

Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial

The RECORD Trial Group*

Summary

Background Elderly people who have a fracture are at high risk of another. Vitamin D and calcium supplements are often recommended for fracture prevention. We aimed to assess whether vitamin D3 and calcium, either alone or in combination, were effective in prevention of secondary fractures.

Methods In a factorial-design trial, 5292 people aged 70 years or older (4481 [85%] of whom were women) who were mobile before developing a low-trauma fracture were randomly assigned 800 IU daily oral vitamin D3, 1000 mg calcium, oral vitamin D3 (800 IU per day) combined with calcium (1000 mg per day), or placebo. Participants who were recruited in 21 UK hospitals were followed up for between 24 months and 62 months. Analysis was by intention-to-treat and the primary outcome was new low-energy fractures.

Findings 698 (13%) of 5292 participants had a new low-trauma fracture, 183 (26%) of which were of the hip. The incidence of new, low-trauma fractures did not differ significantly between participants allocated calcium and those who were not (331 [12.6%] of 2617 vs 367 [13.7%] of 2675; hazard ratio (HR) 0.94 [95% CI 0.81–1.09]); between participants allocated vitamin D3 and those who were not (353 [13.3%] of 2649 vs 345 [13.1%] of 2643; 1.02 [0.88–1.19]); or between those allocated combination treatment and those assigned placebo (165 [12.6%] of 1306 vs 179 [13.4%] of 1332; HR for interaction term 1.01 [0.75–1.36]). The groups did not differ in the incidence of all-new fractures, fractures confirmed by radiography, hip fractures, death, number of falls, or quality of life. By 24 months, 2886 (54.5%) of 5292 were still taking tablets, 451 (8.5%) had died, 58 (1.1%) had withdrawn, and 1897 (35.8%) had stopped taking tablets but were still providing data for at least the main outcomes. Compliance with tablets containing calcium was significantly lower (difference: 9.4% [95% CI 6.6–12.2]), partly because of gastrointestinal symptoms. However, potentially serious adverse events were rare and did not differ between groups.

Interpretation The findings do not support routine oral supplementation with calcium and vitamin D3, either alone or in combination, for the prevention of further fractures in previously mobile elderly people.

Introduction

Low-trauma fractures in elderly people are a substantial and increasing burden of ill health,^{1,2} and those who have a low-trauma fracture are at high risk of another.³ Low serum concentrations of vitamin D metabolites are widespread in elderly people in the UK,⁴ especially in those with low-trauma fractures.⁵ Vitamin D and calcium, alone or in combination, are often recommended for prevention of osteoporotic fractures. Inadequate vitamin D status, exacerbated by low calcium intake, might raise the risk of these fractures by increasing bone resorption and loss from secondary hyperparathyroidism. Vitamin D might also protect against falls that lead to fracture.⁶ Evidence from randomised trials favours the combination of calcium and vitamin D.⁷ In this secondary-prevention study we aimed to test whether calcium and vitamin D, alone or in combination compared with placebo, would lead to one less person per 100 having a fracture every year over a median of 3 years.

Methods

Participants

15 024 people age 70 years or older who had had a low-trauma, osteoporotic fracture in the previous 10 years were assessed between Feb 1, 1999, and March 31, 2002. The trial was based in 21 hospitals in the UK. Ethics approval was obtained from the Multicentre Research Ethics Committee for Scotland and from the local research ethics committee of each hospital, and participants gave written informed consent.

Study nurses identified potential participants from hospital notes of patients seen in a fracture clinic or orthopaedic ward; patients were also recruited by telephone. Reasons for exclusion were: bed or chair bound before fracture; cognitive impairment indicated by an abbreviated mental test score⁸ of less than seven; cancer in the past 10 years that was likely to metastasise to bone; fracture associated with pre-existing local bone abnormality; those known to have hypercalcaemia; renal stone in the past 10 years; life expectancy of less than



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6 months; individuals known to be leaving the UK; daily intake of more than 200 IU vitamin D or more than 500 mg calcium supplements; intake in the past 5 years of fluoride, bisphosphonates, calcitonin, tibolone, hormone-replacement therapy, selective oestrogen-receptor modulators, or any vitamin D metabolite (eg, calcitriol); and vitamin D by injection in the past year. An osteoporotic fracture was defined as a fracture due to a fall from no more than standing height, or as a definite clinical event with radiologist-confirmed evidence of a vertebral fracture. Fractures of the cervical spine, face, or skull, and those caused by road-traffic accidents were not classed as osteoporotic.

Study design

Participants were randomly allocated to four equal groups and assigned two tablets with meals daily consisting of 800 IU vitamin D3, 1000 mg calcium (given as carbonate), vitamin D3 (800 IU) combined with calcium (1000 mg), or placebo. Tablets varied in size and taste and thus each had matching placebos. All materials were delivered by post every 4 months⁹ and participants were asked to take tablets until trial closure.

Randomisation was centralised; computer-generated; stratified by centre; and minimised by age (younger than 80 years or 80 years and older), sex, time since fracture (previous three months or longer), and type of fracture (proximal femur, distal forearm, clinical vertebral, or other).

