Supplementary Online Content

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eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.
**eAppendix 1. Meta-analysis of the Observational Studies**

**Data Extraction**

Studies that classified blood 25(OH)D concentrations into only two categories were excluded as at least three exposure categories are needed to estimate a dose response relationship.\(^1\)\(^2\) Eligibility evaluation and data extraction were carried out by two independent reviewers (PY and RC) and any discrepancies were adjudicated by discussion with a third reviewer (JA). Data extracted from all the identified studies included: author, publication year, country, study design, participants' characteristics (total number, age, sex and residential status), duration of follow-up, blood 25(OH)D concentration, number of fractures (any fracture or hip fracture), cut-offs for 25(OH)D concentrations, covariates included in the analysis, in addition to multivariable adjusted risk estimates (95% CI) for each category of 25(OH)D concentrations. For studies that reported different models to estimate risks, we chose the results that had been more fully adjusted for relevant confounders.

For each of the included studies, we assigned the reported median or mean blood 25(OH)D concentrations for each category. When a study reported only the range of 25(OH)D concentrations for a category, we used the average concentrations of the lower and upper bounds of that category.\(^2\) When the highest category was open-ended, its category 25(OH)D concentration was calculated as its lower bound plus the width of the previous (second-to-highest) interval. When the lowest category was open ended, its category 25(OH)D concentration was calculated as its upper bound minus half the width of the next (second-to-lowest) interval.
**Statistical Analysis**

The analyses assumed that there was a linear relationship between the natural logarithm of RR and 25(OH)D concentrations. For the studies that reported risk estimates separately by race (white, black, Hispanic, Asian and Native American) or gender, we combined these estimates using a fixed-effects model and subsequently used pooled estimates for each meta-analysis.

Heterogeneity was assessed using the $I^2$ statistic ($I^2 > 50\%$ was considered significant heterogeneity). Contour enhanced funnel plots were constructed to assess publication bias. Subgroup analyses by relevant study characteristics were performed in order to identify potential sources of heterogeneity including: study design, age, geographic region, length of follow-up, and baseline blood 25(OH)D concentration. The continuous variables were dichotomised above and below the median values.
eAppendix 2. Meta-analysis of the Randomized Clinical Trials

Data Extraction

Two researchers (PY and RC) independently extracted the relevant data from each trial, including: author, publication year, country, participant characteristics (total number, age, sex, residential status and previous history of fractures/falls), dosing regimen for vitamin D or calcium, type of control, compliance, trial duration, incident fracture types, and blood 25(OH)D concentrations at baseline and year of trial (if appropriate). Disagreements were resolved by discussion with a third reviewer (JA). For factorial or multi-arm randomised trials, relevant data were extracted only for the effects of vitamin D, or vitamin D co-administered with calcium versus placebo.\(^5\)

Risk of Bias Assessment

Trials were assessed for possible bias using the Cochrane Collaboration risk of bias tool for randomised trials.\(^6\) The tool included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain was rated as low risk, unclear risk or high risk of bias, and overall risk of bias was classified as low if all domains were at low risk of bias, or high if at least one domain was at high risk of bias, or as unclear if at least one domain was at unclear risk of bias and no domain was at high risk of bias.

Treatment Difference in 25(OH)D concentrations

Treatment differences in blood 25(OH)D concentrations were calculated as the mean 25(OH)D differences between the treatment groups after approximately one year of
treatment. If blood 25(OH)D concentrations were reported at multiple time points, data for those closest to one year were selected for between trial comparisons.
eAppendix 3. Use of Observational Evidence to Estimate the Power for Future Trials

Estimation of power for individual trials requires information on fracture incidence rates, assumed risk reduction, non-compliance rates and sample sizes with an alpha set at 0.05 (two-tailed). The estimated reduction for risk of fracture associated with a 25 nmol/L higher blood 25(OH)D concentrations was obtained from a meta-analysis of the observational studies of 25(OH)D and risk of fracture. However, in the context of a 5-year trial, one might expect to achieve only about half the risk reduction observed in the observational studies to be reversible. Therefore, trials which achieved differences in blood 25(OH)D concentrations of 25 nmol/L by allocated treatment, would be expected to reduce risks of any fracture by 5% and hip fracture by 10%. The log transformed RR associated with vitamin D supplements was assumed to be proportional to the achieved differences in 25(OH)D concentrations. Taken together, the statistical power of a 5-year trial which achieved a 50 nmol/L 25(OH)D difference was calculated by estimating the risk reduction for any fracture of 9%, and for hip fracture of 19% (when estimated using a two-sample comparison of proportions with a continuity correction and assuming a 20% non-compliance rate). R software (version 3.4.2) was used for statistical analyses and p-values (2-tailed) <0.05 were considered statistically significant.
eFigure 1. Age and Sex-Specific Incidence Rates of Any Fracture and Relative Frequency of Selected Fragility Fractures Among Older People Living in the United Kingdom

