# Long-Term Follow-Up for Mortality and Cancer in a Randomized Placebo-Controlled Trial of Vitamin $D_3$ and/or Calcium (RECORD Trial)

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**Context:** Vitamin D or calcium supplementation may have effects on vascular disease and cancer.

**Objective:** Our objective was to investigate whether vitamin D or calcium supplementation affects mortality, vascular disease, and cancer in older people.

**Design and Setting:** The study included long-term follow-up of participants in a two by two factorial, randomized controlled trial from 21 orthopedic centers in the United Kingdom.

**Participants:** Participants were 5292 people (85% women) aged at least 70 yr with previous low-trauma fracture.

**Interventions:** Participants were randomly allocated to daily vitamin $D_3$ (800 IU), calcium (1000 mg), both, or placebo for 24–62 months, with a follow-up of 3 yr after intervention.

**Main Outcome Measures:** All-cause mortality, vascular disease mortality, cancer mortality, and cancer incidence were evaluated.

**Results:** In intention-to-treat analyses, mortality [hazard ratio (HR) = 0.93; 95% confidence interval (CI) = 0.85–1.02], vascular disease mortality (HR = 0.91; 95% CI = 0.79–1.05), cancer mortality (HR = 0.85; 95% CI = 0.68–1.06), and cancer incidence (HR = 1.07; 95% CI = 0.92–1.25) did not differ significantly between participants allocated vitamin D and those not. All-cause mortality (HR = 1.03; 95% CI = 0.94–1.13), vascular disease mortality (HR = 1.07; 95% CI = 0.92–1.24), cancer mortality (HR = 1.13; 95% CI = 0.91–1.40), and cancer incidence (HR = 1.06; 95% CI = 0.91–1.23) also did not differ significantly between participants allocated calcium and those not. In a *post hoc* statistical analysis adjusting for compliance, thus with fewer participants, trends for reduced mortality with vitamin D and increased mortality with calcium were accentuated, although all results remain nonsignificant.

**Conclusions:** Daily vitamin D or calcium supplementation did not affect mortality, vascular disease, cancer mortality, or cancer incidence. **(*J Clin Endocrinol Metab* 97: 614–622, 2012)**

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Abbreviations: CI, Confidence interval; HR, hazard ratio; ITT, intention to treat; RR, risk ratio; WHI, Women's Health Initiative.

The effect of calcium and/or vitamin D on a wide variety of nonfracture health outcomes is the subject of a great deal of scientific and lay interest. The recent Institute of Medicine report on dietary intake requirements supported a key role for vitamin D and calcium for skeletal health but did not find conclusive evidence for nonskeletal benefits (1).

The active metabolite of vitamin D, 1,25-dihydroxyvitamin $D_3$, and its analogs have *in vivo* anticancer effects, including inhibition of cellular proliferation, activation of apoptosis, inhibition of angiogenesis, and potentiation of cytotoxic drugs (2). Meta-analysis of observational studies suggests an increased risk of colorectal cancer with low vitamin D status (3). Although recently published follow-up data from the Third National Health and Nutritional Examination Survey and the Osteoporotic Fractures in Men Study do not support the hypothesis that serum 25-hydroxyvitamin D is associated with reduced cancer mortality (4, 5).

Meta-analysis of randomized controlled trials by Autier and Gandini (6) suggested that vitamin D supplementation, given mainly for fracture prevention, may reduce all-cause mortality. In the Framingham Offspring Study cohort, low vitamin D status was associated with an increased risk of developing cardiovascular disease (7). However, the Osteoporotic Fractures in Men Study did not find an association between low 25-hydroxyvitamin D and subsequent all-cause or cardiovascular mortality, although lower PTH levels appeared protective (5). Accumulating evidence suggests that vitamin D is essential for normal cardiomyocyte, vascular smooth muscle, and vascular endothelial cell function (8) and may lower blood pressure in people with hypertension (9).

Many trials of vitamin D supplementation for fracture prevention have cosupplemented with calcium (10). Calcium supplementation might reduce the risk of developing colorectal adenomatous polyps (11). However, although systematic review evidence from trials suggests that calcium supplementation may lower systolic blood pressure in people who are hypertensive (12), recently published meta-analyses have found an increased risk of myocardial infarction with calcium supplementation, with or without vitamin D (13, 14).

