

# Primary care

## Randomised controlled trial of supplementation with calcium and cholecalciferol (vitamin D<sub>3</sub>) for prevention of fractures in primary care

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### Abstract

**Objective** To assess whether supplementation with calcium and cholecalciferol (vitamin D<sub>3</sub>) reduces the risk of fracture in women with one or more risk factors for fracture of the hip.

**Design** Pragmatic open randomised controlled trial.

**Setting** Practice nurse led clinics in primary care.

**Participants** 3314 women aged 70 and over with one or more risk factors for hip fracture: any previous fracture, low body weight (< 58 kg), smoker, family history of hip fracture, or fair or poor self reported health.

**Intervention** Daily oral supplementation using 1000 mg calcium with 800 IU cholecalciferol and information leaflet on dietary calcium intake and prevention of falls, or leaflet only (control group).

**Main outcome measures** Primary outcome measure was all clinical fractures and secondary outcome measures were adherence to treatment, falls, and quality of life (measured with the SF-12).

**Results** 69% of the women who completed the follow-up questionnaire at 24 months were still taking supplements (55% with inclusion of randomised participants known to be alive). After a median follow-up of 25 months (range 18 to 42 months), clinical fracture rates were lower than expected in both groups but did not significantly differ for all clinical fractures (odds ratio for fracture in supplemented group 1.01, 95% confidence interval 0.71 to 1.43). The odds ratio for hip fracture was 0.75 (0.31 to 1.78). The odds of a woman having a fall at six and 12 months was 0.99 and 0.98, respectively. Quality of life did not significantly differ between the groups.

**Conclusion** We found no evidence that calcium and vitamin D supplementation reduces the risk of clinical fractures in women with one or more risk factors for hip fracture.

**Registration** ISRCTN26118436, controlled trials registry.

### Introduction

Supplementation with calcium and vitamin D might be expected to prevent fractures in older people not only through reductions in bone loss but by reducing falls. We assessed whether giving calcium and vitamin D supplements to community dwelling older women at increased risk of hip fracture would reduce their risk of any fracture.

### Participants and methods

We identified women aged 70 and over who had at least one self reported risk factor for hip fracture: low bodyweight (< 58 kg), any previous fracture, maternal history of hip fracture, smoker, and poor or fair health. We assessed self reported calcium consumption through a brief 10 item questionnaire and risk factors for fracture. Women were excluded if they were receiving any calcium supplementation of more than 500 mg a day or had a history of kidney or bladder stones, renal failure, or hypercalcaemia.

### Recruitment and randomisation

We asked general practices across England to post information about the study, a consent form, and a questionnaire on risk factors for fracture to all women aged 70 and over. The women were asked to return completed questionnaires to the relevant trial coordinating centres.

Eligible women were randomised (stratified by practice) by computer at the York Trials Unit by an independent person with no knowledge of the participants' characteristics. We initially randomised in favour of the control group in a 2:1 ratio as this was hypothesised to be the most efficient allocation ratio given the study resources.<sup>1</sup> We included research related costs, not the costs of the supplements, in the

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BMJ 2005;330:1003-6



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estimation only. Although a 2:1 ratio in favour of one arm may be considered extreme, the effect is minimal in terms of statistical power—for example, for a fixed sample size the power would be reduced from 80% to 75%. We increased our sample size to compensate for this reduction. A reanalysis of the trial's cost profile once recruitment had started showed that the optimum allocation ratio was 3:2. Towards the end of the study we therefore changed the allocation to 1:1.

**Intervention and control groups**

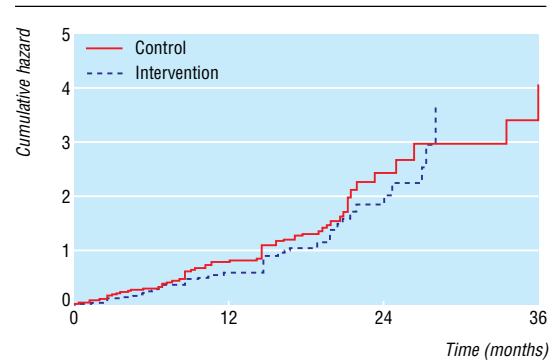
We sought confirmation from the doctors that participants had no contraindications. Participants were seen by a practice nurse, who discussed the study and also checked for contraindications. Women with contraindications to calcium and vitamin D supplements after randomisation were excluded from supplementation but were retained for follow-up and analysis on an intention to treat basis. The nurses gave participants advice on how to reduce their risk of fracture and six months supply of 1000 mg of calcium (calcium carbonate) and 800 IU of cholecalciferol (vitamin D<sub>3</sub>) as two tablets daily (Calcichew D<sub>3</sub> Forte; Shire, Hampshire). Participants saw the practice nurse after six months and were given a further supply of supplements if they wanted to continue with the study.