Data on fracture incidence for women (A) and men (B) aged ≥50 years were derived from the Clinical Practice Research Datalink involving 11.3 million people from 674 practices in the United Kingdom. For women, the numbers of incident fractures included any fracture (n=185,267), vertebra (n=13,485), humerus (n=30,686), radius/ulna (n=54,081), and hip/femur (n=45,727). For men, the number of incident fractures included any fracture (n=75,351), vertebra (n=57,477), humerus (n=98,299), radius/ulna (n=10,931), and hip/femur (n=14,263).
eFigure 2. Flow Chart for the Literature Search for Studies Investigating the Associations of Blood 25(OH)D Concentrations with Risk of Fracture

- 618 relevant studies identified
- 559 studies excluded (did not meet eligibility criteria)
- 59 studies considered potentially eligible
- 48 records excluded:
  - 16 cross-sectional design
  - 19 no 25(OH)D level
  - 3 duplicate studies
  - 8 fracture cases < 200
  - 3 only two 25(OH)D groups
- 11 studies met eligibility criteria
eFigure 3. Contour-Enhanced Funnel Plot for the Meta-analysis of Cohort Studies of Blood 25(OH)D Concentrations and Risk of Fracture
Different levels of statistical significance for cohort studies (points) are indicated by the shaded regions. In particular, the unshaded (i.e., white) region in the middle corresponds to p-values greater than 0.10, the dark blue-shaded region corresponds to p-values between 0.10 and 0.05, the light blue region corresponds to p-values between 0.05 and 0.01, and the grey region outside of the funnel corresponds to p-values below 0.01.
eFigure 4. Rate Ratios (95% CIs) for Any Fracture and Hip Fracture Associated with 10 ng/mL Higher blood 25(OH)D Concentrations in Cohort Studies by Baseline Characteristics

| Subgroups | Any fracture | | Hip fracture | |
|-----------|--------------|-----------------|--------------|-----------------|
|           | No. of studies | Cases/Total | RR (95% CI) | χ² (P for heterogeneity) | No. of studies | Cases/Total | RR (95% CI) | χ² (P for heterogeneity) |
| **Design** | | | | | | | | |
| NCC | 4 | 3469/8052 | 0.97 (0.92, 1.03) | | 2 | 1575/3413 | 0.83 (0.74, 0.93) | |
| Cohort | 6 | 2609/31 089 | 0.90 (0.85, 0.93) | 6.3 (0.01) | 3 | 792/12 807 | 0.78 (0.71, 0.86) | 0.7 (0.40) |
| **Age, year** | | | | | | | | |
| < 73 | 4 | 4220/21 076 | 0.96 (0.92, 1.00) | | 2 | 1575/3413 | 0.83 (0.74, 0.93) | |
| ≥ 73 | 6 | 2058/17 465 | 0.88 (0.83, 0.93) | 5.9 (0.01) | 3 | 792/12 807 | 0.78 (0.71, 0.86) | 0.7 (0.40) |
| **Region** | | | | | | | | |
| Europe | 5 | 3698/26 220 | 0.92 (0.88, 0.96) | | 2 | 1436/8377 | 0.80 (0.74, 0.88) | |
| Other | 5 | 2560/12 921 | 0.95 (0.91, 1.01) | 1.0 (0.92) | 3 | 931/7843 | 0.79 (0.70, 0.89) | 0.1 (0.80) |
| **Follow-up, year** | | | | | | | | |
| < 7 | 4 | 1670/11 553 | 0.93 (0.89, 0.99) | | 1 | 261/5764 | 0.76 (0.68, 0.86) | |
| ≥ 7 | 6 | 4608/27 508 | 0.92 (0.86, 0.96) | 0.2 (0.69) | 4 | 2105/10 456 | 0.82 (0.75, 0.90) | 1.0 (0.62) |
| **Baseline 25(OH)D, nmol/L** | | | | | | | | |
| < 60 | 5 | 4276/30 014 | 0.91 (0.87, 0.95) | | 4 | 2123/13 926 | 0.78 (0.72, 0.84) | |
| ≥ 60 | 5 | 2002/9127 | 0.95 (0.90, 1.01) | 1.9 (0.16) | 1 | 244/2294 | 0.90 (0.76, 1.05) | 2.3 (0.13) |
| **Overall** | 10 | 6278/39 141 | 0.93 (0.89, 0.96) | | 5 | 2367/16 220 | 0.80 (0.75, 0.86) | |
eFigure 5. Flow Chart of Literature Search for Trials Investigating the Effects of Vitamin D Alone or in Combination With Calcium for Prevention of Fracture

1262 records from PubMed, Embase, Cochrane Library, trial registries, and previous systematic reviews

525 excluded (duplicate)

737 records screened through titles and abstracts

685 excluded (did not meet eligibility criteria)

52 trials considered potentially eligible

36 trials excluded
  28 number of participants < 500
  12 did not include placebo or no treatment group
  3 no fracture events reported separately by arm or events number < 10
  1 treatment of multivitamin and mineral
  2 not randomised

