

Should Older People in Residential Care Receive Vitamin D to Prevent Falls? Results of a Randomized Trial

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OBJECTIVES: To determine whether vitamin D supplementation can reduce the incidence of falls and fractures in older people in residential care who are not classically vitamin D deficient.

DESIGN: Randomized, placebo-controlled double-blind, trial of 2 years' duration.

SETTING: Multicenter study in 60 hostels (assisted living facilities) and 89 nursing homes across Australia.

PARTICIPANTS: Six hundred twenty-five residents (mean age 83.4) with serum 25-hydroxyvitamin D levels between 25 and 90 nmol/L.

INTERVENTION: Vitamin D supplementation (ergocalciferol, initially 10,000 IU given once weekly and then 1,000 IU daily) or placebo for 2 years. All subjects received 600 mg of elemental calcium daily as calcium carbonate.

MEASUREMENTS: Falls and fractures recorded prospectively in study diaries by care staff.

RESULTS: The vitamin D and placebo groups had similar baseline characteristics. In intention-to-treat analysis, the incident rate ratio for falling was 0.73 (95% confidence interval (CI) = 0.57–0.95). The odds ratio for ever falling was 0.82 (95% CI = 0.59–1.12) and for ever fracturing was 0.69 (95% CI = 0.40–1.18). An a priori subgroup analysis of subjects who took at least half the prescribed capsules (n = 540), demonstrated an incident rate ratio for falls of 0.63 (95% CI = 0.48–0.82), an odds ratio (OR) for ever falling of 0.70 (95% CI = 0.50–0.99), and an OR for ever fracturing of 0.68 (95% CI = 0.38–1.22).

CONCLUSION: Older people in residential care can reduce their incidence of falls if they take a vitamin D sup-

plement for 2 years even if they are not initially classically vitamin D deficient. *J Am Geriatr Soc* 53:1881–1888, 2005.

Key words: nursing homes; aged 80 and over; falls; vitamin D; randomized controlled trials; fractures

One in three women aged 70 and older fall each year.¹ The incidence is even higher in older women in residential care.² As a consequence of their high falls incidence and because of their bone fragility, women in residential care may account for one-third of all hip fractures.³ Intense interdisciplinary, multifactorial prevention programs may reduce the rate of falls in residential care,⁴ but overall, the evidence that it is possible to reduce falling in institutional settings remains uncertain.¹

In nursing homes in France, calcium and vitamin D supplementation clearly reduced fracture incidence,⁵ but the mechanism for this effect is undetermined. Although it has been proposed that such supplementation had its major effect through effects on bone metabolism—increasing bone mass and decreasing bone turnover⁵—it has also been postulated that vitamin D and calcium supplementation could reduce the risk of fracture through a reduction in the incidence of falls.⁶ Falling may be a consequence of impaired neuromuscular function^{6,7} associated with vitamin D deficiency. Abnormal motor performance, increased body sway, and quadriceps weakness have been reported in those with low vitamin D levels.^{8,9} In addition, secondary elevation in serum levels of parathyroid hormone (PTH) as a consequence of vitamin D deficiency may also be associated with falls in older people in residential care.^{6,10} Despite this rationale, there is little randomized trial evidence to direct clinical practice. Two systematic reviews found insufficient evidence that vitamin D prevents falls.^{1,11} One meta-analysis found positive effects but did not distinguish within its analysis between base vitamin D and its metabolites, which are biologically and pharmacologically distinct.¹²

Studies of healthy rural and urban Australians across a wide age range have found a low prevalence of conven-

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tionally defined vitamin D deficiency.^{13–15} Australia has a generally sunny climate, and fortification of the food supply with vitamin D has not been considered necessary. A high prevalence of vitamin D deficiency (defined as a serum 25-hydroxyvitamin D (25D) <25 nM)^{2,6} has previously been demonstrated in Australian hostel and nursing home residents, and associations between the level of serum 25D and falling in these residents has been demonstrated retrospectively⁶ and prospectively.²

The primary aims of the present study were to test whether administration of vitamin D could reduce the incidence of falls and fractures in these residents. Although frank vitamin D deficiency may be defined as a level of serum 25D that falls below the conventional laboratory reference range (<25 nM), higher levels of serum vitamin D may be required to prevent a rise in serum PTH¹⁶ and optimize musculoskeletal health and neuromuscular function. It was considered unethical to randomize residents with low levels of vitamin D. Thus, this study randomized residents whose vitamin 25D level was in the lower half of the laboratory reference range. In this manner, the study aimed to address whether there was any benefit from vitamin D supplementation on falling and fracture in subjects not classically considered to be vitamin D deficient.

