Non-industry
Grant 2005	Yes	No	Non-industry, drugs from industry
Wissing 2005	No	Unknown	Not stated
Bunout 2006	No	Unknown	Non-industry, drugs and equipment from industry
Law 2006	No	Unknown	Non-industry
Mikati 2006	Yes	No	Non-industry
Broe 2007	No	Unknown	Non-industry
Burleigh 2007	No	Unknown	Not stated, drugs from industry
Lyons 2007	No	Unknown	Non-industry
Smith 2007	Yes	No	Non-industry
Andersen 2008	Yes	No	Non-industry
Prince/Zhu 2008a	Yes	No	Non-industry, drugs from industry
Zhu 2008b	Yes	No	Non-industry
Bischoff-Ferrari 2010	Yes	No	Non-industry
Islam 2010	Yes	No	Non-industry, drugs from industry
Jorde 2010	Yes	No	Non-industry, drugs from industry
Janssen 2010	No	Unknown	Non-industry
Sanders 2010	Yes	No	Non-industry
Witham 2010	Yes	No	Non-industry
Mitri 2011	Yes	No	Non-industry, drugs from industry
Papaioannou 2011	Yes	Yes	Unrestricted grant from industry
Rastelli 2011	No	Yes	Industry
Steffensen 2011	Yes	No	Non-industry, drugs from industry
Verschueren 2011	Yes	No	Non-industry
Glendenning 2012	Yes	No	Non-industry
Grimnes 2012	Yes	No	Non-industry, drugs from industry
Nieves 2012	Yes	No	Non-industry
Iuliano-Burns 2012	Yes	No	Non-industry
Bolland 2013	Yes	No	Non-industry
MacDonald 2013/Wood 2014	Yes	No	Non-industry
Punthakee 2013	Yes	Yes	Industry
Wamberg 2013	Yes	No	Not stated

Witham 2013	Yes	No	Non-industry
Breslavsky 2014	Yes	No	Not stated
Massart 2014	Yes	Yes	Industry funded
Norenstedt 2014	Yes	No	Industry and non-industry funding, drugs from industry
Rizzoli 2014	Yes	Yes	Industry funded
Rolighed 2014	Yes	No	Non-industry
Baron 2015	Yes	Yes	Non-industry, drugs from industry
Cangussu 2015	Yes	No	Non-industry
Hansen 2015	Yes	Yes	Non-industry
Houston 2015	Yes	No	Non-industry
Liyanage 2015	Yes	No	Non-industry
Uusi-Rasi 2015	Yes	No	Non-industry
Aspray 2016	Yes	Yes	Not stated
Bischoff-Ferrari 2016	Yes	Yes	Mixed industry/ non-industry
Jin 2016	Yes	No	Non-industry
Mak 2016	Yes	Yes	Non-industry
Mason 2016	Yes	No	Non-industry
Aloia 2017	Yes	No	Not stated
Eckard 2017	Yes	Yes	Non-industry
Ginde 2017	Yes	No	Non-industry
Hin 2017	Yes	No	Non-industry, drugs from industry
Khaw 2017	Yes	No	Non-industry
Larsen 2017	Yes	No	Non-industry
Levis 2017	Yes	No	Non-industry
Pop 2017	Yes	No	Non-industry
Rahme 2017	Yes	No	Non-industry, drugs from industry
Reid 2017	Yes	No	Non-industry
Schwetz 2017	Yes	Yes	Industry and non-industry funding, drugs from industry
Smith 2017	Yes	No	Non-industry
Havens 2018	Yes	No	Non-industry
Zheng 2018	Yes	No	Non-industry

e8: Table Outcome data by study

Falls, hip fracture and Total fracture

		Falls				Hip fracture				Total fracture			
		Vit D or Higher dose		Controls or lower dose		Vit D or Higher dose		Controls or lower dose		Vit D or Higher dose		Controls or lower dose	
Study	**Treatment arm**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Graafmans 1996		62	177	65	177								
Lips 1996						58	1291	48	1287	135	1291	122	1287
Komulainen 1998						1	232	2	232	18	232	21	232
	Vit D vs P					1	116	2	116	11	116	15	116
	Vit D/HRT vs HRT					0	116	0	116	7	116	6	116
Pfeifer 2000		11	74	19	74	0	74	1	74	3	74	6	74
Meyer 2002						50	569	47	575	69	569	76	575
Bischoff 2003		14	62	18	60	2	62	1	60				
Latham 2003		64	121	60	122								
Trivedi 2003		254	1027	261	1011	21	1345	24	1341	119	1345	149	1341
Avenell 2004						1	70	3	64	6	70	11	64
	Vit D vs Controls					0	35	1	35	3	35	5	35
	CaD vs Ca					1	35	2	29	3	35	6	29
Dhesi 2004		11	70	14	69								
Harwood 2004		2	38	13	37	0	38	1	37	0	38	5	37
Flicker 2005		170	313	185	312					25	313	35	312
Grant 2005		380	2649	381	2643	93	2649	90	2643	387	2649	377	2643
	Vit D vs P	161	1306	185	1311	47	2649	41	2643	208	1343	192	1332
	CaD vs Ca	219	1343	196	1332	46	2649	49	2643	179	1306	185	1311
Bunout 2006		15	48	16	48								
	CaD vs Ca	6	24	11	24								
	CaD/ex vs Ca/ex	9	24	5	24								
Law 2006	Cluster-adjusted	492	1127	533	1250	18	1326	15	1471	48	1326	38	1471
	Raw data	770	1762	833	1955	24	1762	20	1955	64	1762	51	1955
Broe 2007		50	99	11	25								
Burleigh 2007		36	101	45	104	1	101	2	104	1	101	3	104
Lyons 2007						112	1725	104	1715	205	1725	218	1715
Smith 2007		2544	4727	2577	4713	66	4727	44	4713	306	4727	279	4713
Prince 2008		80	151	95	151					4	151	3	151
Bischoff-Ferrari 2010		45	86	47	87	3	86	6	87	7	86	15	87
Janssen 2010						1	36	0	34	1	36	0	34
Sanders 2010		837	1131	769	1125	19	1131	15	1125	155	1131	125	1125
Witham 2010		2	53	5	52	0	53	0	52	2	53	1	52
Mitri 2011										1	86	0	86
	Vit D vs P									1	43	0	43
	CaD vs Ca									0	43	0	43
Papaioannou 2011						0	44	1	21				
Steffensen 2011						0	30	0	30	0	30	0	30
Glendenning 2012		102	353	89	333					10	353	10	333
Grimnes 2012										6	149	6	148
Bolland 2013						0	13	0	14	0	13	0	14
MacDonald 2013		60	203	31	102	0	203	0	203	3	203	3	102
	High vs Low dose	27	101	33	102					0	101	3	102
	High vs P	27	101	31	102					0	101	3	102
	Low vs P	33	102	31	102					3	102	3	102
Punthakee 2013										3	607	3	614
Witham 2013		25	80	26	79					2	80	3	79
Breslavsky 2014						0	24	1	23	0	24	2	23
Massart 2014		0	26	5	29					0	26	5	29
Rizzoli 2014		65	413	21	105								
Baron 2015										55	1130	64	1129
Cangussu 2015		19	80	37	80	0	80	0	80	0	80	0	80
Hansen 2015		46	154	23	76					4	154	4	76
	High vs Low dose	22	79	24	75					2	79	2	75
	High vs P	22	79	23	76					2	79	4	76