The RECORD Trial was a pragmatic, randomized factorial-designed, placebo-controlled, trial of calcium and/or vitamin $D_3$ supplementation for the secondary prevention of fragility fractures in 5292 older people (15). We prespecified in our protocol long-term follow-up for secondary outcomes of mortality due to cardiovascular disease or cerebrovascular disease and cancer (15).

## Subjects and Methods

### Participants

The RECORD Trial was based in 21 centers in England and Scotland. Full details of all the methods can be found in the main trial report for fracture outcomes (15). Participants were recruited from fracture clinics or orthopedic wards. Inclusion criteria were fragility fracture within the last 10 yr and aged at least 70 yr. Exclusion criteria were cancer likely to metastasize to bone within the previous 10 yr, bed- or chair-bound before fracture, abbreviated mental test below 7 (16), fracture associated with preexisting local bone abnormality, known hypercalcemia, renal stone in the last 10 yr, life expectancy less than 6 months, known to be leaving the United Kingdom, taking more than 200 IU (5 $\mu$g) vitamin D or more than 500 mg calcium in supplements daily, treatment with fluoride, bisphosphonates, calcitonin, tibolone, hormone replacement therapy, selective estrogen receptor modulators, or any vitamin D metabolite (such as calcitriol) in the last 5 yr or vitamin D by injection in the last year.

### Interventions

Participants were randomized into four equal groups to receive two tablets daily with meals containing a total of 800 IU (20 $\mu$g) vitamin $D_3$, 1000 mg elemental calcium (as carbonate), both vitamin $D_3$ and calcium, or placebo. Tablets varied in size and taste, and so each had matching placebos. Calcium and calcium and vitamin D tablets were large, and those for vitamin D were small. Placebos matched in size were provided for each of these three types of tablets. All trial materials were delivered by post every 4 months.

### Outcomes and follow-up

All-cause mortality, mortality due to vascular disease and cancer, and cancer registrations were prespecified outcomes in the main trial protocol (http://www.thelancet.com/protocol-reviews/02PRT-35). This paper reports follow-up mortality data that had been notified during the trial and within 3 yr of trial closure as well as cancer notifications relevant to this period. This timing was selected because the effects of calcium and vitamin D may be lost within 2 yr of cessation of supplementation (17). This timing was also based on a power calculation of at least 400 cancer registrations at follow-up from the 5292 trial participants, giving 80% power ($P < 0.05$) to detect an absolute reduction of 2% (from 8 to 6%). Data were derived only from the main cause of death for death registrations, and registrations of new cancers for all trial participants were collected only through the national United Kingdom databases of the General Register of Scotland; the National Health Service Medical Research Information Service, England; and the United Kingdom Association of Cancer Registries (www.ukacr.org). The data presented here were not examined by a trial adjudication committee but were collected completely independent of the trial. The above organizations all undertake rigorous quality checks on a regular basis.

Because the exact mechanisms by which calcium or vitamin D may influence the circulation are unclear, a wide definition from the International Classification of Diseases was adopted *a priori* (ICD codes I00–I99) for total vascular disease deaths. Data are also presented separately for cardiovascular disease deaths (ICD I20–I25) and cerebrovascular disease deaths (ICD I60–I69).

### Randomization

Randomization was centralized, computer generated, stratified by center, and minimized by age (under 80 yr or 80 yr and over), gender, time since fracture (previous 3 months or longer), and type of enrolling fracture (proximal femur, distal forearm, clinical vertebral, and other).

### Compliance

Compliance was measured by 4-monthly postal questionnaire, where participants were asked how many days of the last seven they took tablets. A random 10% sample returned unconsumed tablets for pill counting. In two trial centers, a sample of 60 participants had blood collected for 25-hydroxyvitamin $D_3$ measured using straight-phase HPLC at baseline and 1 yr later (18).

### Dietary calcium and vitamin D assessment

Dietary calcium and vitamin D intake were assessed using food frequency questionnaires, based on Nelson *et al.* (19) and the United Kingdom National Diet and Nutrition Survey (20), respectively, and sunlight exposure by a questionnaire about time outdoors and season.

### Statistical analysis

Survival time was modeled using Cox proportional hazards regression models. Four outcome survival measures were explored: time to death, time to death from vascular disease and cancer (censoring those dying from other causes in each case), and time to cancer incidence. The explanatory variables in the models were the treatment group and the variables used for minimization at randomization (age, gender, time since fracture, and type of fracture). The main analyses focused on main effects reflecting the factorial design: vitamin $D_3$ *vs.* no vitamin $D_3$ and calcium *vs.* no calcium. Interaction between calcium and vitamin $D_3$ was also tested for.