16 trials met eligibility criteria
  11 trials included in vitamin D trial meta-analysis
  6 trials included in vitamin D + calcium meta-analysis
eFigure 6. Assessment of the Risk of Bias and Proportions of Randomized Clinical Trials That Met Each Criteria for Bias in the 16 Included Randomized Clinical Trials
eFigure 7. Contour-Enhanced Funnel Plot for the Meta-analysis of Randomized Clinical Trials of Vitamin D and Risk of Fracture
Different levels of statistical significance of the trials (points) are indicated by the shaded regions. In particular, the unshaded (i.e., white) region in the middle corresponds to p-values greater than 0.10, the dark blue-shaded region corresponds to p-values between 0.10 and 0.05, the dark light blue region corresponds to p-values between 0.05 and 0.01, and the grey region outside of the funnel corresponds to p-values below 0.01.
eFigure 8. Effects of Vitamin D Supplements on Risk of Any Fracture or Hip Fracture by Baseline Characteristics

| Subgroups                | No. of trials | Events/Total | RR (95% CI) | χ² (P for heterogeneity) |
|--------------------------|---------------|--------------|-------------|--------------------------|
| **Any fracture**         |               |              |             |                          |
| Age, year                |               |              |             |                          |
| < 80                     | 7             | 1899/23 364  | 1.08 (0.96, 1.19) |                           |
| ≥ 80                     | 4             | 944/10 879  | 1.03 (0.90, 1.18) | 0.4 (0.53)               |
| Living in institution    |               |              |             |                          |
| No                       | 8             | 2156/25 642  | 1.09 (0.99, 1.19) |                           |
| Yes                      | 3             | 697/8301     | 0.99 (0.85, 1.17) | 0.9 (0.34)               |
| Region                   |               |              |             |                          |
| Europe                   | 8             | 2225/26 191  | 1.02 (0.94, 1.12) |                           |
| Other                    | 3             | 618/8052     | 1.21 (1.03, 1.43) | 3.2 (0.07)               |
| Open label               |               |              |             |                          |
| Yes                      | 1             | 119/3717     | 1.39 (0.97, 2.00) |                           |
| No                       | 10            | 2724/30 526  | 1.05 (0.97, 1.14) | 2.2 (0.14)               |
| Frequency                |               |              |             |                          |
| Daily                    | 3             | 802/6397     | 1.06 (0.91, 1.23) |                           |
| Intermittent             | 8             | 2041/27 846  | 1.06 (0.97, 1.17) | 0.0 (0.95)               |
| Treatment difference in 25(OH)D, nmol/L | | | | |
| < 20                     | 5             | 1430/18 776  | 1.16 (1.04, 1.29) |                           |
| ≥ 20                     | 6             | 1413/15 467  | 0.97 (0.87, 1.09) | 5.0 (0.02)               |
| Overall                  | 11            | 2943/34 243  | 1.06 (0.98, 1.14) | 1.5 (0.75, 1.5)          |

| Subgroups                | No. of trials | Events/Total | RR (95% CI) | χ² (P for heterogeneity) |
|--------------------------|---------------|--------------|-------------|--------------------------|
| **Hip fracture**         |               |              |             |                          |
| Age, year                |               |              |             |                          |
| < 80                     | 4             | 277/17 059   | 1.19 (0.94, 1.51) |                           |
| ≥ 80                     | 4             | 463/10 879   | 1.10 (0.92, 1.33) | 0.2 (0.87)               |
| Living in institution    |               |              |             |                          |
| No                       | 5             | 383/19 637   | 1.18 (0.96, 1.45) |                           |
| Yes                      | 3             | 357/8301     | 1.09 (0.88, 1.35) | 0.9 (0.60)               |
| Region                   |               |              |             |                          |
| Europe                   | 7             | 706/25 680   | 1.13 (0.97, 1.32) |                           |
| Other                    | 1             | 34/2258      | 1.36 (1.04, 1.79) | 1.3 (0.25)               |
| Open label               |               |              |             |                          |
| Yes                      | 1             | 44/3717      | 1.26 (0.71, 2.33) |                           |
| No                       | 7             | 696/24 221   | 1.13 (0.97, 1.31) | 0.2 (0.68)               |
| Frequency                |               |              |             |                          |
| Daily                    | 3             | 291/6397     | 1.12 (0.89, 1.42) |                           |
| Intermittent             | 5             | 448/21 541   | 1.14 (0.95, 1.38) | 0.0 (0.91)               |
| Treatment difference in 25(OH)D, nmol/L | | | | |
| < 20                     | 4             | 276/18 090   | 1.28 (1.01, 1.62) |                           |
| ≥ 20                     | 4             | 464/5648     | 1.06 (0.88, 1.27) | 1.5 (0.22)               |
| Overall                  | 8             | 740/27 938   | 1.14 (0.98, 1.32) | 1.5 (0.75, 1.5)          |
eFigure 9. Rate Ratios (95% CI) for Any Fracture and for Hip Fracture by Treatment Differences in Blood 25(OH)D Concentrations in the Vitamin D Randomized Clinical Trials