The allocation programme was written by the trial programmer (GCM) and the allocation remained concealed until the final analyses (other than for confidential reports to the data monitoring committee). All outcomes were reported or verified by people who were masked to the allocation scheme.

Compliance was measured by a postal questionnaire sent every 4 months, in which participants were asked how many days of the past 7 days they had taken tablets. A randomly selected 10% sample (525 participants) was asked to return unused tablets for pill counting. 375 (71%) individuals returned pills.

Intake of dietary calcium and vitamin D was assessed by food-frequency questionnaires based on those of Nelson¹⁰ and the UK National Diet and Nutrition Survey,⁴ respectively; sunlight exposure was assessed by a question about time spent outdoors during different seasons.

25-OH-vitamin D₃ was quantified after extraction from plasma by use of straight-phase high-performance liquid chromatography¹¹ (lower detection limit 3 ng/mL). Intra-assay coefficient of variation (CV) was less than 10% and interassay CV was less than 12% in the range 10–40 ng/mL. Intact parathyroid hormone was measured by immunometric assay (Nichols Institute, San Juan, Capistrano, CA, USA) with a detection limit of 0.5 pmol/L, and inter-assay and intra-assay CV of less than 5% in the range 1–40 pmol/L. Independent analysis

of the tablets was done by Tepnel Scientific Services, Edinburgh, UK.

The time interval from randomisation to trial closure was between 24 and 62 months (median 45, IQR 37–52). The principal outcome measure was all-new low-energy fractures including clinical, radiologically confirmed vertebral fractures, but not those of the face or skull. Data for further fractures and deaths were obtained from several sources: postal questionnaires every 4 months with telephone follow-up if needed; hospital and general-practice staff; nominated friends or relatives of participants; and national routine data-collection systems of the UK Office of National Statistics, the Information and Statistics Division (Scotland), and the Hospital Episode Statistics gathered by the Department of Health in England. Confirmation of fracture was always sought from a second source. Moreover, data for health status (as assessed by Short-Form 12¹² and Euroqol-5D),¹³ hospital admission, change of residence, falls, and possible adverse events were obtained from the postal questionnaires and were supplemented by further clinical information on potentially serious adverse events. Differential effects on falls were assessed by one question in every questionnaire: “Have you fallen during the last week?”. In two trial centres (Southampton, and Newcastle-Upon-Tyne), a sample of participants had blood taken for assessment of 25-OH-vitamin D3 and parathyroid hormone before starting supplementation and 1 year after randomisation.

Statistical analysis

The sample size was based on a factorial design to test calcium versus no calcium and vitamin D3 versus no vitamin D3. The anticipated incidence of new fractures in the control group was 15%, based on similar trials. The aim was to enrol 4200 participants to give 80% power ($2P < 0.05$) to detect a decrease in incidence to 12%. Furthermore, the sample size was anticipated to have over 80% power to identify a 2% absolute difference in rates of hip fracture. Initially, 6500 participants were sought, on the basis of expected losses to follow-up of 35%. However, this number was adjusted during recruitment (June, 2001) to 5200 participants on the basis of a higher rate of retention. An independent data and safety monitoring committee met yearly, and on each occasion recommended continuation to achieve maximum recruitment.

Analysis was done 2 years after the last person was recruited and was based on intention-to-treat. Dichotomous outcomes (ie, yes/no questions from the questionnaire) were analysed over 24 months by use of logistic regression, and over the total duration of follow-up by use of Cox regression. Quality-of-life outcomes were examined by ANCOVA, with adjustment for 4-month quality-of-life scores as baseline. All analyses were adjusted for minimisation variables. Interaction between calcium and vitamin D3 was tested for. Previously specified subgroup analyses were done after stratification by: high or low weight (less than 55 kg or not); latitude of recruitment

centre (northern, central [south of Durham and north of London], or southern); dietary calcium (high [≥ 700 mg per day], moderate [400–699 mg per day], or low [< 400 mg per day]); and vitamin D exposure from the sun or diet (high or low [ie, participants did or did not go outdoors or had a dietary intake of less than 200 IU vitamin D per day, respectively]). Analysis based on compliance status (still taking tablets on $> 80\%$ days at 2 years or not) was also done, with tests for treatment by subgroup interactions. The main outcome was subdivided into categories of fracture to investigate possible differential effects. Stricter levels of significance ($2P < 0.01$) were sought because of the exploratory nature of the analyses.

We have adhered to the principles outlined in the CONSORT statement for reporting randomised controlled trials,¹⁴ and to those outlined by McAlister and colleagues¹⁵ for reporting of factorial designs.

The protocol for this study was peer reviewed and accepted by *The Lancet*; a summary of the protocol was published on the journal's website, and the journal then made a commitment to peer-review the primary clinical manuscript.