Two methods of handling the noncompliance were used. First, intention-to-treat (ITT, patients analyzed as per the treatment they were randomized to) was used on the complete dataset.

Compliance with trial medication was limited (15). Among those returning questionnaires (or after assuming nonresponders were noncompliers), the rates of pill takers were 67% (54%) at 12 months and 63% (45%) at 24 months. Poorer compliance with tablets containing calcium (difference 9.4% for all participants randomized at 2 yr) appeared to reflect more frequent decisions to stop because of gastrointestinal symptoms (15). We therefore undertook a *post hoc* analysis to explore the effects of compliance with the treatment regimen on outcome. Compliance was based on postal data collected 2 yr after randomization, when compliers were still taking tablets on 80% of days, and we used a simple all or nothing definition of compliance for these analyses. The method of Loeys and Goetghebeur (21) was implemented using the stcomply command in Stata (22). For each model, hazard ratios (HR) with 95% confidence intervals (CI) were calculated.

## Results

### Recruitment and comparability of trial group at entry

A total of 5292 people, with a mean age of 77 (SD 6) years joined the trial between February 1999 and March 2002. The four primary trial groups were well balanced at trial entry (Table 1). The median length of follow-up for the data reported here was 6.2 yr. Participants had poor

**TABLE 1.** Description of groups at trial entry

| | Vitamin $D_3$ and calcium (n = 1306) | Vitamin $D_3$ (n = 1343) | Calcium (n = 1311) | Placebo (n = 1332) | With vitamin $D_3$ (n = 2649) | Without vitamin $D_3$ (n = 2643) | With calcium (n = 2617) | Without calcium (n = 2675) |
|---|---|---|---|---|---|---|---|---|
| Age [mean (SD) yr] | 78 (6) | 77 (6) | 77 (6) | 77 (6) | 77 (6) | 77 (6) | 77 (6) | 77 (6) |
| Sex [n (%) female] | 1104 (84.5) | 1136 (84.6) | 1113 (84.9) | 1128 (84.7) | 2240 (84.6) | 2241 (84.8) | 2217 (84.7) | 2264 (84.6) |
| White [n (%)] | 1298 (99.4) | 1331 (99.1) | 1303 (99.4) | 1320 (99.1) | 2629 (99.2) | 2623 (99.2) | 2601 (99.4) | 2651 (99.1) |
| Months since enrolling fracture [median(IQR)] | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–2) |
| Diabetic [n (%)] | 109 (8.4) | 99 (7.4) | 111 (8.5) | 101 (7.6) | 208 (7.9) | 212 (8.1) | 220 (8.5) | 200 (7.5) |
| Oral hypoglycemics | 57 (4.4) | 62 (4.6) | 59 (4.5) | 49 (3.7) | 119 (4.5) | 108 (4.1) | 116 (4.4) | 111 (4.1) |
| Insulin | 20 (1.5) | 20 (1.5) | 27 (2.1) | 23 (1.7) | 40 (1.5) | 50 (1.9) | 47 (1.8) | 43 (1.6) |
| Calcium intake, mg/d [mean (SD)] | 818 (355) | 813 (359) | 814 336) | 834 (861) | 815 (357) | 823 (349) | 816 (345) | 824 (360) |
| Vitamin D deficiency risk [n (%)] | | | | | | | | |
| High risk | 390 (30.8) | 420 (32.4) | 390 (31.2) | 419 (32.9) | 809 (32.0) | 810 (31.6) | 839 (32.7) | 780 (31.0) |
| Low risk | 876 (69.2) | 875 (67.6) | 862 (68.8) | 854 (67.1) | 1716 (68.0) | 1751 (68.4) | 1729 (67.3) | 1738 (69.0) |
| Weight, kg [mean (SD)] | 65 (13) | 65 (13) | 65 (13) | 65 (12) | 65 (13) | 65 (12) | 65 (13) | 65 (13) |
| Current smoker [n (%)] | 158 (12.1) | 140 (10.5) | 164 (12.5) | 156 (11.7) | 298 (11.3) | 320 (12.1) | 322 (12.3) | 296 (11.1) |
| Daily physical activity [n (%)] | 1221 (93.7) | 1271 (95.0) | 1232 (94.2) | 1255 (94.4) | 2492 (94.4) | 2487 (94.3) | 2453 (93.9) | 2526 (94.7) |
| Could walk out of doors unaccompanied | | | | | | | | |
| Current use [n (%)] | | | | | | | | |
| $T_4$ | 117 (9.1) | 97 (7.3) | 129 (10.0) | 91 (6.9) | 214 (8.2) | 220 (8.4) | 246 (9.5) | 188 (7.1) |
| Oral steroids ≥7.5 mg prednisolone daily | 31 (2.4) | 18 (1.4) | 27 (2.1) | 17 (1.3) | 49 (1.9) | 44 (1.7) | 58 (2.2) | 35 (1.3) |
| Thiazide diuretics | 258 (20.2) | 292 (22.2) | 273 (21.4) | 288 (22.0) | 550 (21.2) | 561 (21.7) | 531 (20.8) | 580 (22.1) |
| Type of enrolling fracture [n (%)] | | | | | | | | |
| Proximal femur | 228 (17.5) | 231 (17.2) | 222 (16.9) | 223 (16.7) | 459 (17.3) | 445 (16.8) | 450 (17.2) | 454 (17.0) |
| Other leg and pelvic | 285 (21.8) | 255 (19.0) | 308 (23.5) | 282 (21.2) | 540 (20.4) | 590 (22.3) | 593 (22.7) | 537 (20.1) |
| Distal forearm | 452 (34.6) | 472 (35.1) | 460 (35.1) | 462 (34.7) | 924 (34.9) | 922 (34.9) | 912 (34.8) | 934 (34.9) |
| Other arm | 339 (26.0) | 383 (28.5) | 319 (24.3) | 362 (27.2) | 722 (27.3) | 681 (25.8) | 658 (25.1) | 745 (27.9) |
| Other | 2 (0.2) | 2 (0.1) | 2 (0.2) | 3 (0.2) | 4 (0.2) | 5 (0.2) | 4 (0.2) | 5 (0.2) |