	Low vs P	24	75	23	76					2	75	4	76
Houston 2015	Cluster-adjusted	11	37	12	29								
	Raw data	11	38	12	30								
Uusi-Rasi 2015		136	204	145	205	2	204	0	205	9	204	11	205
	Vit D vs P	66	102	75	102	2	102	0	102	6	102	6	102
	Vit D/ex vs P/ex	70	102	70	103	0	102	0	103	3	102	5	103
Bischoff-Ferrari 2016		45	67	32	67								
Jin 2016		2	209	0	204								
Mak 2016		7	111	23	107					3	111	3	107
Aloia 2017		51	130	50	130								
Ginde 2017		20	55	15	52					4	55	8	52
Hin 2017		34	204	14	101					6	204	1	101
Khaw 2017		1312	2558	1326	2552	9	2558	8	2552	156	2558	136	2552
Larsen 2017						0	256	0	255	15	256	13	255
Levis 2017		8	66	11	64	0	66	0	64	0	66	0	64
Schwetz 2017		27	249	33	243					2	249	2	243
Smith 2017		78	235	15	38	0	235	0	38	5	235	1	38
	High vs Low dose	51	168	27	67	0	168	0	67	5	168	0	67
	High vs P	51	168	15	38	0	168	0	38	5	168	1	38
	Low vs P	27	67	15	38	0	67	0	38	0	67	1	38

Bone density outcomes

			Vit D or Higher dose			Controls or lower dose			Between-group difference			
Study	**Treatment arm**	**Site/Year**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SE**	**N1**	**N2**
Dawson-Hughes 1991		LS1							0.70	0.34	110	110
		TB1							0.11	0.16	125	125
Dawson-Hughes 1995		LS1							-0.34	0.40	110	105
		FN1							0.98	0.42	121	122
		TB1							0.30	0.17	124	124
		LS2							-0.21	0.41	110	105
		FN2							1.48	0.50	121	122
		TB2							0.16	0.20	124	122
Ooms 1995		FN1							1.80	0.61	135	148
		FR1							-2.40	1.61	135	148
		FN2							1.90	0.77	118	126
		FR2							-0.30	2.35	118	126
Komulainen 1999		LS3	-1.84	5.64	221	-2.17	5.28	226				
		FN3	-2.75	5.12	223	-2.85	5.04	228				
	Vit D/HRT vs HRT	LS3	0.90	6.18	111	0.20	5.67	112				
		FN3	-1.30	5.20	115	-1.40	5.18	114				
	Vit D vs P	LS3	-4.60	5.08	110	-4.50	4.90	114				
		FN3	-4.30	5.04	108	-4.30	4.90	114				
Hunter 2000		LS1	1.11	3.08	64	1.06	3.19	64				
		TH1	-1.14	2.24	64	-1.13	2.28	64				
		FN1	0.22	3.08	64	-0.40	3.17	64				
		FR1	-0.96	2.84	64	-0.88	3.43	64				
		TB1	-0.27	2.33	64	-0.29	2.12	64				
		LS2							-0.10	0.90	64	64
		TH2							0.70	0.63	64	64
		FN2							0.50	0.79	64	64
		FR2							-0.70	0.51	64	64
		TB2							0.20	0.57	64	64
Patel 2001		LS1							-0.56	0.37	35	35
		TH1							-0.07	0.36	35	35
		FN1							0.64	0.63	35	35
		TB1							-0.59	0.30	35	35
Cooper 2003		LS1	-0.19	4.13	74	0.44	4.20	84				
		FN1	-1.81	3.90	74	-0.40	3.72	84				
		FR1	-1.69	2.53	74	-0.69	3.60	84				
		LS2	0.30	4.98	73	0.48	4.70	80				

		FN2	0.52	4.28	73	1.18	4.12	80				
		FR2	-1.72	4.28	73	-1.46	4.12	80				
Harwood 2004		LS1	-1.05	3.08	28	0.35	3.19	22				
		TH1							2.00	0.79	22	28
		FN1							1.07	1.09	22	28
Aloia 2005		LS1	0.67	3.40	104	0.52	2.44	104				
		TH1	1.10	2.09	104	1.03	2.30	104				
		FR1	1.60	3.15	104	1.16	4.02	104				
		TB1	1.49	3.79	104	1.54	2.83	104				
		LS2	0.81	3.04	104	0.75	3.44	104				
		TH2	-0.03	2.62	104	-0.24	2.48	104				
		FR2	-1.08	3.15	104	-0.50	2.99	104				
		TB2	-1.13	2.59	104	-1.29	3.29	104				
		LS3	0.25	1.82	104	0.30	1.82	104				
		TH3	-0.40	1.20	104	-0.40	1.80	104				
		FR3	-0.80	1.30	104	-0.55	1.80	104				
		TB3	-0.35	1.60	104	-0.30	1.50	104				
Wissing 2005		LS1	-3.44	7.08	38	-1.42	8.12	41				
		FN1	-1.56	8.05	38	1.02	7.82	41				
Bunout 2006		LS1	1.61	4.07	46	1.17	4.07	46				
		FN1	1.14	3.80	46	-1.08	3.73	46				
Mikati 2006		LS1	1.13	2.70	36	0.65	3.19	36				
		TH1	0.81	1.96	36	0.62	2.23	36				
		FN1	-0.71	3.82	36	-0.92	3.98	36				
		FR1	0.78	2.14	36	0.89	3.06	36				
Zhu 2008a		TH1	0.50	3.33	123	0.20	2.31	133				
		TB1	0.40	2.22	123	0.40	2.31	133				
Zhu 2008b		TH1	-0.17	2.71	34	0.20	1.68	37				
		TH3	-0.39	4.32	34	-1.53	3.87	29				
Andersen 2008		LS1	2.77	3.08	87	2.13	3.19	37				
		TB1	0.17	2.33	84	2.21	2.12	37				
	High vs Low dose	LS1	4.85	3.08	47	0.85	3.19	40				
		TB1	-0.86	2.33	45	1.38	2.12	39				
Islam 2010		LS1	1.45	4.01	40	-0.34	5.50	35				
		FN1	1.50	3.50	40	-1.30	1.56	35				
Jorde 2010		LS1	0.64	2.99	207	0.56	3.36	105				
		TH1	0.87	1.29	207	0.82	1.56	105				
	High vs Low dose	LS1	0.63	2.83	110	0.65	3.16	97				
		TH1	0.72	1.26	110	1.03	1.31	97				
Rastelli 2011		LS1	0.12	3.76	21	-0.36	3.82	26				
		TH1	-0.01	3.16	21	0.04	3.21	26				
		FN1	0.45	3.30	21	-1.39	3.37	26				
Steffensen 2011		LS2							-0.20	0.77	33	35
		TH2							0.70	0.66	33	35
		FR2							1.00	1.40	33	35
Verschueren 2011		TH1							-0.08	0.44	56	55
Grimnes 2012		LS1	0.25	3.19	149	0.32	3.23	148				
		TH1	0.31	1.59	149	0.56	1.70	148				
		FN1	0.03	2.08	149	0.17	1.87	148				
		TB1	0.18	1.14	149	0.20	1.23	148				
Iuliano-Burns 2012		LS1	-0.76	3.76	71	-1.40	3.60	31				
		TH1	-0.16	2.85	71	-0.10	2.80	31				
		FN1	-0.36	3.99	71	0.40	3.70	31				
Nieves 2012		LS2	-0.48	2.57	55	-0.59	2.40	48				
		TH2	-0.50	1.52	55	-0.69	1.46	48				
		FN2	-0.19	1.90	55	-0.80	1.80	48				
Bolland 2013		LS1	0.03	2.55	13	0.06	2.11	13				
		TH1	-0.53	2.04	13	-0.78	2.43	13				
		FN1	0.37	1.80	13	-0.93	2.05	13				
		TB1	-0.62	0.94	13	-0.79	2.00	12				
MacDonald 2013		LS1	0.01	2.79	171	-0.46	2.79	88				