Different point symbols indicate the adjusted rate ratios (RR) in individual trials, and the size of symbols is inversely proportional to the variance of the RR. The dashed line depicts the estimated linear relationship with 95% CI (grey area) between RR of fracture associated with treatment difference in 25(OH)D concentrations.
**eFigure 10. Contour-Enhanced Funnel Plot for the Meta-analysis of Randomized Clinical Trials of Calcium Plus Vitamin D Supplements and Risk of Fracture**

Different levels of statistical significance of the trials (points) are indicated by the shaded regions. In particular, the unshaded (i.e., white) region in the middle corresponds to p-values greater than 0.10, the dark blue-shaded region corresponds to p-values between 0.10 and 0.05, the dark light blue region corresponds to p-values between 0.05 and 0.01, and the grey region outside of the funnel corresponds to p-values below 0.01.
eFigure 11. Effects of Combined Vitamin D and Calcium Supplementation on Risk of Any Fracture or Hip Fracture by Baseline Characteristics

| Subgroups                  | Any fracture | Hip fracture |
|----------------------------|--------------|--------------|
|                            | No. of trials| Events/Total | RR (95% CI) | No. of trials | Events/Total | RR (95% CI) |
| **Age, year**              |              |              |             |              |              |             |
| < 80                       | 4            | 4969/45429   | 0.96 (0.90, 1.02) | 4            | 492/45429     | 0.92 (0.77, 1.10) |
| ≥ 80                       | 2            | 480/3853     | 0.76 (0.62, 0.92) | 2            | 238/3853      | 0.69 (0.53, 0.90)  |
| **Living in institution**  |              |              |             |              |              |             |
| No                         | 4            | 4969/45429   | 0.96 (0.90, 1.02) | 4            | 492/45429     | 0.92 (0.77, 1.10) |
| Yes                        | 2            | 480/3853     | 0.76 (0.62, 0.92) | 2            | 238/3853      | 0.69 (0.53, 0.90)  |
| **Region**                 |              |              |             |              |              |             |
| Europe                     | 5            | 1189/13000   | 0.85 (0.75, 0.96) | 5            | 358/13000     | 0.80 (0.65, 0.99)  |
| Other                      | 1            | 4200/36282   | 0.77 (0.91, 1.03) | 1            | 374/36282     | 0.87 (0.71, 1.07)  |
| **Open label**             |              |              |             |              |              |             |
| Yes                        | 2            | 338/5509     | 0.89 (0.71, 1.11) | 2            | 31/6509       | 0.88 (0.63, 1.26)  |
| No                         | 4            | 5111/42773   | 0.94 (0.89, 1.00) | 4            | 699/42773     | 0.84 (0.72, 0.97)  |
| **Calcium, mg/d**         |              |              |             |              |              |             |
| 1000                       | 4            | 4969/45429   | 0.96 (0.90, 1.02) | 4            | 492/45429     | 0.92 (0.77, 1.10) |
| 1200                       | 2            | 480/3853     | 0.76 (0.62, 0.92) | 2            | 238/3853      | 0.69 (0.53, 0.90)  |
| **Treatment difference in 25(OH)D, nmol/L** |              |              |             |              |              |             |
| Unknown                    | 1            | 109/2314     | 0.96 (0.69, 1.34) | 1            | 25/3314       | 0.72 (0.32, 1.61)  |
| < 50                       | 3            | 4820/42115   | 0.96 (0.90, 1.02) | 3            | 467/42115     | 0.93 (0.77, 1.12)  |
| ≥ 50                       | 2            | 480/3853     | 0.76 (0.62, 0.92) | 2            | 238/3853      | 0.69 (0.53, 0.90)  |

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eFigure 12. Rate Ratios (95% CIs) for Any Fracture or for Hip Fracture by Treatment Differences in Blood 25(OH)D Concentrations in the Calcium plus Vitamin D Randomized Clinical Trials

Different point symbols indicate the adjusted rate ratios (RR) in the individual trials, and the size of symbols is inversely proportional to the variance of the RR. The dashed line depicts the estimated linear relationship with 95% CI (grey area) between RR of fracture associated with treatment differences in 25(OH)D concentrations.
eFigure 13. Overall Effects of Supplementation of Vitamin D Alone or in Combination With Calcium on Risk of Any Fracture or of Hip Fracture in Meta-analyses of Randomized Clinical Trials in Their Epidemiological Context

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eFigure 14. Estimated Power for a Meta-analysis of Randomized Clinical Trials of Vitamin D for Prevention of Fracture Associated with a 20 ng/mL difference in Blood 25(OH)D Concentrations for 5 Years