The control group were sent a leaflet with general advice on prevention of falls and consumption of adequate calcium and vitamin D from dietary sources. The intervention group also received this leaflet.

**Outcomes**

The main outcome was fracture. Secondary outcomes included hip fracture; quality of life (SF-12<sup>2</sup> and European quality of life instrument, EuroQol); death; visits to the doctor and hospital admissions; falls and fear of falling. Falls were self reported over the previous six months, and fear of falling was measured on a simple six point Likert scale.

Outcome data were mainly collected from questionnaires every six months. Doctors were asked to confirm fractures in women who reported a fracture in the previous six months. Information on fractures was also collected from the doctors of non-responders to the final questionnaire. For the principal analysis we included only confirmed fractures. Adherence was measured through self report every six months. We chose to report quality of life data at six and 12 months because of the reduction in follow-up rates with time for the quality of life questionnaires.



Time to first fracture in women allocated calcium and vitamin D supplementation or only advice on diet and prevention of falls

**Statistical analysis**

All participants were included in the analysis on an intention to treat basis. For our main analysis we used survival analysis to compare time to first fracture between the groups. We also undertook a logistic regression analysis adjusting for practice. We undertook subgroup analyses to compare rates for hip and wrist fracture between the two groups and secondary analyses with all reported fractures whether or not these had been confirmed. If a woman had more than one fracture we included only the first fracture in the analysis. We adjusted for practice because we changed the allocation ratio during the trial. In our unadjusted analysis we present the incidence of fracture by equally or unequally allocated groups as in any meta-analysis these need to be entered as two separate studies.

**Results**

Between September 2001 and November 2002 we recruited 3197 women in addition to 117 participants recruited during a pilot trial (3314 in total). The recruitment rate of 7% instead of the presumed 5% allowed us to exceed our planned sample size by 16%.

Overall, 48 987 women registered with 107 general practices were invited to take part in our trial (see bmj.com). Of the 11 022 women who returned the questionnaire, 3079 were ineligible and 4490 did not want to take part, leaving 3453 women. The intervention and control groups were well balanced across all important predictors of fracture (see bmj.com).

Odds of fracture in women receiving calcium and cholecalciferol (vitamin D<sub>3</sub>) supplementation (intervention group) and those receiving only advice on diet and prevention of falls. Values are percentages (numbers) unless stated otherwise

Confirmed fractures	Intervention group (n=1321)	Control group (n=1993)	Adjusted odds ratio (95% CI)*	P value
All fractures:				
Unequally allocated group†	4.8 (34/714)	5.0 (69/1391)	1.01 (0.71 to 1.43)	0.97
Equally allocated group	4.0 (24/607)	3.7 (22/602)		
Hip fractures:				
Unequally allocated group	0.4 (3/714)	1.1 (15/1391)	0.75 (0.31 to 1.78)	0.51
Equally allocated group	0.8 (5/607)	0.3 (2/602)		
Hip and wrist fractures:				
Unequally allocated group	2.4 (17/714)	3.2 (44/1391)	0.89 (0.56 to 1.44)	0.64
Equally allocated group	2.0 (12/607)	1.5 (9/602)		

\*Adjusted for practice.

†Two women randomised to control group for every one allocated to treatment group.

Over a median follow-up of 25 months, 149 confirmed fractures were reported, lower than anticipated. Time to fracture did not differ between the groups (figure) and we found no evidence of a benefit of supplementation in the prevention of fractures (table). When we took into account all reported fractures (including those not confirmed by a doctor) the results were not changed (adjusted odds ratio 1.60, 95% confidence interval 0.75 to 3.40).