		TH1	-0.30	1.40	171	-0.60	1.66	88
	High vs Low dose	LS1	0.23	2.88	88	-0.23	2.69	83
		TH1	-0.05	1.46	88	-0.57	1.33	83
	High vs P	LS1	0.23	2.88	88	-0.46	2.79	88
		TH1	-0.05	1.46	88	-0.60	1.66	88
	Low vs P	LS1	-0.23	2.69	83	-0.46	2.79	88
		TH1	-0.57	1.33	83	-0.60	1.66	88
Wamberg 2013		LS1	0.92	1.97	22	0.10	1.89	21
		TH1	-0.37	2.25	22	-0.32	1.55	21
		FN1	0.34	2.99	22	-0.16	2.92	21
		FR1	0.37	1.53	22	-0.02	1.19	21
		TB1	0.41	2.12	22	-0.48	2.02	21
Norenstedt 2014		LS1	3.60	4.07	66	3.00	4.22	69
		TH1	2.80	2.37	66	2.10	2.30	69
		FN1	3.20	2.37	66	2.30	2.74	69
		FR1	0.20	3.85	66	0.30	3.26	69
Rolighed 2014		LS1	3.30	4.56	20	1.90	4.30	20
		TH1	2.80	2.28	20	1.50	4.68	20
		FN1	2.20	2.85	20	0.10	4.34	20
		FR1	-1.30	3.88	20	-1.00	4.22	20
Hansen 2015		LS1	-0.15	2.64	148	0.20	3.18	73
		TH1	-0.35	2.64	148	-0.90	3.19	73
		FN1	-0.60	0.67	148	-0.80	3.17	73
		TB1	-0.45	2.64	148	-0.50	3.19	73
	High vs Low dose	LS1	-0.30	3.08	74	0.00	2.11	74
		TH1	-0.20	3.09	74	-0.50	2.11	74
		FN1	-0.30	3.08	74	-0.90	2.12	74
		TB1	-0.40	3.08	74	-0.50	2.12	74
	High vs P	LS1	-0.30	3.08	74	0.20	3.18	73
		TH1	-0.20	3.09	74	-0.90	3.19	73
		FN1	-0.30	3.08	74	-0.80	3.17	73
		TB1	-0.40	3.08	74	-0.50	3.19	73
	Low vs P	LS1	0.00	2.11	74	0.20	3.18	73
		TH1	-0.50	2.11	74	-0.90	3.19	73
		FN1	-0.90	2.12	74	-0.80	3.17	73
		TB1	-0.50	2.12	74	-0.50	3.19	73
Liyanage 2015		LS1	1.78	3.08	41	-1.41	3.19	41
		TH1	2.62	2.24	41	-0.58	2.28	41
		FN1	2.05	3.08	41	-1.38	3.17	41
		TB1	2.02	2.33	41	-0.67	2.12	41
Uusi-Rasi 2015		LS1	0.71	3.19	185	0.23	3.34	189
		FN1	-0.35	2.96	183	-0.83	3.16	186
		LS2	1.07	3.97	182	0.78	3.91	180
		FN2	-1.01	3.37	179	-1.19	3.50	176
	Vit D vs P	LS1	0.94	3.41	89	0.23	3.19	97
		FN1	-0.18	2.93	86	-1.33	2.82	94
		LS2	1.27	4.30	87	1.01	4.03	93
		FN2	-0.77	3.42	84	-1.34	3.36	89
	Vit D/ex vs P/ex	LS1	0.49	2.98	96	0.24	3.49	92
		FN1	-0.51	2.99	97	-0.31	3.48	92
		LS2	0.89	3.65	95	0.53	3.78	87
		FN2	-1.23	3.32	95	-1.04	3.63	87
Aspray 2016		TH1	-0.20	2.53	230	0.07	2.43	113
Mason 2016		LS1	-1.28	3.08	90	0.02	3.19	92
		FN1	-1.16	3.08	88	-1.18	3.17	92
Aloia 2017		TH3	-1.69	3.56	98	-2.47	2.90	93
		FN3	-1.28	4.65	98	-2.01	4.80	93
		FR3	-1.68	3.08	98	-1.50	3.49	93
Eckard 2017		LS1	2.80	5.36	51	1.40	3.78	30
		TH1	0.93	2.89	51	0.61	3.48	30
Larsen 2017		TH3	-0.52	2.74	201	-0.89	2.88	213

	FN3	-0.70	3.26	201	-1.28	3.26	213
Pop 2017	LS1	-0.40	3.08	39	-0.88	3.19	19
	TH1	0.52	2.24	39	0.00	2.28	19
	FN1	0.00	3.08	39	-2.22	3.17	19
	FR1	0.00	2.84	39	0.00	3.43	19
	TB1	0.43	2.33	39	0.00	2.12	19
Rahme 2017	LS1	1.65	3.21	110	1.34	3.42	112
	TH1	0.47	2.22	110	0.50	2.26	112
	FN1	0.66	4.16	110	0.55	3.78	112
	TB1	1.18	4.13	110	0.19	2.66	112
Reid 2017	LS2	-0.06	3.57	228	-0.64	3.61	224
	TH2	-0.71	2.43	228	-1.34	2.44	224
	FN2	-0.55	2.97	228	-1.20	2.99	224
	TB2	-0.70	1.66	228	-0.70	1.68	224
Havens 2018	LS1	1.15	2.59	99	0.09	3.01	89
	TH1	-0.17	2.85	99	-0.42	1.76	89
	TB1	0.00	2.33	99	-0.27	1.90	89
Zheng 2018	LS1	5.49	3.08	27	5.62	3.19	28
	FN1	17.54	3.08	27	6.90	3.17	28

Vit D- vitamin D; HRT- hormone replacement therapy; CaD- coadministered calcium and vitamin D; Ca- calcium; P-placebo; Ex- exercise; LS- lumbar spine; TH- total hip; FN- femoral neck; FR- forearm; TB- total body

e9. Table: Analyses by population, duration of trial, and study design for bone density outcomes.