IQR, Interquartile range.

**TABLE 2.** Outcomes according to allocation

| Outcome | Vitamin $D_3$ and calcium | Vitamin $D_3$ | Calcium | Placebo | With vitamin $D_3$ | Without vitamin $D_3$ | With calcium | Without calcium |
|---|---|---|---|---|---|---|---|---|
| n | 1306 | 1343 | 1311 | 1332 | 2649 | 2643 | 2617 | 2675 |
| All new cancer events total | 182 | 187 | 189 | 165 | 369 | 354 | 371 | 352 |
| Breast | 20 | 23 | 21 | 16 | 43 | 37 | 41 | 39 |
| Colorectal | 24 | 17 | 22 | 8 | 41 | 30 | 46 | 25 |
| Lung | 10 | 14 | 14 | 18 | 24 | 32 | 24 | 32 |
| Prostate | 8 | 9 | 4 | 8 | 17 | 12 | 12 | 17 |
| Other | 120 | 124 | 128 | 115 | 244 | 243 | 248 | 239 |
| Participants with cancer events | 166 | 172 | 163 | 152 | 338 | 315 | 329 | 324 |
| 1 | 154 | 157 | 140 | 140 | 311 | 280 | 294 | 297 |
| 2 | 9 | 15 | 20 | 11 | 24 | 31 | 29 | 26 |
| ≥3 | 3 | 0 | 3 | 1 | 3 | 4 | 6 | 1 |
| All deaths total | 415 | 421 | 447 | 434 | 836 | 881 | 862 | 855 |
| All cancer deaths total | 78 | 73 | 95 | 83 | 151 | 178 | 173 | 156 |
| Breast | 7 | 7 | 9 | 4 | 14 | 13 | 16 | 11 |
| Colorectal | 13 | 7 | 7 | 6 | 20 | 13 | 20 | 13 |
| Lung | 14 | 10 | 13 | 21 | 24 | 34 | 27 | 31 |
| Prostate | 2 | 4 | 3 | 3 | 6 | 6 | 5 | 7 |
| Other | 42 | 45 | 63 | 49 | 87 | 112 | 105 | 94 |
| All vascular disease deaths total | 177 | 173 | 194 | 182 | 350 | 376 | 371 | 355 |
| Cardiovascular | 88 | 74 | 91 | 85 | 162 | 176 | 179 | 159 |
| Cerebrovascular | 56 | 59 | 54 | 51 | 115 | 105 | 110 | 110 |
| Other | 33 | 40 | 49 | 46 | 73 | 95 | 82 | 86 |

vitamin D status at recruitment (25-hydroxyvitamin D 38 nmol/liter in a subgroup from all groups in the trial at baseline) (11).