Role of the funding source

The UK Medical Research Council funded the central organisation of RECORD, and Shire Pharmaceuticals funded the drugs, which were cofunded and manufactured by Nycomed. Shire Pharmaceuticals and Nycomed were given the opportunity to comment on the penultimate version of the trial report. No funding source had any role in the collection, management, analysis, or interpretation of the data; writing of the report; or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

Figure 1 shows the trial profile. Of 15 024 people assessed, about a third joined the trial and about 3500 of those who were eligible did not participate. Those recruited were younger (mean age 77 years [SD 6]) than were those who declined (80 years [6]) or who were ineligible (82 years [7]). The main reasons for ineligibility were cognitive impairment (2666 [43.0%]), current antiosteoporotic

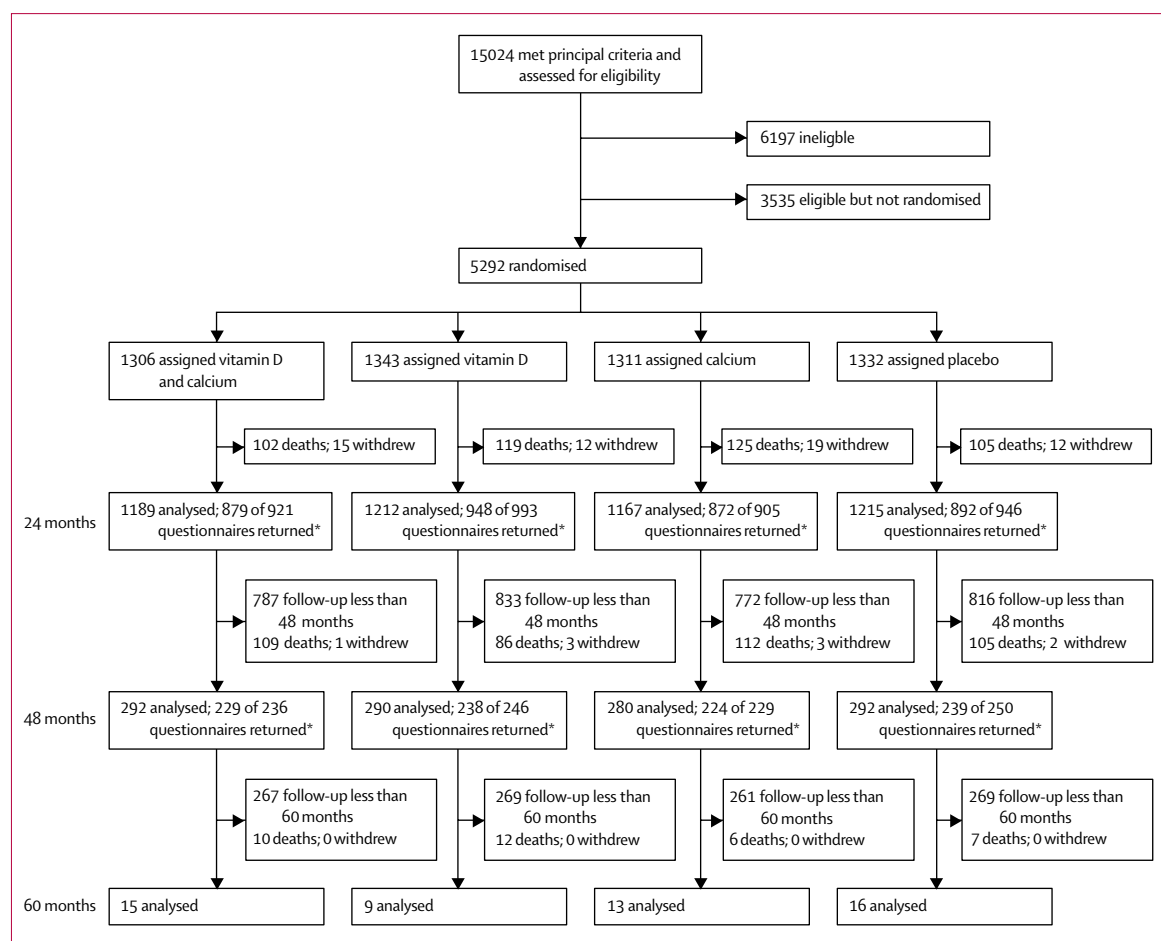


Figure 1: Trial profile

*Some participants who remained in the trial asked not to be sent questionnaires.