Site	Factors	Population	Design	Group	N, mean (95%CI)	Group	N, mean (95%CI)	Group	N, mean (95%CI)	P[a]
Compare trials with missing measures of spread										
Lumbar spine	Year 1	Unselected	Vit D vs Control	Spread present	11, 0.20 (-0.12, 0.52)	Spread absent	5, 0.24 (-1.31, 1.78)			0.96
Total hip	Year 1	Unselected	Vit D vs Control	Spread present	9, 0.17 (-0.05, 0.39)	Spread absent	2, 1.58 (-1.57, 4.73)			0.38
Femoral neck	Year 1	Unselected	Vit D vs Control	Spread present	9, 0.86 (0.11, 1.60)	Spread absent	3, 1.30 (-0.57, 3.17)			0.66
Forearm	Year 1	Unselected	Vit D vs Control	Spread present	4, -0.21 (-1.14, 0.72)	Spread absent	1, -0.08 (-1.17, 1.01)			0.86
Total body	Year 1	Unselected	Vit D vs Control	Spread present	6, -0.02 (-0.30, 0.26)	Spread absent	3, 0.22 (-2.30, 2.74)			0.86
Lumbar spine	Year 1	Unselected	High vs low dose	Spread present	4, -0.01 (-0.44, 0.43)	Spread absent	1, 0.48 (-1.23, 2.19)			0.59
Total hip	Year 1	Unselected	High vs low dose	Spread present	5, -0.19 (-0.44, 0.07)	Spread absent	1, 0.52 (-0.71, 1.76)			0.27
Femoral neck	Year 1	Unselected	High vs low dose	Spread present	4, 0.15 (-0.50, 0.79)	Spread absent	1, 2.22 (0.52, 3.93)			0.03
Total body	Year 1	Unselected	High vs low dose	Spread present	3, 0.26 (-0.15, 0.66)	Spread absent	1, 0.43 (-0.81, 1.67)			0.79
Lumbar spine	Year 1	Selected	Vit D vs Control	Spread present	4, 0.30 (-0.69, 1.28)	Spread absent	1, -0.12 (-1.78, 1.54)			0.67
Femoral neck	Year 1	Selected	Vit D vs Control	Spread present	4, 0.92 (-0.18, 2.03)	Spread absent	1, 10.65 (9.00, 12.30)			<0.01
Compare results by year for each population type and study design for dose										
Lumbar spine		Unselected	Vit D vs Control	Year 1	16, 0.22 (-0.21, 0.65)	Year 2	6, 0.27 (-0.11, 0.65)	Year 3+	2, 0.02 (-0.42, 0.47)	0.70
Lumbar spine		Unselected	High vs low dose	Year 1	5, 0.02 (-0.40, 0.45)	Year 2	1, -0.21 (-1.01, 0.59)			0.61
Lumbar spine		Selected	Vit D vs Control	Year 1	5, 0.19 (-0.66, 1.03)	Year 2	1, -0.20 (-1.70, 1.30)			0.66
Total hip		Unselected	Vit D vs Control	Year 1	11, 0.44 (0.01, 0.88)	Year 2	5, 0.43 (0.13, 0.74)	Year 3+	1, 0.27 (-0.09, 0.62)	0.75
Total hip		Selected	Vit D vs Control	Year 1	3, 0.68 (0.00, 1.37)	Year 2	1, 0.70 (-0.60, 2.00)			0.98
Femoral neck		Unselected	Vit D vs Control	Year 1	12, 0.96 (0.29, 1.63)	Year 2	6, 0.49 (0.04, 0.94)	Year 3+	3, 0.47 (-0.02, 0.95)	0.45
Femoral neck		Unselected	High vs low dose	Year 1	5, 0.40 (-0.38, 1.17)	Year 2	1, 1.48 (0.50, 2.46)			0.09
Forearm		Unselected	Vit D vs Control	Year 1	5, -0.15 (-0.85, 0.55)	Year 2	4, -0.55 (-1.13, 0.02)	Year 3+	2, -0.24 (-0.63, 0.15)	0.60
Forearm		Selected	Vit D vs Control	Year 1	2, -0.14 (-1.22, 0.95)	Year 2	1, 1.00 (-1.75, 3.75)			0.45
Total body		Unselected	Vit D vs Control	Year 1	9, 0.08 (-0.53, 0.69)	Year 2	3, 0.04 (-0.24, 0.32)	Year 3+	1, -0.05 (-0.47, 0.37)	0.92
Total body		Unselected	High vs low dose	Year 1	4, 0.25 (-0.10, 0.60)	Year 2	1, 0.16 (-0.23, 0.55)			0.74
Compare results by population type and study design for dose for each year										
Lumbar spine	Year 1	Unselected	Vit D vs Control		16, 0.22 (-0.21, 0.65)					0.14
		Unselected	High vs low dose		5, 0.02 (-0.40, 0.45)					
		Selected	Vit D vs Control		5, 0.19 (-0.66, 1.03)					
		Selected	High vs low dose		4, 0.92 (0.29, 1.55)					
	Year 2	Unselected	Vit D vs Control		6, 0.27 (-0.11, 0.65)					0.51
		Unselected	Vit D vs Control		1, -0.21 (-1.01, 0.59)					
		Selected	Vit D vs Control		1, -0.20 (-1.70, 1.30)					

Total hip	Year 1	Unselected	Vit D vs Control	11, 0.44 (0.01, 0.88)	0.02
		Unselected	High vs low dose	6, -0.16 (-0.41, 0.09)	
		Selected	Vit D vs Control	3, 0.68 (0.00, 1.37)	
		Selected	High vs low dose	4, 0.22 (-0.28, 0.72)	
	Year 2	Unselected	Vit D vs Control	4, 0.43 (0.13, 0.74)	0.69
		Selected	Vit D vs Control	1, 0.70 (-0.60, 2.00)	
Femoral neck	Year 1	Unselected	Vit D vs Control	12, 0.96 (0.29, 1.63)	0.55
		Unselected	High vs low dose	5, 0.40 (-0.38, 1.17)	
		Selected	Vit D vs Control	5, 2.58 (-1.37, 6.53)	
		Selected	High vs low dose	2, 0.99 (-0.59, 2.58)	
	Year 2	Unselected	Vit D vs Control	6, 0.49 (0.04, 0.94)	0.07
		Unselected	High vs low dose	1, 1.48 (0.50, 2.46)	
Forearm	Year 1	Unselected	Vit D vs Control	5, -0.15 (-0.85, 0.55)	>0.99
		Unselected	High vs low dose	1, 0.00 (-1.67, 1.67)	
		Selected	Vit D vs Control	2, -0.14 (-1.22, 0.95)	
		Selected	High vs low dose	1, -0.12 (-1.34, 1.10)	
	Year 2	Unselected	Vit D vs Control	4, -0.55 (-1.13, 0.02)	0.28
		Selected	Vit D vs Control	1, 1.00 (-1.75, 3.75)	
Total body	Year 1	Unselected	Vit D vs Control	9, 0.08 (-0.53, 0.69)	0.97
		Unselected	High vs low dose	4, 0.25 (-0.10, 0.60)	
		Selected	Vit D vs Control	1, 0.17 (-1.04, 1.38)	
		Selected	High vs low dose	1, 0.27 (-0.34, 0.88)	
	Year 2	Unselected	Vit D vs Control	3, 0.04 (-0.24, 0.32)	0.24
		Selected	Vit D vs Control	1, 0.16 (-0.23, 0.55)	

Compare results by year, pooling studies by population type and study design for dose

Lumbar spine	Year 1	30, 0.25 (-0.04, 0.54)	Year 2	8, 0.16 (-0.17, 0.50)	Year 3+	2, 0.02 (-0.42, 0.47)	0.71
Total hip	Year 1	24, 0.26 (0.01, 0.51)	Year 2	5, 0.45 (0.15, 0.74)	Year 3+	4, 0.27 (-0.09, 0.62)	0.60
Femoral neck	Year 1	24, 1.23 (0.12, 0.54)	Year 2	7, 0.63 (0.06, 0.16)	Year 3+	3, 0.47 (0.06, -0.02)	0.20
Forearm	Year 1	9, -0.08 (-0.48, 0.32)	Year 2	5, -0.49 (-1.05, 0.07)	Year 3+	2, -0.24 (-0.63, 0.15)	0.50
Total body	Year 1	15, 0.16 (-0.18, 0.50)	Year 2	4, 0.08 (-0.15, 0.31)	Year 3+	1, -0.05 (-0.47, 0.37)	0.75
Femoral neck, Zheng 2018 excluded	Year 1	23, 0.81 (0.37, 1.25)	Year 2	7, 0.63 (0.16, 1.10)	Year 3+	3, 0.47 (-0.02, 0.95)	0.59