### Outcomes (Table 2)

Overall, during the trial and 3 yr of follow-up, 1717 of 5292 participants (32.4%) died. The main cause of death was recorded as vascular disease for 726 participants (42.3% of deaths) and cancer for 329 participants (19.2% of deaths). Of 5292 participants (12.3%), 653 developed a new cancer.

### Vitamin D (Table 3 and Fig. 1)

In the ITT analysis, 836 participants (31.6%) of 2649 participants allocated vitamin D died compared with 881 of 2643 (33.3%) not allocated vitamin D (HR = 0.93; 95% CI = 0.85–1.02). The incidence of vascular disease deaths (HR = 0.91; 95% CI = 0.79–1.05), cancer deaths (HR = 0.85; 95% CI = 0.68–1.06), and participants developing cancer (HR = 1.07; 95% CI = 0.92–1.25) did not differ significantly in the ITT analysis between participants allocated vitamin D and those who were not.

### Calcium (Table 3 and Fig. 2)

In the ITT analysis, 862 participants (32.9%) of 2617 participants allocated calcium died compared with 855 of 2675 (32.0%) not allocated calcium (HR = 1.03; 95% CI = 0.94–1.13). The incidence of vascular disease deaths (HR = 1.07; 95% CI = 0.92–1.24), cancer deaths (HR = 1.13; 95% CI = 0.91–1.40), and participants developing cancer (HR = 1.06; 95% CI = 0.91–1.23) did not differ significantly in the ITT analysis between participants allocated calcium or those who were not.

**TABLE 3.** HR for mortality, vascular disease mortality, cancer mortality, and cancer: ITT analysis

| | With vitamin $D_3$ or calcium | | | Without vitamin $D_3$ or calcium | | | | |
|---|---|---|---|---|---|---|---|---|
| | Events | No. of participants | % with event | Events | No. of participants | % with event | HR (95% CI): ITT estimate | *P* value |
| Vitamin $D_3$ | | | | | | | | |
| All deaths | 836 | 2649 | 31.6 | 881 | 2643 | 33.3 | 0.93 (0.85–1.02) | 0.132 |
| Vascular deaths | 350 | 2649 | 13.2 | 376 | 2643 | 14.2 | 0.91 (0.79–1.05) | 0.175 |
| Cancer deaths | 151 | 2649 | 5.7 | 178 | 2643 | 6.7 | 0.85 (0.68–1.06) | 0.157 |
| Cancer incidence | 338 | 2649 | 12.8 | 315 | 2643 | 11.9 | 1.07 (0.92–1.25) | 0.376 |
| Calcium | | | | | | | | |
| All deaths | 862 | 2617 | 32.9 | 855 | 2675 | 32.0 | 1.03 (0.94–1.13) | 0.460 |
| Vascular deaths | 371 | 2617 | 14.2 | 355 | 2675 | 13.3 | 1.07 (0.92–1.24) | 0.333 |
| Cancer deaths | 173 | 2617 | 6.6 | 156 | 2675 | 5.8 | 1.13 (0.91–1.40) | 0.249 |
| Cancer incidence | 329 | 2617 | 12.6 | 324 | 2675 | 12.1 | 1.06 (0.91–1.23) | 0.485 |