We also examined the risk of falls, falling, and quality of life. We found no evidence of an effect on falls. After adjusting for practice, the risk of a woman having a fall at six months was 0.99 (odds ratio 0.81 to 1.20). At 12 months we found no evidence that supplementation reduced falling (0.98, 0.79 to 1.20). We also found no differences in quality of life (see [bmj.com](http://bmj.com)).

We compared women taking supplements with those in the control group to determine whether women who adhered to treatment might have had a reduced fracture rate. We found no evidence of any benefit (1.03, 0.68 to 1.56).

## Discussion

We found no evidence that supplementation with calcium and cholecalciferol (vitamin D<sub>3</sub>) affects fracture rates over two years in women aged 70 or over with one or more risk factors for fracture of the hip.

### Combined calcium and cholecalciferol

Five trials have been published on combined calcium and vitamin D (see [bmj.com](http://bmj.com)). Two were in French nursing homes.<sup>3,4</sup> Our population was recruited from the community. A community study in Denmark showed a modest (16%), statistically significant, reduction in fractures.<sup>5</sup> The latest study on calcium and vitamin D, the Medical Research Council RECORD Trial Group trial,<sup>6</sup> is a secondary prevention study in hospital based fracture clinics in the United Kingdom. This study essentially showed the same findings as our trial, that there was no evidence of a benefit from calcium or vitamin D supplementation either alone or in combination in preventing fractures.

Our study differs from the two French studies,<sup>3,4</sup> which showed a large benefit from supplementation on hip fractures, in that our population was generally more healthy and living in the community. People in sheltered accommodation or nursing homes may be at more risk of a low calcium and vitamin D intake and at higher risk of fracture. Our results do not apply to men, those in residential care, or those with dementia.

### Vitamin D alone

Four large randomised studies looked at vitamin D supplementation (see [bmj.com](http://bmj.com)). One trial found a non-significant increase in the risk of hip fractures in men and women in primary care receiving a daily dose of 400 IU vitamin D, whereas a more recent trial of an annual injection of 300 000 IU of vitamin D reported a small non-significant increase in all fractures with a large, borderline statistically significant increase in hip fractures.<sup>7,8</sup> In contrast, a trial of high dose oral vitamin D (100 000 units) every four months in male doctors showed a borderline statistically significant 22% reduction in osteoporotic fractures.<sup>9</sup> The Medical Research Council RECORD trial also studied vitamin D alone and found no

## What is already known on this topic

Calcium and vitamin D supplements have been shown to reduce hip fractures among older women living in French nursing homes

No randomised trials have been carried out of supplements among high risk women living in the community in the United Kingdom

## What this study adds

No evidence was found that calcium and vitamin D supplementation reduces the risk of fractures among community dwelling older women

evidence of benefit in preventing fractures (see [bmj.com](http://bmj.com)). Our study differed from these four in that we included only women and selected them on the basis of risk factors for fracture, whereas these studies included men and may have sampled a population at lower risk. Nevertheless, putting our study in the context of these trials, with only one showing a significant benefit, suggests that overall vitamin D supplementation may not be an effective intervention for reducing fractures in primary care.

### Falls

We found no evidence that vitamin D supplementation reduced the incidence of falls, as previously hypothesised.<sup>10</sup>

### Strengths and weaknesses of the study

Our study was large and targeted women at high risk of fracture. We chose to use a pragmatic design, which allows our results to be generalised to a usual care setting. We did not use a placebo in the control group and this could have biased the results in several ways. Firstly, dilution effects could have occurred if significant numbers of control participants had started calcium and vitamin D. This was not a problem, however, as by 18 months this applied to fewer than 6% of the participants, with about 3% being prescribed supplements by their doctor. Secondly, differential reporting of fracture outcomes could have occurred. We therefore confirmed fractures with the doctors and we ascertained fracture status from the doctors of non-responders to the questionnaires.

Fewer fractures occurred than we anticipated, thus reducing the power of our study to observe modest differences between groups. This was, however, offset to some degree by us exceeding our planned sample size. Furthermore, a trial published subsequent to the start of our study noted little effect of supplementation on all fractures<sup>4</sup> (our main end point). Including this result in a meta-analysis would have reduced the difference in fracture rates we might have expected to find. Therefore, our study was underpowered so that we could not reliably exclude a reduction in all fractures of less than 30%. Furthermore, adherence rates were only a little more than 60% at 12 months. This may have attenuated any effect of treatment. As this was a pragmatic trial this will be the level of adherence seen routinely in general practice.