	Vitamin D3 and calcium (n=1306)	Vitamin D3 (n=1343)	Calcium (n=1311)	Placebo (n=1332)	With calcium (n=2617)	Without calcium (n=2675)	With vitamin D3 (n=2649)	Without vitamin D3 (n=2643)
Age (years)	78 (6)	77 (6)	77 (6)	77 (6)	77 (6)	77 (6)	77 (6)	77 (6)
Sex (% female)	1104 (85%)	1136 (85%)	1113 (85%)	1128 (85%)	2217 (85%)	2264 (85%)	2240 (85%)	2241 (85%)
White	1298 (99%)	1331 (99%)	1303 (99%)	1320 (99%)	2601 (99%)	2651 (99%)	2629 (99%)	2623 (99%)
Type of enrolling fracture for trial entry								
Proximal femur	228 (17.5%)	231 (17.2%)	222 (16.9%)	223 (16.7%)	450 (17.2%)	454 (17.0%)	459 (17.3%)	445 (16.8%)
Other leg and pelvic	285 (21.8%)	255 (19.0%)	308 (23.5%)	282 (21.2%)	593 (22.7%)	537 (20.1%)	540 (20.4%)	590 (22.3%)
Distal forearm	452 (34.6%)	472 (35.1%)	460 (35.1%)	462 (34.7%)	912 (34.8%)	934 (34.9%)	924 (34.9%)	922 (34.9%)
Other arm	339 (26.0%)	383 (28.5%)	319 (24.3%)	362 (27.2%)	658 (25.1%)	745 (27.9%)	722 (27.3%)	681 (25.8%)
Clinical vertebral	2 (0.2%)	2 (0.1%)	1 (0.1%)	3 (0.2%)	3 (0.1%)	5 (0.2%)	4 (0.2%)	4 (0.2%)
Other	1 (0.1%)	..	1 (0.04%)	1 (0.04%)
Time since enrolling fracture (months)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)
Previous fracture since age 50 years	452 of 1303 (34.7%)	469 of 1332 (35.2%)	457 of 1309 (34.9%)	472 of 1323 (35.7%)	909 of 2612 (34.8%)	941 of 2655 (35.4%)	921 of 2635 (35.0%)	929 of 2632 (35.3%)
Weight (kg)	65 (13)	65 (13)	65 (13)	65 (12)	65 (13)	65 (13)	65 (13)	65 (12)
Current smoker	158 of 1306 (12.1%)	140 of 1337 (10.5%)	164 of 1311 (12.5%)	156 of 1332 (11.7%)	322 of 2617 (12.3%)	296 of 2669 (11.1%)	298 of 2643 (11.3%)	320 of 2643 (12.1%)
Daily physical activity (ie, could walk outdoors unaccompanied)	1221 of 1303 (93.7%)	1271 of 1338 (95.0%)	1232 of 1308 (94.2%)	1255 of 1330 (94.4%)	2453 of 2611 (93.9%)	2526 of 2668 (94.7%)	2492 of 2641 (94.4%)	2487 of 2638 (94.3%)
Current use of thyroxine	117 of 1291 (9.1%)	97 of 1328 (7.3%)	129 of 1291 (10.0%)	91 of 1320 (6.9%)	246 of 2583 (9.5%)	188 of 2648 (7.1%)	214 of 2620 (8.2%)	220 of 2611 (8.4%)
Oral steroids ≥ 7.5 mg prednisolone per day	31 of 1292 (2.4%)	18 of 1330 (1.4%)	27 of 1296 (2.1%)	17 of 1316 (1.3%)	58 of 2588 (2.2%)	35 of 2646 (1.3%)	49 of 2622 (1.9%)	44 of 2612 (1.7%)
Thiazide diuretics	258 of 1275 (20.2%)	292 of 1316 (22.2%)	273 of 1278 (21.4%)	288 of 1310 (22.0%)	531 of 2553 (20.8%)	580 of 2626 (22.1%)	550 of 2591 (21.2%)	561 of 2588 (21.7%)

Data are number of patients (%), mean (SD), or median (IQR).

Table 1: Baseline characteristics at trial entry by randomised group and by supplement groups

treatment (2103 [33.9%]), and previous excluding cancer (680 [11.0%]); this group also had a higher incidence of previous proximal-femur fracture than those recruited (2239 vs 904 [36.1% vs 17.1%]). Table 1 shows baseline characteristics. Half the initial notifications of further fractures came from responses to the participant questionnaire alone and half from other sources.

Postal-questionnaire data for compliance and quality of life after excluding deaths were available for 4514 (86.6%) of 5210 participants at 4 months, 3991 (78.7%) of 5068 at 12 months, and for 3591 (74.2%) of 4841 at 24 months. Based on questionnaire responses at 24 months, 2886 (54.5%) of 5292 were still taking tablets, 451 (8.5%) had died, 58 (1.1%) had withdrawn,

and 1897 (35.8%) had stopped tablets but were still providing data on at least the main outcome measures.

Table 2 shows compliance at 24 months. Throughout the trial about 80% of those taking tablets did so on more than 80% of days, which is consistent with pill counts in the subsample (data not shown). However, the number who were taking any tablets fell over time. At 4 months, 3398 (68.7%) of the 4949 who returned questionnaires had taken pills on more than 80% of days (or 3398 [65.2%] of 5210 after assuming non-responders were non-compliers and excluding known deaths). The equivalent figures up to 12 months were 2554 of 4251 (60.1%) or 2554 of 5068 (50.4%), and up to 24 months were 2268 of 3765 (60.2%) or 2268 of 4841 (46.8%).