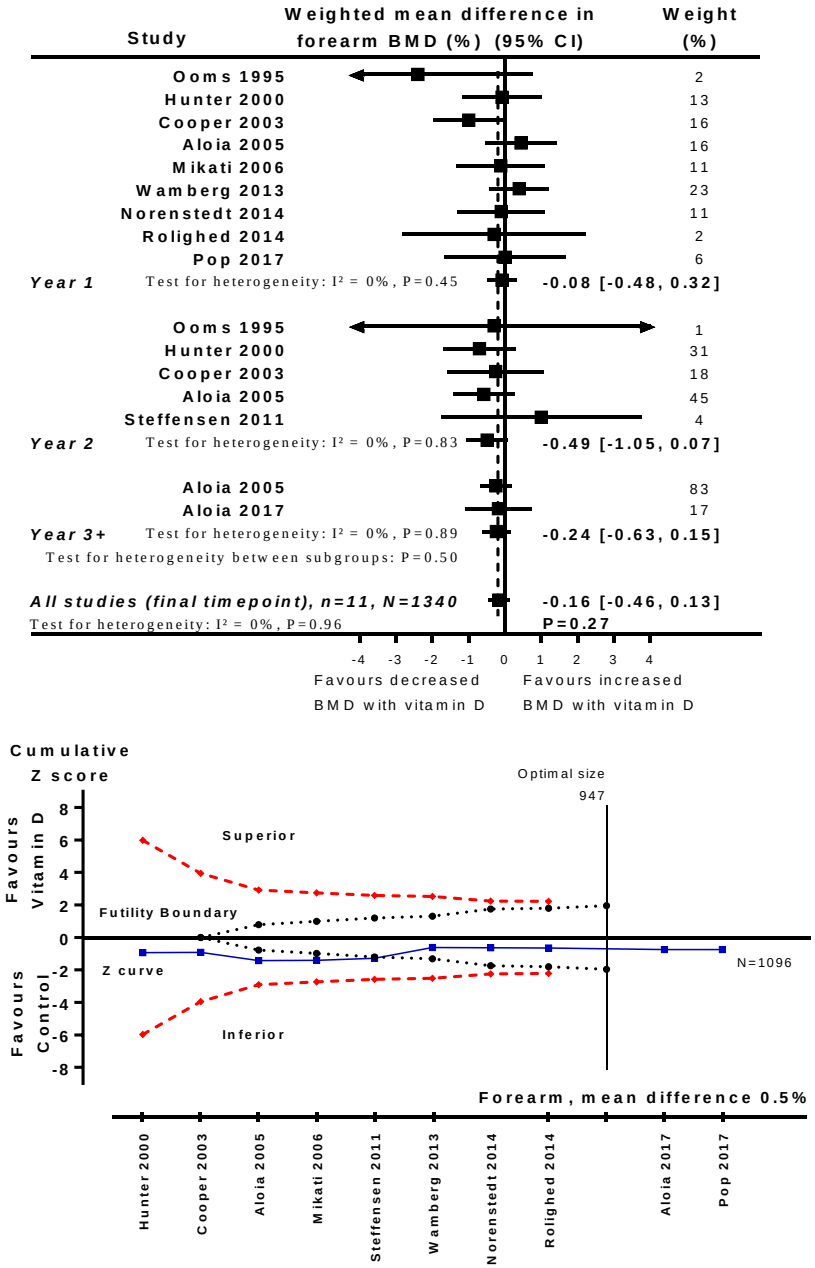
Compare results by site using final time point results only from each study

Lumbar spine	34, 0.25 (0.00, 0.49)
Total hip	29, 0.34 (0.13, 0.55)
Femoral neck	29, 1.12 (0.58, 1.65)
Forearm	11, -0.16 (-0.46, 0.13)

Total body	16, 0.13 (-0.16, 0.42)
Femoral neck, Zheng 2018 excluded	28, 0.76 (0.42, 1.09)

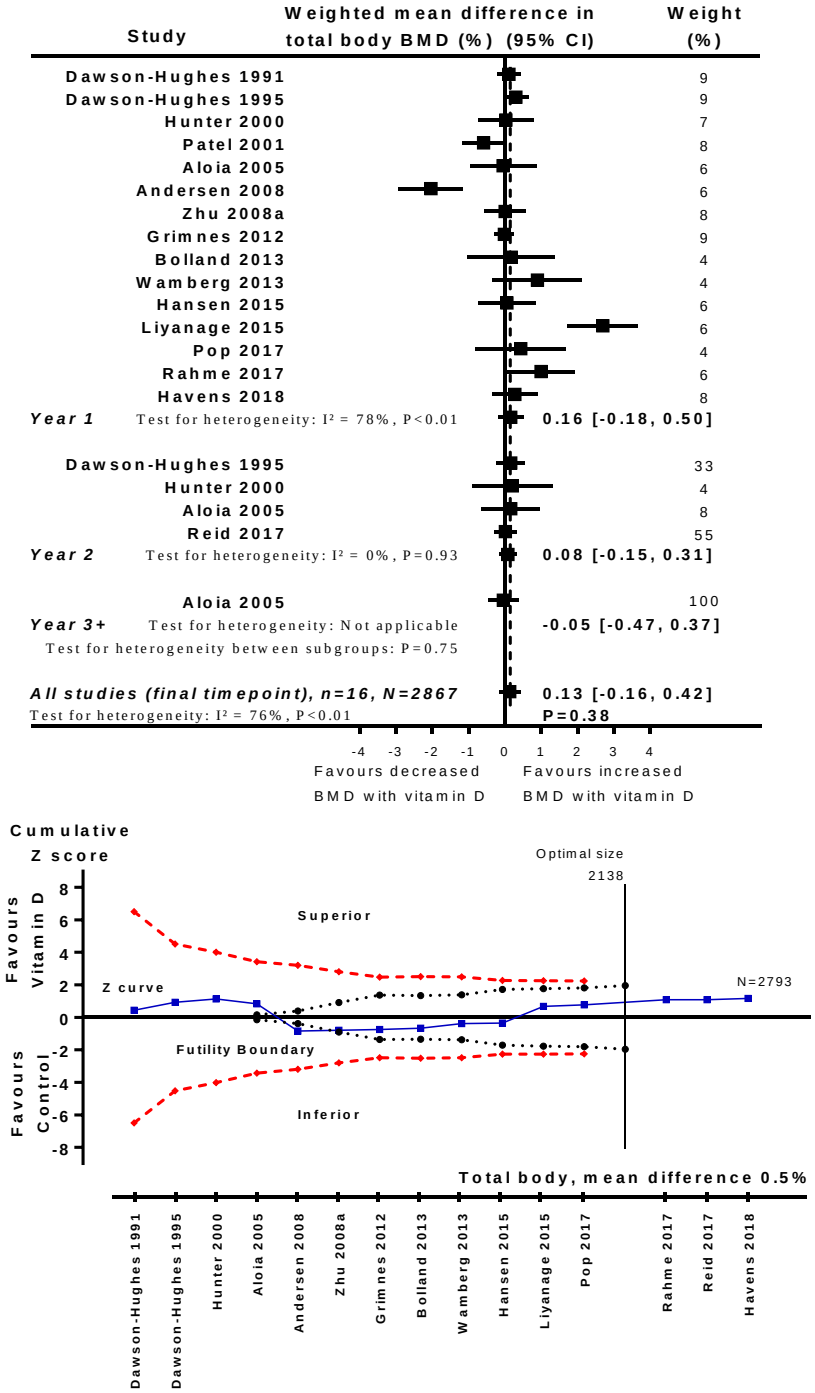
N- number of studies; mean- weighted mean between-group difference in bone mineral density; Vit D- vitamin D;.
[a] P values are for the test of interaction between subgroups.