A meta-analysis of ongoing vitamin D trials of high daily doses of vitamin D would be expected to achieve a treatment difference of ~50 nmol/L in blood 25(OH)D concentrations, and currently involve ~62 000 participants (equivalent to an effective population of ~50 000 assuming a 20% non-compliance rate). The power to detect a risk reduction of 9% for any fracture assuming annual event rates (AER) of 0.5%, 1.0%, and 2.0%, and a risk reduction of 19% for hip fracture assuming AER of 0.125%, 0.25%, and 0.5% are plotted.
| Meta-analysis         | Database | Search strategy                                                                 |
|----------------------|----------|---------------------------------------------------------------------------------|
| Randomised trials    | PubMed   | #1 "vitamin d"[MeSH Terms] OR "ergocalciferol" [MeSH Terms] OR "cholecalciferol" [MeSH Terms] OR "vitamin d"[All Fields] #2 "calcium"[MeSH Terms] #3 "fractures, bone"[MeSH Terms] OR "fracture"[Title/Abstract] OR "hip fracture"[Title/Abstract] #4 “trial”[Title/Abstract] OR "randomised trial"[Title/Abstract] OR "randomised controlled trial"[Title/Abstract] #5 “meta-analysis”[Title/Abstract] OR “systematic”[Title/Abstract] 
|                      |          | #6 #1 or #2 #7 #3 and #6 #8 #4 and #7 #9 #5 and #7 #10 #8 or #9 Filters: Humans; English |
| Prospective studies  | PubMed   | #1 “vitamin D”[Title/Abstract] OR “25-hydroxyvitamin D”[Title/Abstract] OR “25(OH) vitamin D”[Title/Abstract] #2 “fracture, bone”[MeSH Terms] OR “fracture” [Title/Abstract] OR “hip fracture” [Title/Abstract] #3 “cohort”[Text Word] OR “cohort studies”[MeSH Terms] OR “epidemiology”[MeSH Terms] OR “epidemiology”[All Fields] 
|                      |          | #3 #1 and #2 and #3 Filters: Humans; English                                    |
| Study                        | Design                  | No. of people | Age (year) | Wome n | Living in institution | Follow-up (year) | Baseline 25(OH)D (nmol/L) | Calcium intake (mg/d) | No. of any fracture | No. of hip fracture | Covariates                                                                 |
|-----------------------------|-------------------------|---------------|------------|--------|-----------------------|------------------|---------------------------|-----------------------|----------------------|---------------------|-----------------------------------------------------------------------------|
| Looker (2013) US<sup>7</sup> | cohort                  | 4749          | 73.5       | 49%    | no                    | 7.0              | 59.8                      | 735                   | 525                  | 287                 | Height, BMI, smoking, PA, milk intake, osteoporosis use, health status      |
| Buchebner (2014) Sweden<sup>8</sup> | cohort                  | 1044          | 75.5       | 100%   | no                    | 13.1             | 62.0                      | 349                   |                      |                     | Smoking, PA, bisphosphonate use                                             |
| Barbour (2012) US<sup>9</sup> | cohort                  | 2614          | 74.7       | 49%    | no                    | 6.4              | 60.6                      | 718                   | 247                  |                     | Age, sex, BMI, bone density, race, alcohol, fracture history, IL-6, serum calcium, eGFR, PTH, Clinical Comorbidity Index, Health ABC Performance Score, time of blood draw |
| Robinson-Cohen (2011) US<sup>11</sup> | cohort                  | 2294          | 73.9       | 70%    | no                    | 13.0             | 62.8                      | 244                   | 244                  |                     | Age, sex, BMI, smoking, alcohol, education, PA, race, region, calcium supplement, health status, cystatin C, diabetes, estrogen use, thiazide and loop diuretic use, time of blood draw |
| Holvik (2013) Norway<sup>11</sup> | case-cohort            | 2613          | 73.1       | 70%    | no                    | 10.7             | 55.9                      | 1175                  | 1175                 |                     | Age, sex, BMI, region, time of blood draw                                  |
| Steingrimsdottir (2014) Iceland<sup>15</sup> | cohort                  | 5764          | 76.7       | 57%    | no                    | 5.4              | 53.6                      | 261                   | 261                  |                     | Age, sex, height, BMI, smoking, alcohol, PA, time of blood draw             |
| Cauley (2011) US<sup>13</sup> | nested case-control    | 2264          | 64.1       | 100%   | no                    | 8.6              | 53.5                      | 616                   | 1132                 |                     | Age, weight, height, WC, PA, calcium intake, fracture history, time of blood draw |
| Cauley (2008) US<sup>15</sup> | nested case-control    | 800           | 71.0       | 100%   | no                    | 7.1              | 57.8                      | 1144                  | 400                  |                     | Age, BMI, smoking, alcohol, calcium intake, fracture history, corticosteroid use, region |
| Swanson (2015) US<sup>14</sup> | case-cohort            | 1000          | 74.6       | 0%     | no                    | 5.1              | 62.3                      | 432                   |                      |                     | Age, height, weight, race, region, PA, bone density, falls history, 1,25(OH)D, time of blood draw |
| Roddam (2007) UK<sup>4</sup> | nested case-control    | 2175          | 52.0       | 79%    | no                    | 5.0              | 81.0                      | 1002                  | 730                  |                     | BMI, smoking, alcohol, PA, method of recruitment, calcium intake, energy intake, marital status, parity and use of hormone therapy (women) |
| Julian (2016) UK<sup>15</sup> | cohort                  | 14 624         | 63.3       | 56%    | no                    | 15.0             | 58.1                      | 939                   | 1183                 |                     | Age, sex, BMI, smoking, alcohol, PA, supplement use, fracture history, time of blood draw |