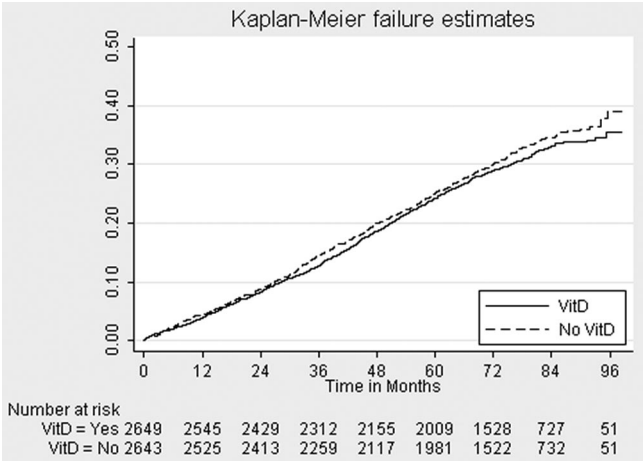


**FIG. 1.** Cumulative all-cause mortality by allocation to vitamin D or no vitamin D (VitD).

We undertook *post hoc* analyses to examine whether participants using thiazide diuretics at baseline, which cause calcium retention, or participants with higher calcium intakes at baseline had increased risk of vascular disease mortality. There was no evidence of a higher risk of cardiovascular death in those that were using thiazide diuretics at baseline (tested for by examining the interaction of thiazide by calcium). Nor was there any evidence of a higher risk of vascular death in those with a high baseline intake of calcium at baseline, defined as more than 800 mg a day (tested for by examining the interaction between calcium intake at baseline and calcium).

Forty-six new colorectal cancers were diagnosed in participants allocated calcium and 25 in those not allocated calcium. Twenty participants allocated calcium died of colorectal cancer compared with 13 participants not allocated calcium (Table 2).

### Analyses adjusted for compliance (Table 4)

In the *post hoc* analyses adjusted for compliance with vitamin D, all-cause mortality (HR = 0.80; 95% CI = 0.61–1.11), vascular disease mortality (HR = 0.76; 95% CI = 0.49–1.40), cancer mortality (HR = 0.61; 95% CI = 0.37–1.30), and participants developing cancer (HR = 1.24; 95% CI = 0.80–2.28) also did not differ significantly in response to vitamin D, although all trends were accentuated compared with the ITT analysis.

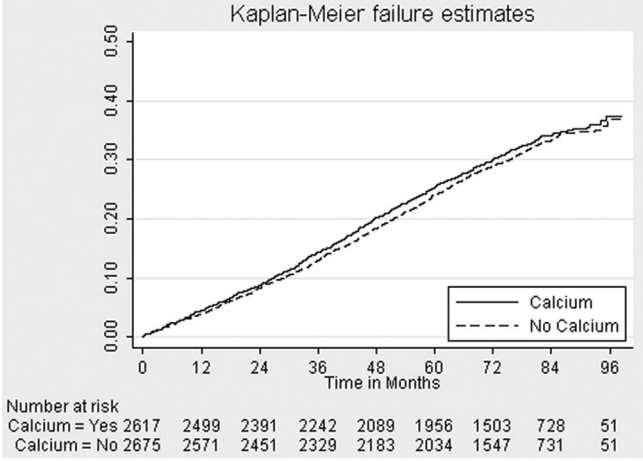


**FIG. 2.** Cumulative all-cause mortality by allocation to calcium or no calcium.

**TABLE 4.** HR for mortality, vascular disease mortality, cancer mortality, and cancer: adjusted treatment-received analysis

| | HR (95% CI) |
|---|---|
| Vitamin D *vs.* no vitamin D | |
| All deaths | 0.80 (0.61–1.11) |
| Vascular deaths | 0.76 (0.49–1.40) |
| Cancer deaths | 0.61 (0.37–1.30) |
| Cancer incidence | 1.24 (0.80–2.28) |
| Calcium *vs.* no calcium | |
| All deaths | 1.21 (0.83–2.05) |
| Vascular deaths | 1.43 (0.75–7.61) |
| Cancer incidence | 1.26 (0.73–3.26) |

Similarly, for calcium in the analyses adjusted for compliance, all-cause mortality (HR = 1.21; 95% CI = 0.83–2.05), vascular disease mortality (HR = 1.43; 95% CI = 0.75–7.61), and cancer incidence (HR = 1.26; 95% CI = 0.73–3.26) were not significantly different between those participants allocated calcium and those not. Again, all trends were accentuated in this compared with the ITT analysis. There were insufficient data to provide confidence intervals for cancer mortality.

## Discussion

### Principal findings for vitamin D

In this older age group at high risk of refracture, daily 800 IU vitamin $D_3$ supplementation was not found to significantly reduce all-cause and vascular disease mortality or cancer incidence or mortality in the ITT analyses. Previously, we found that vitamin D supplementation did not affect glycemic control or fracture risk in the RECORD Trial population (15, 23).

We do not know whether the results reported here would be found in younger populations, older people without a history of previous fragility fracture, or very high-risk populations in nursing homes. In the United Kingdom, 47% of people aged 45 yr have also been found to fall below a level for 25-hydroxyvitamin D of 40 nmol/liter in winter and spring, a level similar to the baseline level in the RECORD Trial subgroup (24). Thus even young populations may be at risk at higher latitudes with little food fortification.