	Vitamin D3 and calcium	Vitamin D3	Calcium	Placebo	With calcium	Without calcium	With vitamin D3	Without vitamin D3
All participants still taking tablets*	673	806	641	766	1314	1572	1479	1407
>80% of days	508 (75.5%)	651 (80.8%)	498 (77.7%)	611 (79.8%)	1006 (76.6%)	1262 (80.3%)	1159 (78.4%)	1109 (78.8%)
<80% of days	165 (24.5%)	155 (19.2%)	143 (22.3%)	155 (20.2%)	308 (23.4%)	310 (19.7%)	320 (21.6%)	298 (21.2%)
All participants still completing questionnaires*†	921	993	905	946	1826	1939	1914	1851
>80% of days	508 (55.2%)	651 (65.6%)	498 (55.0%)	611 (64.6%)	1006 (55.1%)	1262 (65.1%)	1159 (60.6%)	1109 (59.9%)
<80% of days	413 (44.8%)	342 (34.4%)	407 (45.0%)	335 (35.4%)	820 (44.9%)	677 (34.9%)	755 (39.4%)	742 (40.1%)
All randomised*‡	1204	1224	1186	1227	2390	2451	2428	2413
>80% of days	508 (42.2%)	651 (53.2%)	498 (42.0%)	611 (49.8%)	1006 (42.1%)	1262 (51.5%)	1159 (47.7%)	1109 (46.0%)
<80% of days	696 (57.8%)	573 (46.8%)	688 (58.0%)	616 (50.2%)	1384 (57.9%)	1189 (48.5%)	1269 (52.3%)	1304 (54.0%)

Data are number of patients (%). *Participants who did not return a questionnaire at 24 months but were known to be compliant later were assumed to be compliant at 24 months. †Assuming that those not taking tablets were non-compliant. ‡Excluding known deaths.

Table 2: Compliance at 24 months

	Vitamin D3 and calcium (n=1306)	Vitamin D3 (n=1343)	Calcium (n=1311)	Placebo (n=1332)	With calcium (n=2617)	Without calcium (n=2675)	HR (95% CI)	With vitamin D3 (n=2649)	Without vitamin D3 (n=2643)	HR (95% CI)
New fractures	184 (14.1%)	212 (15.8%)	189 (14.4%)	196 (14.7%)	373 (14.3%)	408 (15.3%)	0.99 (0.86–1.15)	396 (14.9%)	385 (14.6%)	1.01 (0.88–1.17)
Confirmed fractures	179 (13.7%)	208 (15.5%)	185 (14.1%)	192 (14.4%)	364 (13.9%)	400 (15.0%)	0.99 (0.86–1.15)	387 (14.6%)	377 (14.3%)	1.01 (0.87–1.16)
Low-trauma fractures only	165 (12.6%)	188 (14.0%)	166 (12.7%)	179 (13.4%)	331 (12.6%)	367 (13.7%)	0.94 (0.81–1.09)	353 (13.3%)	345 (13.1%)	1.02 (0.88–1.19)
Proximal femur	46 (3.5%)	47 (3.5%)	49 (3.7%)	41 (3.1%)	95 (3.6%)	88 (3.3%)	..	93 (3.5%)	90 (3.4%)	..
Other leg and pelvic	37 (2.8%)	48 (3.6%)	41 (3.1%)	54 (4.1%)	78 (3.0%)	102 (3.8%)	..	85 (3.2%)	95 (3.6%)	..
Distal forearm	33 (2.5%)	33 (2.5%)	33 (2.5%)	28 (2.1%)	66 (2.5%)	61 (2.3%)	..	66 (2.5%)	61 (2.3%)	..
Other arm	46 (3.5%)	48 (3.6%)	33 (2.5%)	49 (3.7%)	79 (3.0%)	97 (3.6%)	..	94 (3.5%)	82 (3.1%)	..
Clinical vertebral	0	4 (0.3%)	3 (0.2%)	1 (0.1%)	3 (0.1%)	5 (0.2%)	..	4 (0.2%)	4 (0.2%)	..
Other	3 (0.2%)	8 (0.6%)	7 (0.5%)	6 (0.5%)	10 (0.4%)	14 (0.5%)	..	11 (0.4%)	13 (0.5%)	..
Deaths	221 (16.9%)	217 (16.2%)	243 (18.5%)	217 (16.3%)	464 (17.7%)	434 (16.2%)	..	438 (16.5%)	460 (17.4%)	..
Time to death(months)	24 (13.5–38.0)	22 (10.5–35.0)	22 (10.0–33.0)	24 (13.0–34.0)	24 (11.0–34.0)	23 (12.0–35.0)	1.13 (0.98–1.3)	23 (12–36)	23.5 (11–33)	0.92 (0.80–1.05)
Reported falls during window weeks*	161 (12.3%)	219 (16.3%)	185 (14.1%)	196 (14.7%)	346 (13.2%)	414 (15.5%)	0.89 (0.77–1.02)	380 (14.3%)	381 (14.4%)	0.97 (0.84–1.12)

Data are number of patients (%) or median (IQR). *Window weeks=the single weeks before completion of 4-monthly questionnaires.