e10. Figure: Forearm bone density



The top panel shows random effects meta-analyses of vitamin D supplementation on forearm bone mineral density (BMD) by trial duration and the pooled analysis of all trials using the final time point. The bottom panel shows trial sequential analysis of all trials of vitamin D on forearm BMD for a mean difference of 0.5% (see Figure 1 for detailed description).

e11. Figure: Total body bone density



The top panel shows random effects meta-analyses of vitamin D supplementation on total body bone mineral density (BMD) by trial duration and the pooled analysis of all trials using the final time point. The bottom panel shows the trial sequential analysis of all trials of vitamin D on total body BMD (see Figure 1 for description).

e12. Table: Reported subgroup analyses based on baseline 25-hydroxyvitamin D

	Fracture			Falls			Bone density		
	Threshold (nmol/L)	Result	Comparison to primary analysis	Threshold (nmol/L)	Result	Comparison to primary analysis	Threshold (nmol/L)	Result	Comparison to primary analysis
Patel 2001							<60 only	No effect	Similar to primary
Latham 2003				<25	No effect	Similar to primary			
Harwood 2004	<30 (and PTH <50) only	No effect	Similar to primary	<30 (and PTH <50) only	No effect	Similar to primary	<30 (and PTH <50) only	Mixed	Similar to primary
Aloia 2005							Not stated	No effect	Similar to primary
Zhu 2008b							<68, >68	Positive	Mixed
Jorde 2010							<45 only	No effect	Similar to primary
Grimnes 2012							<69.7, >69.7 <55, >55	No interaction	Similar to primary
MacDonald 2013							<50 only	Mixed	Similar to primary
Norenstedt 2014							<50 or >50	No effect	Similar to primary
Bischoff-Ferrari 2016				<50, >50	Mixed	Similar to primary			
Mason 2016							<50 only	Mixed	Mixed
Ginde 2017				<50, >50	No interaction	Similar to primary			
Khaw 2017	<50; <25, 25-50, 50-75 vs 75+	No effect	Similar to primary	<50 only	No effect	Similar to primary			
Larsen 2017							<50 only	No effect	Similar to primary
Rahme 2017							<50, >50 and PTH <76	Mixed	Mixed
Reid 2017							<25, >25; <30, >30; <40, >40; <50, >50	Mixed	Similar to primary
Schwetz 2017	<25, >25	No effect	Similar to primary	<25, >25	No effect	Similar to primary	<25 or >25	No difference	Similar to primary
Havens 2018							<50 or >50 only in vit D group	No difference	Similar to primary

25OHD- 25 hydroxyvitamin D; PTH- parathyroid hormone; Vit D- vitamin D;

e13. Table: Results of subgroups analyses for falls and fracture

Subgroups	Group	N, RR, 95% CI	Group	N, RR, 95% CI	Group	N, RR, 95% CI	P[a]
Total fracture							
Age	<65 years	7, 0.88 (0.67, 1.14)	65+ years	29, 1.00 (0.92, 1.09)			0.34
BMI	<30 kg/m^2	26, 0.95 (0.87, 1.03)	30+ kg/m^2	4, 0.78 (0.32, 1.90)			0.66
Duration	≤12 m	22, 0.92 (0.71, 1.19)	>12 m	14, 1.00 (0.92, 1.09)			0.52
Trial size	≤200	12, 0.50 (0.32, 0.77)	>200	24, 1.02 (0.96, 1.09)			0.002
Site	Community-dwelling	28, 1.01 (0.93, 1.09)	Residential Care	8, 0.98 (0.84, 1.14)			0.73
Risk of bias	Low	9, 1.00 (0.90, 1.11)	Moderate/High	27, 0.99 (0.88, 1.10)			0.85
Vit D Dose	>800 IU/d	18, 1.07 (0.94, 1.22)	≤800 IU/d	17, 0.98 (0.90, 1.08)			0.29
Dose Frequency	Daily	19, 0.97 (0.88, 1.07)	Intermittent	16, 1.03 (0.92, 1.16)	Mixed	1, 0.49 (0.13, 1.92)	0.43
Coadministered therapy	No	25, 1.04 (0.97, 1.12)	Yes	11, 0.89 (0.77, 1.04)			0.07
Therapy			Calcium	9, 0.89 (0.77, 1.04)			0.76
			Calcium/Exercise	1, 0.61 (0.15, 2.47)			
			Exercise	1, 1.17 (0.40, 3.37)			
Baseline 25OHD	<25 nmol/L	2, 0.79 (0.14, 4.33)	25+ nmol/L	29, 1.05 (0.98, 1.13)			0.74
	<50 nmol/L	18, 1.03 (0.93, 1.14)	50+ nmol/L	13, 1.08 (0.97, 1.21)			0.52
	<75 nmol/L	31, 1.05 (0.98, 1.14)	75+ nmol/L	-			
Achieved 25OHD	<50 nmol/L	5, 0.70 (0.36, 1.35)	50+ nmol/L	27, 1.02 (0.95, 1.09)			0.27
	<75 nmol/L	16, 1.03 (0.93, 1.14)	75+ nmol/L	16, 0.96 (0.85, 1.09)			0.42
High vs low dose within study		7, 0.65 (0.39, 1.07)					
Hip fracture							
Age	<65 years	1, 0.50 (0.05, 5.48)	65+ years	19, 1.11 (0.97, 1.26)			0.51
BMI	<30 kg/m^2	14, 0.99 (0.81, 1.22)					
Duration	≤12 m	9, 0.95 (0.56, 1.62)	>12 m	11, 1.12 (0.98, 1.28)			0.57
Trial size	≤200	9, 0.53 (0.24, 1.16)	>200	11, 1.13 (0.99, 1.29)			0.06
Site	Community-dwelling	13, 1.09 (0.90, 1.32)	Residential Care	7, 1.12 (0.94, 1.34)			0.84
Risk	Low	7, 1.12 (0.98, 1.29)	Moderate/High	13, 0.96 (0.62, 1.49)			0.50
Vit D Dose	>800 IU/d	3, 1.17 (0.68, 2.00)	≤800 IU/d	15, 1.11 (0.97, 1.28)			0.88
Dose Frequency	Daily	12, 1.06 (0.87, 1.28)	Intermittent	8, 1.15 (0.96, 1.38)			0.51
Coadministered therapy	No	13, 1.15 (1.00, 1.32)	Yes	7, 0.91 (0.63, 1.32)			0.24
Therapy			Calcium	7, 0.91 (0.63, 1.32)			
Baseline 25OHD	<25 nmol/L	1, 0.51 (0.05, 5.59)	25+ nmol/L	16, 1.15 (0.98, 1.35)			0.51
	<50 nmol/L	13, 1.06 (0.89, 1.27)	50+ nmol/L	4, 1.43 (1.05, 1.96)			0.10
	<75 nmol/L	17, 1.15 (0.98, 1.34)	75+ nmol/L	-			
Achieved 25OHD	<50 nmol/L	4, 0.43 (0.11, 1.66)	50+ nmol/L	15, 1.12 (0.98, 1.28)			0.17
	<75 nmol/L	13, 1.14 (0.97, 1.33)	75+ nmol/L	6, 1.05 (0.83, 1.34)			0.61
High vs low dose within study		2, 0.42 (0.12, 1.47)					
Falls							
Age	<65 years	4, 0.83 (0.55, 1.24)	65+ years	33, 0.98 (0.94, 1.02)			0.42
BMI	<30 kg/m^2	28, 0.95 (0.89, 1.02)	30+ kg/m^2	3, 0.76 (0.52, 1.11)			0.25
Duration	≤12 m	28, 0.91 (0.83, 1.01)	>12 m	9, 1.00 (0.96, 1.04)			0.10
Trial size	≤200	16, 0.84 (0.69, 1.03)	>200	21, 0.99 (0.95, 1.03)			0.12
Site	Community-dwelling	30, 0.97 (0.92, 1.02)	Residential Care	7, 0.98 (0.92, 1.05)			0.74
Risk	Low	22, 0.99 (0.94, 1.04)	Moderate/High	15, 0.90 (0.81, 1.00)			0.12
Vit D Dose	>800 IU/d	21, 0.95 (0.89, 1.02)	≤800 IU/d	15, 0.98 (0.95, 1.01)			0.45
Dose Frequency	Daily	18, 0.92 (0.87, 0.98)	Intermittent	18, 1.01 (0.95, 1.07)	Mixed	1, 0.99 (0.65, 1.50)	0.13
Coadministered	No	24, 0.98 (0.93, 1.03)	Yes	12, 0.95 (0.87, 1.04)			0.55