### Comparison with other studies: all-cause mortality

Autier and Gandini (6) undertook a meta-analysis in 57,311 participants of randomized trials of vitamin D supplementation with or without calcium, which included the RECORD Trial data from the initial trial report (15). They found that the risk ratio (RR) for all-cause mortality was 0.93 (95% CI = 0.87–0.99), similar to the point estimate for the ITT result found here. Vitamin D doses were 300–833 IU/d, and additional supplementation with calcium did not appear to influence this result. Most of these trials were fracture prevention trials.

A recent Cochrane review has examined the effect of vitamin D on mortality in randomized trials (25). Vitamin $D_3$ given without calcium was not found to significantly reduce mortality (RR = 0.95; 95% CI = 0.82–1.02).

### Comparison with other studies: vascular disease

The Women's Health Initiative (WHI) randomized trial examined the effect of daily 400 IU vitamin $D_3$ and 1000 mg calcium together for a mean of 7 yr in 36,282 postmenopausal women (mean age 62 yr) on myocardial infarction and coronary heart disease death (HR = 1.04; 95% CI = 0.92–1.18) and stroke (HR = 0.95; 95% CI = 0.82–1.10) (26). Baseline 25-hydroxyvitamin D levels in two subgroups were around 47 nmol/liter (27). WHI also found no statistically significant effect of supplementation on systolic or diastolic blood pressure (28). However, the effects of vitamin D could not be disassociated from those of calcium, and 54% of women were taking their own calcium supplements at randomization (14). For the women in WHI, who did not take calcium supplements at randomization, calcium and vitamin D supplementation was associated with an increased risk of cardiovascular events (14). Trial-level meta-analysis, including women in WHI who did not take calcium supplements at randomization, also suggests increased cardiovascular events with calcium and vitamin D given together (14).

Trivedi *et al.* (29) randomized 2686 men and women (mean age 75 yr) to 100,000 IU vitamin $D_3$ or placebo every 4 months for 5 yr. Vitamin D only supplementation was associated with a decrease in vascular disease mortality (age-adjusted RR = 0.84; 95% CI = 0.65–1.10). Baseline vitamin D status was not assessed.

### Comparison with other studies: cancer

The WHI trial also examined the effect of calcium and vitamin D on the risk of developing cancer (HR = 0.98; 95% CI = 0.91–1.05), invasive breast cancer (HR = 0.96; 95% CI = 0.85–1.09), or invasive colorectal cancer (HR = 1.08; 95% CI = 0.86–1.34) (30, 31). Cancer deaths (HR = 0.89; 95% CI = 0.77–1.03), deaths from breast cancer (HR = 0.99; 95% CI = 0.55–1.76), and deaths from colorectal cancer (HR = 0.82, 95% 0.52–1.29) were not significantly reduced (30, 31). There is evidence to suggest that coadministration of estrogen in WHI may have modified the effect of calcium and vitamin D on colorectal cancer risk (32).

Trivedi *et al.* (29) also found that mortality from cancer was reduced, although not significantly (age-adjusted RR = 0.86; 95% CI = 0.61–1.20).

Lappe *et al.* (33) randomized 1179 women (median age 67 yr, baseline 25-hydroxyvitamin D 72 nmol/liter) to 1100 IU vitamin $D_3$ and 1500 mg calcium, calcium alone, or placebo for 4 yr and reported a reduced risk of cancer on calcium and vitamin D compared with placebo group, which had a higher than expected rate of cancer. However, the methods and analysis of this trial have been criticized, and reanalysis suggests that calcium but not vitamin D was associated with reduced cancer risk (6).

### Principal findings for calcium

Daily supplementation with 1000 mg calcium carbonate was not found to significantly affect cancer incidence or mortality, overall mortality, or vascular mortality.

### Comparisons with other studies

In an individual patient data meta-analysis, which includes RECORD Trial data collected during the trial, Bolland *et al.* (14) reported a significantly increased risk of myocardial infarction with supplemental calcium (HR = 1.31; 95% CI = 1.02–1.67), which did not appear to relate to the form of calcium supplement (mostly calcium carbonate or citrate). We examined all vascular mortality, which increased our statistical power. Our results are consistent with the Bolland meta-analysis. We found trends in the same direction, especially in the analysis adjusted for compliance, with confidence intervals overlapping those in the Bolland meta-analysis.