Table 3: Main outcomes by randomised group and by supplement groups

Poor compliance with calcium tablets (table 2; difference 9.4%, 95% CI 6.6–12.2) was associated with more frequent decisions to stop because of gastrointestinal symptoms or difficulties in taking the tablets. Furthermore, gastrointestinal symptoms were the main reason why more people allocated calcium than those allocated vitamin D3 reported possible side-effects (428 [16.4%] for those assigned calcium vs 319 [11.9%] for those not; 363 [13.7%] for people assigned vitamin D3 vs 386 [14.5%] for those not). Possible serious adverse effects were rare: renal insufficiency (seven participants), renal stones (four) and hypercalcaemia (21) and did not differ between the groups (data not shown). At 1 year, 35 (3.5%) of 997 of participants allocated placebo were taking drugs active on bone (mainly bisphosphonates), and 20 (2.0%) participants allocated placebo were taking prescribed calcium or vitamin D either alone or in combination. At 2 years, 40 (4.5%) of 892 participants assigned placebo were taking bone-active drugs and 25 (2.8%) were taking open calcium or vitamin D either alone or in combination. These rates were similar in the calcium and vitamin D groups.

Overall, 698 (13%) participants had a new low-trauma fracture, 183 (4%) of whom had a hip fracture. 331 (12.6%) of 2617 participants allocated calcium had a new low-trauma fracture compared with 367 (14%) of 2675 participants not allocated calcium (hazard ratio [HR] 0.94 [0.81–1.09]). The incidence of new low-trauma fractures did not differ significantly between those allocated vitamin D3 and those who were not (table 3 and figure 2), or between those allocated combination treatment and those allocated placebo (HR for interaction term 1.01 [0.75–1.36]). No differences were seen between the trial groups with respect to the incidence of all fractures, radiographically confirmed fractures, hip fractures, other types of fracture; death; and time to fracture or death (table 3). Moreover, there was no evidence of differential effects on fracture risk or that calcium or vitamin D3 had an effect in the previously

specified subgroups (figure 3), especially for the type of fracture at recruitment. No difference was recorded in the groups who complied with treatment (ie, per protocol analysis). Overall, 761 (14.4%) participants reported having a fall during the weeks studied and the groups did not differ significantly in this respect. Table 4 shows no difference in quality of life at 4 months and at 2 years.

Two batches analysed by inductively coupled plasma emission spectrometry had a mean value of 421 mg calcium per tablet (SD 14), and five batches analysed by high-performance liquid chromatography had a mean value of 372 IU vitamin D3 per tablet (SD 38).

The mean baseline concentration of 25(OH) vitamin D3 for a sample of 60 participants was 15.2 ng/mL (SD 6.5). After 1 year of supplementation, concentrations rose by 9.6 ng/mL (6.9) for participants allocated combination treatment, 9.7 ng/mL (8.7) for participants allocated vitamin D3, 1.4 ng/mL (5.7) for those assigned calcium, and by 3.1 ng/mL (7.2) for those allocated placebo.

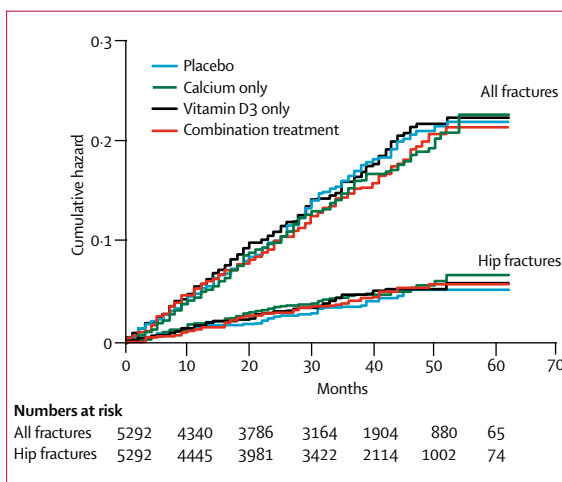


Figure 2: Cumulative rates of all fractures and of hip fractures by group
Numbers at risk of hip fracture are higher because they include participants who had another type of fracture.