therapy					
Therapy			Calcium	8, 0.92 (0.82, 1.03)	0.25
			Calcium/Exercise	1, 1.80 (0.71, 4.59)	
			Exercise	2, 1.03 (0.89, 1.20)	
			Strontium	1, 0.79 (0.51, 1.23)	
Baseline 25OHD	<25 nmol/L	2, 0.80 (0.57, 1.11)	25+ nmol/L	31, 0.98 (0.93, 1.03)	0.24
	<50 nmol/L	22, 0.92 (0.83, 1.02)	50+ nmol/L	11, 0.99 (0.94, 1.03)	0.25
	<75 nmol/L	33, 0.97 (0.92, 1.03)	75+ nmol/L	-	
Achieved 25OHD	<50 nmol/L	4, 0.60 (0.33, 1.07)	50+ nmol/L	30, 0.99 (0.94, 1.03)	0.10
	<75 nmol/L	19, 0.96 (0.91, 1.03)	75+ nmol/L	15, 0.99 (0.90, 1.10)	0.66
High vs low dose within study		7, 0.90 (0.69, 1.18)			

N- number of studies; RR- relative risk; BMI- body mass index; vit D- vitamin D; 25OHD- 25-hydroxyvitamin D

e14. Table: Results of subgroups analyses for bone density

Subgroups	Group	N, mean, 95% CI	Group	N, mean, 95% CI	Group	N, mean, 95% CI	P
Lumbar spine							
Age	<65 years	6, 0.30 (-0.11, 0.70)	65+ years	28, 0.27 (-0.03, 0.56)			0.91
BMI	<30 kg/m2	25, 0.38 (0.07, 0.69)	30+ kg/m2	9, -0.05 (-0.41, 0.32)			0.08
Duration	≤12 m	24, 0.39 (0.03, 0.75)	>12 m	10, 0.03 (-0.23, 0.29)			0.11
Trial size	≤200	21, 0.39 (-0.05, 0.83)	>200	13, 0.16 (-0.13, 0.45)			0.39
Site	Community-dwelling	34, 0.25 (0.00, 0.49)	Residential Care	-			
Risk of bias	Low	22, 0.35 (0.04, 0.67)	Moderate/High	12, 0.03 (-0.35, 0.41)			0.20
Vit D Dose	>800 IU/d	14, 0.30 (-0.21, 0.81)	≤800 IU/d	13, 0.10 (-0.21, 0.41)			0.51
Dose Frequency	Daily	18, 0.15 (-0.13, 0.44)	Intermittent	15, 0.42 (-0.05, 0.88)	Mixed	1, -0.35 (-1.14, 0.44)	0.25
Coadministered therapy	No	14, 0.29 (-0.28, 0.85)	Yes	12, 0.16 (-0.12, 0.44)			0.70
Therapy			Calcium	9, 0.14 (-0.16, 0.43)			0.87
			Calcium/Cinacalcet	1, -0.12 (-1.78, 1.54)			
			Exercise	1, 0.36 (-0.72, 1.44)			
Baseline 25OHD	<25 nmol/L	31, 0.23 (-0.04, 0.51)	25+ nmol/L	1, 0.64 (-0.56, 1.83)			0.52
	<50 nmol/L	15, 0.34 (0.07, 0.61)	50+ nmol/L	17, 0.13 (-0.29, 0.56)			0.42
	<75 nmol/L	1, -0.18 (-1.71, 1.35)	75+ nmol/L	31, 0.26 (-0.02, 0.53)			0.58
Achieved 25OHD	<50 nmol/L	3, 0.05 (-0.97, 1.06)	50+ nmol/L	31, 0.26 (0.00, 0.52)			0.69
	<75 nmol/L	12, 0.36 (-0.01, 0.73)	75+ nmol/L	22, 0.22 (-0.10, 0.54)			0.58
High vs low dose within study		13, 0.57 (0.03, 1.11)					
Total hip							
Age	<65 years	8, 0.34 (-0.06, 0.73)	65+ years	21, 0.34 (0.08, 0.60)			0.97
BMI	<30 kg/m2	20, 0.45 (0.14, 0.76)	30+ kg/m2	8, 0.08 (-0.12, 0.29)			0.05
Duration	≤12 m	20, 0.35 (0.05, 0.65)	>12 m	9, 0.32 (0.10, 0.53)			0.87
Trial size	≤200	17, 0.59 (0.15, 1.04)	>200	12, 0.16 (-0.02, 0.34)			0.08
Site	Community-dwelling	28, 0.35 (0.14, 0.57)	Residential Care	1, -0.08 (-0.93, 0.77)			0.33
Risk of bias	Low	22, 0.31 (0.08, 0.55)	Moderate/High	7, 0.43 (-0.05, 0.92)			0.66
Vit D Dose	>800 IU/d	15, 0.62 (0.29, 0.96)	≤800 IU/d	6, 0.19 (-0.16, 0.55)			0.09
Dose Frequency	Daily	13, 0.23 (0.04, 0.42)	Intermittent	15, 0.42 (0.05, 0.80)	Mixed	1, 0.55 (-0.25, 1.35)	0.54
Coadministered therapy	No	11, 0.74 (0.25, 1.22)	Yes	8, 0.18 (-0.02, 0.39)			0.04
Therapy			Calcium	8, 0.18 (-0.02, 0.39)			
Baseline 25OHD	<25 nmol/L	28, 0.32 (0.11, 0.54)	25+ nmol/L	-			
	<50 nmol/L	12, 0.19 (0.00, 0.38)	50+ nmol/L	16, 0.43 (0.07, 0.79)			0.25
	<75 nmol/L	28, 0.32 (0.11, 0.54)	75+ nmol/L	-			
Achieved 25OHD	<50 nmol/L	1, 2.00 (0.46, 3.55)	50+ nmol/L	28, 0.31 (0.10, 0.51)			0.03
	<75 nmol/L	8, 0.34 (0.08, 0.59)	75+ nmol/L	21, 0.34 (0.07, 0.62)			0.97
High vs low dose within study		13, -0.01 (-0.20, 0.18)					
Femoral neck							
Age	<65 years	7, 0.74 (0.23, 1.25)	65+ years	21, 0.75 (0.32, 1.17)			0.98
BMI	<30 kg/m2	19, 0.79 (0.33, 1.25)	30+ kg/m2	8, 0.63 (0.13, 1.12)			0.64
Duration	≤12 m	17, 0.95 (0.38, 1.52)	>12 m	11, 0.57 (0.27, 0.87)			0.25
Trial size	≤200	17, 1.08 (0.49, 1.67)	>200	11, 0.39 (0.09, 0.69)			0.04
Site	Community-dwelling	28, 0.76 (0.42, 1.09)	Residential Care	-			
Risk of bias	Low	18, 0.72 (0.31, 1.12)	Moderate/High	10, 0.87 (0.30, 1.44)			0.67
Vit D Dose	>800 IU/d	12, 0.76 (0.32, 1.20)	≤800 IU/d	10, 0.82 (0.11, 1.52)			0.89
Dose Frequency	Daily	15, 0.88 (0.46, 1.29)	Intermittent	12, 0.67 (0.06, 1.29)	Mixed	1, 0.20 (-0.33, 0.73)	0.14