eGFR: estimated glomerular filtration rate; PA: physical activity; PTH: parathyroid hormone; WC: waist circumference;
eTable 3. Assessment of the Risk of Bias in the Observational Studies Included in the Meta-analysis of the Observational Studies

| Study                  | Bias due to confounding | Bias in selection of study participants | Bias in measurement classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of reported results | Overall risk of bias |
|------------------------|-------------------------|-----------------------------------------|-----------------------------------------------------|--------------------------------------------------|-------------------------|----------------------------------|--------------------------------------|---------------------|
| Looker (2013)          | low                     | serious                                  | low                                                 | low                                              | low                     | low                              | low                                  | serious              |
| Buchebner (2014)       | low                     | low                                     | low                                                 | low                                              | serious                 | low                              | low                                  | serious              |
| Barbour (2012)         | low                     | moderate                                | low                                                 | low                                              | serious                 | low                              | low                                  | serious              |
| Robinson-Cohen (2011)  | low                     | serious                                  | low                                                 | low                                              | low                     | low                              | low                                  | serious              |
| Holvik (2013)          | serious                 | serious                                 | low                                                 | low                                              | low                     | low                              | low                                  | serious              |
| Steingrimsdottir (2014)| low                     | moderate                                | low                                                 | low                                              | low                     | low                              | low                                  | low                  |
| Cauley (2011)          | low                     | low                                     | low                                                 | low                                              | low                     | moderate                         | low                                  | moderate             |
| Cauley (2008)          | low                     | low                                     | low                                                 | low                                              | low                     | moderate                         | low                                  | moderate             |
| Swanson (2015)         | low                     | moderate                                | low                                                 | low                                              | low                     | serious                          | low                                  | serious              |
| Roddam (2007)          | low                     | low                                     | low                                                 | low                                              | low                     | low                              | low                                  | low                  |
| Julian (2016)          | low                     | low                                     | low                                                 | low                                              | low                     | low                              | low                                  | low                  |

ROBINS-I: Risk of bias in nonrandomized studies of interventions. The categories for risk of bias for each domain are “low risk”, “moderate risk”, “serious risk”, “critical risk” of bias and “no information”. We classified the overall risk of bias as low if all domains were at low risk of bias, as moderate if all domains were at low/moderate risk of bias, as serious if at least one domain was at serious risk of bias and not at critical risk of bias in any domain. We classified risk of bias as critical if at least one domain was at critical risk of bias. No information was defined if there is a lack of information in one or more key domains of bias.
| Excluded trials                      | No. of people | Other reasons for exclusion                                                                                                    | Treatment groups                                      |
|-------------------------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| Inkovaara (1983)                    | 327           | A total fracture events of 4<10                                                                                               | CaD vs VitD vs placebo                                  |
| Heikinheimo (1992)                  | 799           | Participants in vitamin D injection group who rejected injection were added to the control group. We excluded this trial like previous meta-analyses | VitD vs control                                        |
| Dawson-Hughes (1997)                | 390           |                                                                                                                                | CaD vs placebo                                         |
| Komulainen (1998)                   | 332           |                                                                                                                                | VitD vs placebo                                         |
| Peacock (2000)                      | 316           |                                                                                                                                | VitD vs Ca vs placebo                                   |
| Pfeifer (2000)                      | 148           | Did not include placebo or no treatment group                                                                               | CaD vs Ca                                              |
| Bischoff-Ferrari (2003)             | 122           | Did not include placebo or no treatment group                                                                               | CaD vs Ca                                              |
| Avenell (2004)                      | 134           |                                                                                                                                | VitD vs Ca vs control                                   |
| Harwood (2004)                      | 150           |                                                                                                                                | VitD injection vs VitD injection+ oral calcium vs oral CaD vs control |
| Larsen (2004)                       | 9605          | Not randomised (cluster randomised factorial design)                                                                            | CaD vs dietary advice                                  |
| Flicker (2005)                      | 625           | Did not include placebo or no treatment group                                                                               | CaD vs Ca+placebo                                      |
| Bolton-Smith (2007)                 | 244           |                                                                                                                                | VitK vs CaD vs VitK+CaD vs placebo                      |
| Burleigh (2007)                     | 205           | Did not include placebo or no treatment group                                                                               | CaD vs Ca                                              |
| Prince (2008)                       | 302           | Did not include placebo or no treatment group                                                                               | CaD vs Ca                                              |
| Pfeifer (2009)                      | 242           | Did not include placebo or no treatment group                                                                               | CaD vs Ca                                              |
| Bischoff-Ferrari (2010)             | 173           | Did not include placebo or no treatment group                                                                               | Extended physiotherapy vs standard physiotherapy vs VitD|
| Janssen (2010)                      | 70            | Did not include placebo or no treatment group                                                                               | CaD vs Ca+placebo                                      |
| Witham (2010)                       | 105           |                                                                                                                                | VitD vs placebo                                         |
| Mitri (2011)                        | 92            | 2<2 factorial design: VitD, Ca, placebo                                                                                       |                                                       |
| Papaioannou (2011)                  | 65            | High-dose VitD vs low dose VitD vs placebo                                                                                    |                                                       |
| Punthakee (2012)                    | 1221          | A fracture events number of 6<10                                                                                              | VitD vs placebo                                         |
| MacDonald (2013)                    | 305           | High dose VitD vs low dose VitD vs placebo                                                                                    |                                                       |
| Witham (2013)                       | 159           |                                                                                                                                | VitD vs placebo                                         |
| Breslavsky (2014)                   | 47            |                                                                                                                                | VitD vs placebo                                         |
| Massart (2014)                      | 55            |                                                                                                                                | VitD vs placebo                                         |
| Takano (2014)                       | 1054          | Did not include placebo or no treatment group                                                                               | Eldercalcitrol vs alfalcacidol                         |
| Baron (2015)                        | 2259          | No fracture events reported separately by arm                                                                                 |                                                       |
| Hansen (2015)                       | 230           |                                                                                                                                | Monthly VitD vs daily VitD vs placebo                  |
| Liu (2015)                          | 98            |                                                                                                                                | CaD vs control                                         |
| Uusi-Rasi (2015)                    | 409           | Factorial design: VitD and exercise                                                                                          |                                                       |
| Wang (2015)                         | 3318          | Multivitamin and mineral vs placebo                                                                                        |                                                       |
| Mak (2016)                          | 218           | Did not include placebo or no treatment group                                                                               | Injection VitD + CaD vs placebo + CaD                  |
| Hin (2017)                          | 305           | high dose VitD vs intermediate dose VitD vs placebo                                                                           |                                                       |
| Ginde (2017)                        | 107           | Did not include placebo or no-treatment group                                                                               | High vs standard dose VitD                             |
| Smith (2017)                        | 273           |                                                                                                                                | VitD vs placebo                                         |
| Xue (2017)                          | 312           |                                                                                                                                | CaD vs control                                         |