Although we found no evidence of a benefit on fractures in older community dwelling women given calcium and vitamin D supplementation, we cannot

exclude a clinically significant benefit of supplementation owing to the relatively wide confidence intervals around our estimate of effect.

We thank Nicky Cullum, Bill Gillespie, and Jill Mollison for acting as the independent trial steering group and data monitoring committee; Sue New for scoring the calcium questionnaire; and Corrina Petre for helping with randomisation.

Contributors: See [bmj.com](http://bmj.com)

Funding: Grants from Northern and Yorkshire NHS research and development, healthy ageing programme (TA, RMF, AS, IW, DJT), Shire, and Nycomed. Shire also supplied the calcium and vitamin D supplements. None of the funders were involved in the design, analysis, or writing up of the study.

Competing interests: RMF has served as an adviser to, and spoken at meetings organised by, Shire and Nycomed. JP and SP have been sponsored by Shire to attend conferences. AS has spoken at meetings organised by Shire and served as nurse adviser. DJT has received funding from Shire and other pharmaceutical companies for research and sponsorship to attend conferences and meetings.

Ethical approval: Northern and Yorkshire multicentre research ethics committee 1/3/12 and relevant local research ethics committees.

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(Accepted 15 March 2005)

### When I use a word

#### Faux amis

An English rugby fan, in Paris for a Six Nations match, wants a beer. He doesn't know that beer is served in *un café* or *un bistro*, but asks the concierge for a pub. The concierge is puzzled. *La pub* means publicity (*il aime beaucoup la pub*), not a public house. OK, what about *une maison publique*? Ah, now the concierge understands. She points out the nearby red light district.

Our friend has fallen foul of the phenomenon known as faux amis, or false friends, foreign words that seem to mean one thing but actually mean another. The term was put on the map in a dictionary called *Les Faux Amis, ou les Trahisons du Vocabulaire Anglais*, by Maxine Koessler and Jules Derocquigny (Librairie Vuibert, 1928). The French word *sensible*, for example, means not sensible (*sage, raisonnable*) but sensitive, a meaning that we recognise in Jane Austen's *Sense and Sensibility*. And faux amis are not limited to French. In Spanish *simpatía* means friendship not sympathy. In Dutch *een verloren hoop*, the origin of the English phrase "a forlorn hope," actually means a lost troop of soldiers. And when in Germany it does well to remember that *Gift* means a poison not a present (*Geschenk*) and when visiting a pharmaceutical factory that *Präservativ* means a condom not a preservative (*Konservierungsmittel*).

Doctors travelling in France may need to be aware of some medical faux amis. *La médecine libérale* is not, alas, free at the point of delivery; in fact, quite the reverse—it means private practice, since the members of *les professions libérales* are those who receive fees for their labours. And *un médecin de permanence* is not a doctor with a tenured position but merely one who is on duty.

Looking for over the counter drugs? Don't ask for *une droguerie*, which is a hardware store. What you want is *une pharmacie*. And when you're there ask for

*médicaments*, not *drogues*, unless you want to risk arrest. If it's prescription drugs you're after, go to the doctor's surgery (*cabinet*, not *chirurgie*) and ask for *une ordonnance*, not *une prescription*, which is a chit for a medical appliance or simply an instruction. If the doctor refers you to the hospital don't ask for *la clinique*; that means a private hospital, not an outpatient clinic.

If you're an academic and have been invited to speak at a symposium, don't say that you have come to give *une lecture* (a reading), but *une conférence* (a lecture). And for those lecturing on Viagra, *impotent* means crippled, not impotent, which is *impuissant*.

As bad as these false friends are, worse perhaps are fickle friends, which sometimes mean what you think they mean and sometimes not. *Tension*, for instance, means tension, but also blood pressure and sometimes high blood pressure. And in the family planning clinic try to remember that *fertilité* refers to the land; the word you want there is *fécondité*.

After all of which, I think I need a quick one at *la maison publique*.

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