A Cochrane systematic review (11) based on two randomized trials with 1346 participants with previous colorectal adenomas concluded that calcium supplementation of 1200–2000 mg/d over 3–4 yr reduced recurrence of adenomas. In the RECORD Trial, we did not have sufficient statistical power to evaluate the effect of calcium on colorectal cancer, but events and deaths were higher in the calcium-supplemented group. A New Zealand trial reported that supplementation with 1000 mg calcium over 5 yr in 1471 women (mean age 74 yr, baseline 25-hydroxyvitamin D 52 nmol/liter) did not reduce the incidence of any cancer (34).

### Analyses adjusted for compliance

Our *post hoc* analyses adjusted for compliance did not significantly change our findings, although all trends were

accentuated. Compliance was based on the details provided by participants in postal questionnaires rather than tablet counting for all participants. The pragmatic nature of the RECORD Trial, without frequent follow-up visits and tablet counting reflects real-world practice, where compliance with tablet taking in older people, including for osteoporosis treatment, is frequently poor (35). Owing to the staggered nature of recruitment, 5292 participants were in the trial for 2 yr, 4090 participants were in the trial for 3 yr, and 1979 were in the trial for 4 yr (these figures include all people randomized). The worst-case scenario for compliance, assuming that people failing to return questionnaires did not take any tablets, indicated tablet taking on more than 80% of days for 45% at 2 yr, 35% at 3 yr, and 25% at 4 yr.

Our analyses adjusted for compliance had reduced statistical power, and we were unable to provide CI for calcium and cancer mortality. Adjusting for compliance also made no difference to the results for fracture from the RECORD Trial (data not shown), which could also have been influenced by inadequate statistical power.

Poorer compliance with calcium-containing tablets appeared to partly relate to a variety of gastrointestinal symptoms rather than the larger size of calcium tablets (15). Compliance with the larger placebo calcium tablets was only 2% less than with the small placebo vitamin D tablets.

Future trials of vitamin D will need to address the issue of compliance. Intermittent oral vitamin D dosing, such as used by Trivedi *et al.* (29), might improve compliance with vitamin D, and higher doses may help to circumvent poor compliance. However, annual dosing with large doses of vitamin D was recently found to increase the risk of falls and fractures in an Australian trial by Sanders and colleagues (36).

The RECORD Trial was able to examine outcomes in response to calcium or vitamin D supplementation separately in the same trial. The blinded, placebo-controlled nature of the trial and the independent collection of the data presented here through national databases mean that bias in data collection is unlikely.

Participants were older and had poorer vitamin D status at recruitment than many other trials (25-hydroxyvitamin D 38 nmol/liter at baseline) (15) so might have been more likely to benefit from vitamin D supplementation. 25-Hydroxyvitamin D was recorded in only a very small subgroup of 60 participants in the RECORD Trial. These participants may not have been representative of the wider trial population, because they had agreed to extra study visits and may thus have been fitter than the general RECORD population. However, with such a large trial, it is likely that baseline 25-hydroxyvitamin D status was very similar between the groups. Supplementation achieved a level of 25-hydroxyvitamin D of 62 nmol/liter in this subgroup (15), a level that could be suboptimal (37).

In the United Kingdom, cod liver oil is a common over-the-counter supplement (also containing retinol) purchased by older people for themselves. In the RECORD Trial, over-the-counter use of up to 200 IU/d (5 $\mu$g) of vitamin D was permitted, and 17% of RECORD participants reported using cod liver oil at recruitment, with numbers balanced between groups. Over-the-counter use of calcium is, however, rare in the United Kingdom, and only 1.5% of RECORD participants reported using calcium at baseline (permitted use up to 400 mg/d). Data on calcium and vitamin were not collected during the open follow-up period. But in an open trial run in parallel with the blinded part of the RECORD Trial (38), no person reported purchasing calcium or vitamin D supplements, and only one person was prescribed vitamin D by their doctor, of a total number of 180 participants in the trial. Because RECORD found no significant effect on fractures, we think it is unlikely that substantial numbers of participants would have started to use supplements during the open period of follow-up.

Our results add to the body of evidence on nonskeletal benefits from supplementation with vitamin D and calcium and are consistent with the view that, at least for vascular disease and cancer, conclusive evidence for such benefits is absent.

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