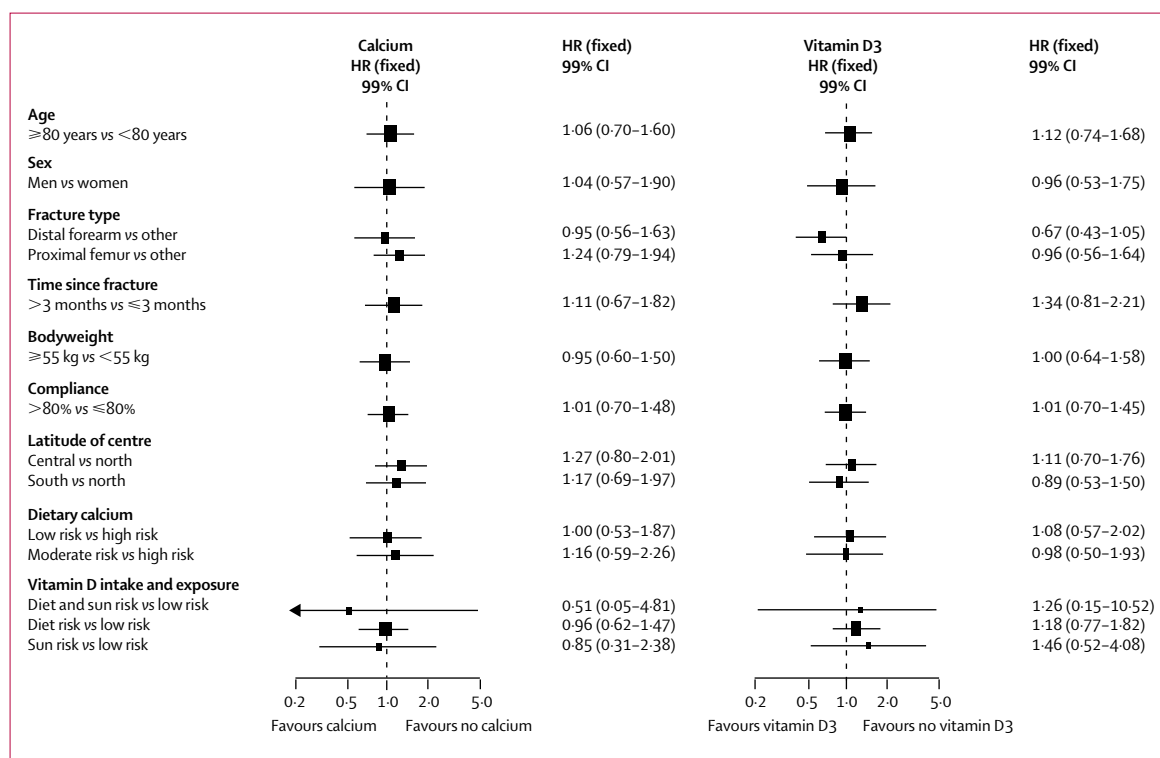


Figure 3: Subgroup analysis of fracture incidence

Similarly, a subsample of 60 participants had mean baseline concentrations of parathyroid hormone of 5.5 pmol/L (11 [19%] of whom had a concentration of >6.9 pmol/L, SD 2.4), which decreased by 1.9 pmol/L (2.2) for participants assigned combination treatment, 0.7 (1.6) for vitamin D3, 1.6 (1.6) for calcium, and by 0.7 (1.5) for placebo.

Discussion

In this trial of secondary-fracture prevention, incidence of fractures did not differ between those allocated any calcium versus no calcium, between those allocated any vitamin D3 versus no vitamin D3, or between those allocated combination treatment versus placebo.

As expected, the rate of further low-trauma fracture was high (one in eight). However, there were fewer hip fractures than anticipated, which was related to the tendency for older people to be ineligible because of cognitive impairment (43% of participants in this trial) or because they had already been prescribed bone-active drugs (34%). Both these groups are likely to be at higher risk of further fractures than participants in this trial. Few participants were enrolled after a vertebral fracture, and such patients might be more responsive to treatment.¹⁶ A possible explanation for the findings is that true differences were underestimated because of chance. The trial was large, involving more than 5000 participants with a minimum follow-up of 24 months, and 698 had at least

	Vitamin D3 and calcium	Vitamin D3	Calcium	Placebo	With calcium	Without calcium	Effect size (95% CI)	With vitamin D3	Without vitamin D3	Effect size (95% CI)
EQ-5D, 4 months	n=952	n=1052	n=965	n=958	n=1917	n=1990	..	n=1984	n=1923	..
Score	0.7 (0.2)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.7 (0.2)	0.7 (0.3)	..	0.7 (0.3)	0.7 (0.3)	..
SF12, 4 months	n=887	n=946	n=904	n=902	n=1791	n=1848	..	n=1833	n=1806	..
Physical score	40.9 (10.8)	40.7 (11.1)	41.1 (11.2)	40.2 (11.3)	41.0 (11.0)	40.4 (11.2)	..	40.8 (11.0)	40.6 (11.3)	..
Mental score	50.4 (10.6)	50.5 (10.4)	49.8 (10.8)	50.5 (9.9)	50.1 (10.7)	50.5 (10.2)	..	50.5 (10.5)	50.1 (10.4)	..
ED-5Q, 2 years	n=775	n=861	n=771	n=797	n=1546	n=1658	..	n=1264	n=1226	..
Score	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.01 (0.00 to 0.03)	0.7 (0.3)	0.7 (0.3)	0.015 (-0.002 to 0.031)
SF12, 2 years	n=772	n=816	n=765	n=796	n=1537	n=1612	..	n=1588	n=1561	..
Physical score	40.8 (10.7)	41.7 (11.6)	41.4 (10.8)	40.9 (11.4)	41.1 (10.7)	41.3 (11.5)	0.46 (-0.15 to 1.07)	41.2 (11.2)	41.1 (11.1)	0.135 (-0.48 to 0.74)
Mental score	50.4 (10.5)	50.6 (10.4)	50.1 (10.8)	50.4 (10.0)	50.3 (10.7)	50.5 (10.2)	0.02 (-0.63 to 0.68)	50.55 (10.4)	50.2 (10.4)	-0.03 (-0.69 to 0.62)

Data are mean (SD). SF12=short-form 12. EQ-5D=Euroqol-5D.