METHODS

Recruitment of Subjects and Baseline Measures

Older people resident in 60 hostels and 89 nursing homes in urban and rural centers across three states of Australia were approached between 1996 and 1999 (see ² for details of recruitment and measures). After written informed consent, baseline data were recorded as follows. Age, date of admission to residential care, current medication use, specific medical conditions, and a history of previous fractures were obtained from institution records. Weight and tibial length (as a surrogate for height) were measured. A trained research nurse administered the Abbreviated Mental Test Score as a measure of cognitive function.¹⁷ Each resident's own nursing staff was asked to rate each resident's walking ability (on a 7-point scale, with 1 = bedbound and 7 = walking independently without a gait aid), frequency of going outdoors (on a 4-point scale with 1 = never going outdoors and 4 = going outdoors weekly or more frequently), and whether the subject was "a wanderer" (if residential care staff reported aimless wandering as a problem). Venipuncture was performed at baseline for measurement of serum 25D. This is the vitamin D metabolite present in serum in greatest abundance and reflects vitamin D nutrition.¹⁸ Recruitment and venipuncture were not seasonally restricted. All sera were assayed blind in a single central laboratory using radioimmunoassay (Incstar, Stillwater, MN). The reference range was 25 to 168 nmol/L, whereas the interassay coefficient of variation was 9.2% for the low control (24 nmol/L) and 11.8% for the medium control (58 nmol/L).

Because it was not considered ethical or scientifically informative for any subject whose 25D level was less than 25 nmol/L to be potentially randomized to placebo, all such subjects were excluded from further participation, and their attending physicians were notified of their 25D results and encouraged to treat them. Subjects whose 25D levels were

above 90 nmol/L were also excluded because they were considered to be vitamin D sufficient. This left the subjects whose 25D level was greater than 25 nmol/L and less than 90 nmol/L as potentially eligible for randomization. These subjects fell within the lower half of the classical laboratory reference range for 25D.

Exclusion criteria included use of agents that could affect bone and mineral metabolism, such as warfarin, chronic heparin therapy, vitamin D therapy within the previous 3 months, glucocorticoids at an average daily dose of greater than 5 mg prednisolone (or equivalent) for more than 1 month within the preceding year, current use of bisphosphonates, and hormone replacement therapy. Other exclusion criteria included thyrotoxicosis within the previous 3 years, primary hyperparathyroidism treated within the previous 3 years, multiple myeloma, Paget's disease of bone, history of malabsorption, intercurrent active malignancy, and other disorders affecting bone and mineral metabolism.

Subjects were randomized via computer-generated lists, after giving specific informed consent to be involved in the randomized trial component of the study. Within each institution, subjects were randomized in blocks of eight. Each block was stratified by use of furosemide, thiazide, both, or neither. This was based on previous work demonstrating an association between furosemide and elevated PTH levels in nursing home residents.¹⁹ An individual who was not involved in contact with the subjects or the residential care institutions performed randomization. In February 2000, based on the observed fall rates for both groups (because the investigators were still blinded), a revised recruitment target of 620 subjects was chosen based on the study having 80% power to detect a difference in the proportion of fallers of 11% and an 18% change in the falls rate ($\alpha = 0.05$).

The Royal Melbourne Hospital Clinical research and ethics committee gave ethics approval, and many of the institutions invited their own ethics committees to review the study protocol before agreeing to their residents being approached.

Intervention

All randomized subjects were prescribed 600 mg of elemental calcium in the form of calcium carbonate (Caltrate, Whitehall Laboratories, Sydney, Australia) to be taken at night before bed. Subjects were randomized to receive sequentially numbered bottles containing vitamin D supplementation or placebo. Until November 1998, the supplement used was 10,000 IU ergocalciferol tablets (Ostelin, Boots Healthcare Pharmaceuticals, Sydney, Australia) given orally once per week. Because of the discontinuation of this preparation, this supplement was changed to 1,000 IU ergocalciferol capsules (Ostelin 1000) given once daily. Both supplements had matching placebo preparations given in identical fashion, and residents, institutional staff, and study staff were blinded to treatment allocation.

OUTCOMES

Residential care staff recorded falls prospectively in diaries, and these were mailed monthly to the central study center in Melbourne. A study research nurse provided training in the definition of falls and the use of the falls diaries during a single visit to the institution at the commencement of the

monitoring phase. If the diaries were not returned, the residential care institutions were reminded via telephone to return the diaries. Falls were defined as “an event that results in a person coming to rest inadvertently on the ground or other lower level.”²⁰ Fractures were also recorded and were verified using x-ray report when possible. Compliance with vitamin D therapy was monitored using pill counts, which study staff reviewed and recorded every 6 months. Each subject was followed for 2 years. Compliance was categorized as less than 25%, 25% to 49%, 50% to 74%, and 75% or greater according to the percentage of the

vitamin D supplements removed from the subject’s medication container. These compliance categories were determined before completion of the study. Calcium compliance was also recorded.