Ca: calcium; CaD: calcium and vitamin D; VitD: vitamin D
| Author (year) Country | No. of people | Age (year) | Wome n (%) | Instituti onalize d | Previou s fracture (%) | Vitamin D regimen | EDD (IU/d) | Control | Compliance (%) | Duration (year) | ∆25(OH)D (nmol/L)* | No. of any fracture VitD/Control | No. of hip fracture VitD/Contra ol | AER in control Any/Hip (%)† |
|---------------------|--------------|------------|-----------|---------------------|-----------------------|-------------------|-------------|---------|----------------|----------------|-----------------|-----------------------------|-----------------------------|-----------------------------|
| Glendenning (2012) Australia | 686 | 76.7 | 100 | no | 150 000 IU/3 m | 1667 | placebo | 0.8 (9 m) | 15.9 (n=40) | 10/10 | 3.7 |
| Larsen (2018) Norway | 511 | 61.8 | 38 | no | 20 000 IU/w | 2857 | placebo | 95–99 | 5.0 | 44.0 (n=256) | 15/13 | 1.0 |
| Law (2006) UK | 3717 | 85.0 | 76 | yes | 100000 IU/3 m | 1100 | no treatment | 0.8 (10 m) | 18.0 (n=18) | 66/53 | 24/20 | 3.4/1.3 |
| Meyer (2002) Norway | 1144 | 84.7 | 75 | yes | 28 | 5 ml of cod liver oil, 400 IU/d | 400 | placebo | 95 | 2.0 | 22.0 (n=65) | 69/76 | 50/47 | 6.6/4.1 |
| Lips (1996) The Netherlands | 2578 | 80.0 | 37 | no | 0 | 400 IU/d | 400 | placebo | 85 | 3.5 | 28.0 (n=270) | 135/122 | 58/48 | 2.7/1.1 |
| Trivedi (2003) UK | 2686 | 74.8 | 24 | no | 100 000 IU/ 4 m | 833 | placebo | 80 | 5.0 | 20.9 (n=235) | 119/149 | 21/24 | 2.2/0.4 |
| Sanders (2010) Australia | 2258 | 76.1 | 100 | no | 35 | 500 000 IU/y | 1370 | placebo | 4.0 | 12.0 (n=131) | 171/135 | 19/15 | 3.0/0.3 |
| Khaw (2017) New Zealand | 5108 | 65.9 | 42 | no | 47 | 200 000 IU at baseline, then 100 000 IU/m | 3412 | placebo | 84 | 3.4 | 59.0 (n=441) | 156/136 | 1.6 |
| Grant (2005) UK | 2275 | 77.0 | 85 | no | 35 | 800 IU/d | 800 | placebo | 81% ± 80% | 3.8 | 16.5 (n=60) | 208/192 | 47/41 | 3.8/0.8 |
| Lyons (2007) UK | 3440 | 84.0 | 76 | no/yes | 100 000 IU/4 m | 833 | placebo | 3.0 | 23.3 (n=102) | 205/218 | 112/104 | 4.2/2.0 |
| Smith (2007) UK | 9440 | 79.1 | 54 | no | 38 | 300 000 IU/y (intramuscular injection) | 822 | placebo | 3.0 | 14.8 (n=43) | 306/279 | 66/44 | 2.0/0.3 |