Table 4: Quality of life at follow-up of 4 months and 2 years

one new low-trauma fracture. At the start of the trial the aim was to identify a 20% relative difference (3% absolute difference). The lower ends of the 95% CI around the HR for the principal analyses were 0.805 for calcium and 0.879 for vitamin D3, indicating that a true effect of that size is very unlikely, on the basis of these results.

As expected, it was difficult to maintain compliance with allocated tablets: participants were elderly, usually taking other medications, and comorbidity was common. By the time data collection had stopped, one in six had died. By 2 years, compliance (defined as a participant who took >80% of tablets) was 60% of those who returned questionnaires. All analyses were based on the intention-to-treat principle, and so effectiveness in this context rather than efficacy was measured. Comparison of compliance in this trial with that of other trials is difficult because rates of compliance with tablets and drop-outs are often not well reported. There were different rates of questionnaire response in the trial groups, especially for comparisons of calcium because of increased rates of possible side-effects in these groups. Although imbalances in the response rate in different groups could introduce bias into comparisons that are based only on questionnaire responses (eg, quality of life), this bias seems unlikely for fractures and deaths because these data were derived from several sources and the pattern of results was similar irrespective of the source of identification.

There was no evidence that supplementation might be especially useful for specific groups (figure 3) or that true differences could have been obscured by poor compliance. A possible mechanism for fracture prevention was a reduced incidence of falls. For pragmatic reasons, we chose to address this issue through one question in every follow-up questionnaire that was sent every 4 months asking about falls during the previous week. Although this method undoubtedly underestimated true rates of falls, there was no evidence of any difference between groups.

The results for participants assigned vitamin D3 alone and those assigned calcium alone are consistent with an overview of similar trials in that they suggest no significant effect.^{7,17} However, results of individual trials using vitamin D vary. In a primary-prevention trial of a single dose of 100 000 IU oral vitamin D every 4 months, Trivedi and colleagues¹⁸ reported a marginally significant 22% beneficial effect. However, primary-prevention trials^{19,20} of 400 IU oral vitamin D3 taken every day have shown no significant effect on the incidence of all types of fracture. A UK study²¹ of 9000 healthy mobile older women and men showed no reduction in fracture risk after three injections of 300 000 IU vitamin D3 per year.

By contrast with Chapuy and colleagues²²⁻²⁴ and Dawson-Hughes²⁵ primary-prevention trials, we did not find a significant effect of combined calcium and vitamin D3 on fracture prevention. However, our study population was younger and less frail than were the participants in Chapuy and co-workers' trials, and most were mobile and

living in the community. Therefore, the participants in our trial might have been less likely to have vitamin D insufficiency and secondary hyperparathyroidism than those in the trials by Chapuy and colleagues. Our participants were, however, older than were participants in Dawson-Hughes' trial. Concentrations of 25-OH-vitamin D3 achieved with supplementation seem lower in our trial than in these other trials,^{18,22-25} although differences in analytical techniques make comparisons difficult. We also showed less suppression of parathyroid hormone than did others,^{22,23,25} but more suppression than in a later trial.²⁵ The amount of vitamin D needed to ensure optimum blood concentrations of 25-OH-vitamin D3 and parathyroid hormone is debatable. As much as 4000 IU per day has been suggested,²⁶ but this amount has yet to be tested in a fracture-prevention trial.

Secondary-fracture prevention is now widely practised. Our trial indicates that routine supplementation with calcium and vitamin D3, either alone or in combination, is not effective in the prevention of further fractures in people who have had a recent low-trauma fracture. Secondary analyses did not identify subgroups that might benefit from supplementation, such as those individuals (17% of those enrolled) who had had a hip fracture before enrolment. These participants were older (mean 79.4 years [SD 6.3] vs 77.0 [5.3]) and twice as likely to die (28% vs 15%) during the trial than those with a non-hip fracture. Policies for secondary prevention should therefore consider other strategies. The main pharmacological intervention is antiresorptive drugs, such as bisphosphonates, which have rarely been assessed in patients who have not been taking calcium or vitamin D.

This trial was not designed to directly address whether supplementation should be used as a primary-prevention measure or in those who live in a care-home environment. Clarification of the role of supplementation in these settings awaits the results of other trials.

Contributors

A M Grant, F H Anderson, A Avenell, M K Campbell, C Cooper, C Donaldson, R M Francis, W J Gillespie, C M Robinson, D J Torgerson, and W A Wallace designed and coordinated the study. G C McPherson and G S MacLennan did data management and statistical analyses. A M McDonald was the principal trial manager. All contributed to writing or editing of the paper.

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I Howe acted as liaison between the investigators and the company and attended project-management group meetings as an observer. He was not involved in analysis, interpretation, or reporting.

Conflict of interest statement

C Cooper has given one lecture and received one consultancy during the past 5 years supported by Shire Pharmaceuticals. R M Francis has served as an adviser to, and spoken at meetings organised by, Shire Pharmaceuticals and Nycomed. D J Torgerson has received speaker's and consultancy fees from Shire Pharmaceuticals, which is partly or fully funding two research projects in which he is involved.

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