Coadministered therapy	No	14, 1.02 (0.53, 1.50)	Yes	8, 0.27 (-0.19, 0.72)			0.03
Therapy			Calcium	6, 0.34 (-0.24, 0.93)			0.66
			Exercise	1, -0.19 (-1.20, 0.82)			
			HRT	1, 0.10 (-1.24, 1.44)			
Baseline 25OHD	<25 nmol/L	25, 0.68 (0.33, 1.04)	25+ nmol/L	1, 1.90 (0.40, 3.40)			0.12
	<50 nmol/L	10, 1.11 (0.55, 1.67)	50+ nmol/L	16, 0.50 (0.08, 0.92)			0.09
	<75 nmol/L	1, -0.66 (-1.99, 0.67)	75+ nmol/L	25, 0.77 (0.42, 1.13)			0.04
Achieved 25OHD	<50 nmol/L	2, 0.25 (-0.60, 1.11)	50+ nmol/L	26, 0.78 (0.43, 1.14)			0.26
	<75 nmol/L	11, 0.95 (0.28, 1.61)	75+ nmol/L	17, 0.64 (0.26, 1.02)			0.43
High vs low dose within study		8, 0.59 (-0.05, 1.23)					
<u>Forearm</u>							
Age	<65 years	2, -0.18 (-1.10, 0.73)	65+ years	9, -0.16 (-0.47, 0.15)			0.96
BMI	<30 kg/m2	6, -0.28 (-0.84, 0.28)	30+ kg/m2	4, -0.11 (-0.48, 0.26)			0.62
Duration	≤12 m	5, 0.11 (-0.43, 0.66)	>12 m	6, -0.27 (-0.62, 0.07)			0.24
Trial size	≤200	8, -0.06 (-0.51, 0.38)	>200	3, -0.24 (-0.63, 0.15)			0.56
Site	Community-dwelling	11, -0.16 (-0.46, 0.13)	Residential Care	-			
Risk of bias	Low	7, -0.12 (-0.44, 0.21)	Moderate/High	4, -0.37 (-1.05, 0.30)			0.50
Vit D Dose	>800 IU/d	6, 0.06 (-0.43, 0.55)	≤800 IU/d	3, -0.32 (-0.71, 0.07)			0.24
Dose Frequency	Daily	8, -0.18 (-0.48, 0.13)	Intermittent	3, -0.01 (-0.99, 0.96)			0.75
Coadministered therapy	No	4, -0.06 (-0.68, 0.55)	Yes	5, -0.21 (-0.56, 0.15)			0.69
Therapy			Calcium	5, -0.21 (-0.56, 0.15)			
Baseline 25OHD	<25 nmol/L	9, -0.16 (-0.47, 0.15)	25+ nmol/L	1, -0.30 (-4.90, 4.30)			0.95
	<50 nmol/L	5, -0.11 (-0.46, 0.23)	50+ nmol/L	5, -0.34 (-1.02, 0.33)			0.56
	<75 nmol/L	1, -0.26 (-1.59, 1.07)	75+ nmol/L	9, -0.16 (-0.47, 0.16)			0.88
Achieved 25OHD	<50 nmol/L	-	50+ nmol/L	11, -0.16 (-0.46, 0.13)			
	<75 nmol/L	3, -0.11 (-0.96, 0.73)	75+ nmol/L	8, -0.17 (-0.48, 0.14)			0.90
High vs low dose within study							
<u>Total body</u>							
Age	<65 years	3, 0.18 (-0.27, 0.63)	65+ years	13, 0.11 (-0.25, 0.48)			0.82
BMI	<30 kg/m2	11, 0.05 (-0.31, 0.42)	30+ kg/m2	5, 0.30 (-0.14, 0.73)			0.39
Duration	≤12 m	11, 0.27 (-0.19, 0.73)	>12 m	5, -0.03 (-0.25, 0.18)			0.24
Trial size	≤200	7, 0.23 (-0.91, 1.37)	>200	9, 0.07 (-0.07, 0.20)			0.78
Site	Community-dwelling	16, 0.13 (-0.16, 0.42)	Residential Care	-			
Risk of bias	Low	10, 0.21 (-0.23, 0.65)	Moderate/High	6, 0.04 (-0.20, 0.28)			0.50
Vit D Dose	>800 IU/d	6, 0.59 (-0.14, 1.32)	≤800 IU/d	6, -0.36 (-0.89, 0.17)			0.04
Dose Frequency	Daily	8, -0.17 (-0.57, 0.23)	Intermittent	7, 0.56 (0.03, 1.08)	Mixed	1, 0.05 (-0.74, 0.84)	0.10
Coadministered therapy	No	8, 0.13 (-0.63, 0.90)	Yes	3, 0.04 (-0.19, 0.27)			0.82
Therapy			Calcium	3, 0.04 (-0.19, 0.27)			
Baseline 25OHD	<25 nmol/L	1, -2.04 (-2.92, -1.16)	25+ nmol/L	13, 0.27 (-0.05, 0.59)			<0.01
	<50 nmol/L	6, -0.15 (-0.78, 0.47)	50+ nmol/L	8, 0.37 (-0.12, 0.87)			0.20
	<75 nmol/L	14, 0.15 (-0.22, 0.51)	75+ nmol/L	-			
Achieved 25OHD	<50 nmol/L	1, -2.04 (-2.92, -1.16)	50+ nmol/L	15, 0.22 (-0.03, 0.47)			<0.01
	<75 nmol/L	2, -0.99 (-2.99, 1.01)	75+ nmol/L	14, 0.24 (-0.03, 0.51)			0.23
High vs low dose within study		7, -0.02 (-0.52, 0.47)					

N- number of studies; mean- weighted mean between group difference in bone density; BMI- body mass index; vit D- vitamin D; 25OHD- 25-hydroxyvitamin D.

[a] P values are for the test of interaction between subgroups.

e15: References in the appendix