AER: annual event rate; EDD: equivalent daily dose; y: year; m: month; w: week; d: day

* Total number of participants who have tested blood 25(OH)D levels. Achieved treatment difference in 25(OH)D concentration.
† AER in control group was estimated as: [(number of events in control group / (Total number in control group × duration in years)) × 100]
| Author (year) | Country | No. of people | Age (year) | Women (%) | Living in institution | Previous Fracture/Fall (%) | Vitamin D (IU/d) | Calcium (mg/d) | Control | Compliance (%) | Duration (year) | Δ 25(OH)D* (nmol/L) | Any fracture CaD/Control | Hip fracture CaD/Control | AER in control Any/Hip (%)† |
|--------------|---------|---------------|------------|-----------|----------------------|---------------------------|------------------|----------------|---------|----------------|----------------|-------------------|-----------------------------|-----------------------------|-----------------------------|
| Chapuy (2002) Fiance | 583 | 85.2 | 100 | yes | 16 | 800 | 1200 | placebo | >95% | 2.0 | 68.0 (n=583) | 70/35 | 27/21 | 9.2/5.5 |
| Porthouse (2005) UK | 3314 | 76.8 | 100 | no | 58 | 800 | 1000 | general advice | 2.1 | 58/91 | 8/17 | 2.2/0.4 |
| Salovaara (2010) Finland | 3195 | 67.3 | 100 | no | 37 | 800 | 1000 | no treatment | 3.0 | 17.8 (n=574) | 86/103 | 4/2 | 2.1/0.04 |
| Grant (2005) UK | 2638 | 77.1 | 85 | no | 100 | 800 | 1000 | placebo | 76% ≥ 80% | 3.8 | 16.2 (n=60) | 179/192 | 46/41 | 3.8/0.8 |
| Chapuy (1992) France | 3270 | 84.0 | 100 | yes | 13 | 800 | 1200 | placebo | 1.5 | 72.5 (n=142) | 160/215 | 80/110 | 8.8/4.5 |
| Jackson (2006) US | 36282 | 62.4 | 100 | no | 34 | 400 | 1000 | placebo | 59% ≥ 80% | 7.0 | 23.0 (n=292) | 2102/2158 | 175/199 | 1.7/0.2 |

* Achieved treatment difference in blood 25(OH)D concentrations (Total number of participants who had blood 25(OH)D concentration measured)
† AER in control group was estimated as: number of events in control group / (Total number in control group x duration in years)) x 100
### eTable 7. Ongoing Large Randomized Clinical Trials of Supplementation With Vitamin D Alone or in Combination With Calcium for Prevention of Fracture or Other Disease Outcomes

| Trial (Country) | No. of participants | Age (year) | Duration (year) | Treatment | Primary endpoint |
|----------------|---------------------|------------|-----------------|-----------|-----------------|
| VITAL (United States) | 25,874 | ≥50 (M) ≥55 (W) | 5 | 2000 IU/d VitD | Cancer, CVD |
| D-Health (Australia) | 21,315 | 65-84 | 5 | 60 000 IU/m VitD | Total mortality, cancer |
| TIPS-3 (Canada) | 5713 | ≥55 (M) ≥60 (W) | 5 | 60 000 IU/m VitD | CVD, fracture, cancer |
| FiND (Finland) | 2500 | ≥60 (M) ≥65 (W) | 5 | 3200 or 1600 IU/d VitD | Cancer, CVD |
| D2d (United States) | 2423 | ≥30 | 4 | 4000 IU/d VitD | Diabetes, fracture |
| DO-HEALTH (Europe) | 2159 | ≥70 | 3 | 2000 IU/d VitD | Fracture |
| CAPS (United States) | 2303 | ≥55 (W) | 4 | 1500 mg/d calcium + 2000 IU/d VitD | Cancer, CVD, fracture |
| **Total** | **62,287** | | | | |

Trials were included with ≥1000 participants; CAPS Clinical Trial of Vitamin D3 to Reduce Cancer Risk in Postmenopausal Women; D2d The Vitamin D and Type 2 Diabetes Study; DO-HEALTH Vitamin D3 Omega-3 Home Exercise Healthy Aging and Longevity Trial; FiND Finnish Vitamin D Trial; TIPS-3 The International Polycap Study-3; VITAL ViTamin D and Omega-3 Trial; M: men; W: women; m: month; d: day

* Locations included Canada, Bangladesh, Colombia, India, Malaysia, Philippines, Tanzania, Tunisia
† Due to difficulties in recruitment and funding, the study size is approximately 2500 in FiND⁵,⁶,²
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