Statistical Analyses

Data were stored using Microsoft Access (Microsoft Corp., Redmond, WA) and analyses performed using Stata/SE 8.0 (Stata Corp., College Station, TX). Logistic regression and Cox proportional hazard and negative binomial models

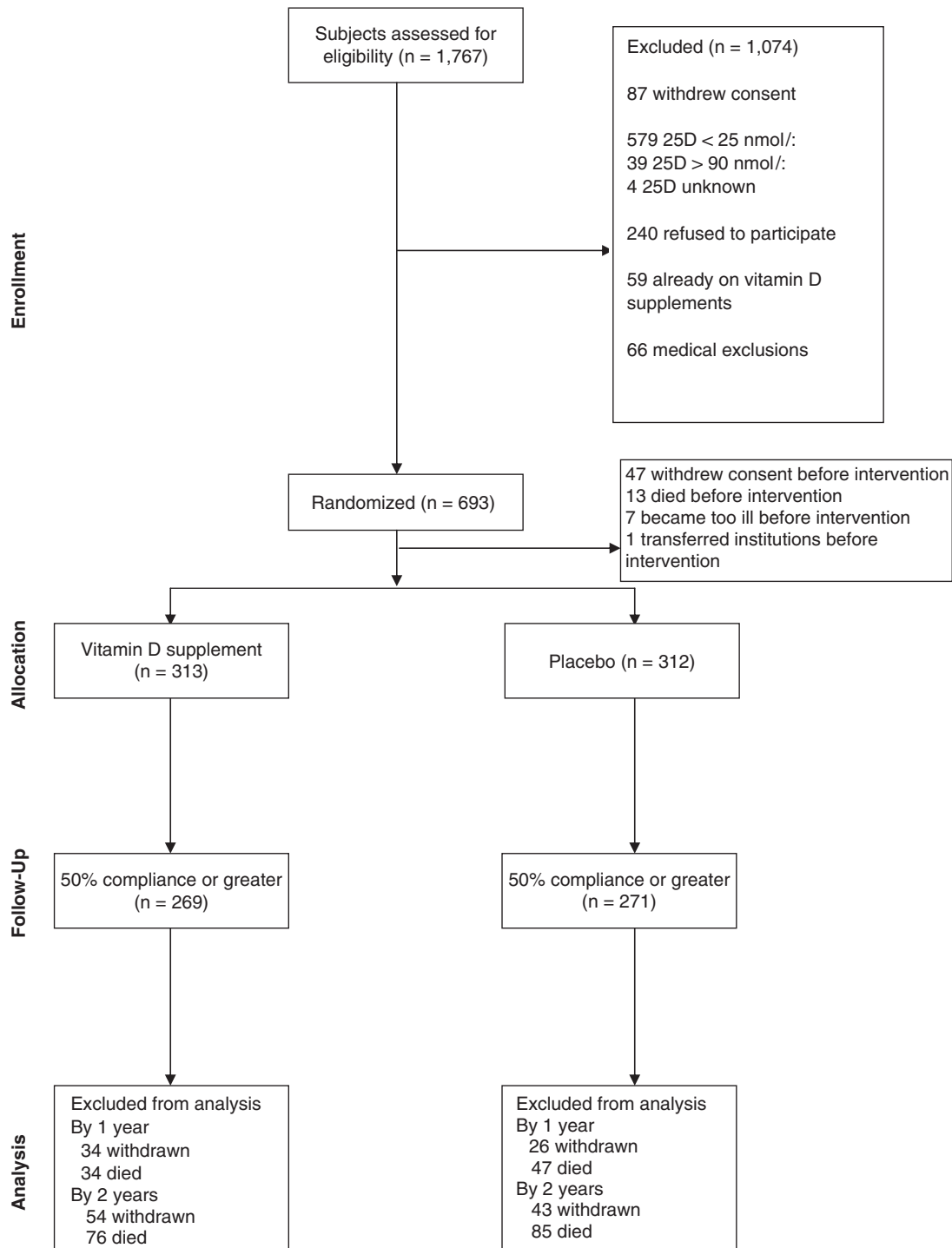


Figure 1. Flow diagram of recruitment and progress through randomized trial of 2 years of vitamin D supplementation.

were used to examine the effect of vitamin D supplementation on the outcomes of falls and fractures before (intention-to-treat analysis) and after exclusion of subjects with less than 50% compliance with vitamin D. This level of compliance was determined a priori. The distributions of the residuals against time were examined to test adherence to the Cox proportional hazards model assumptions. In addition, the Anderson-Gill adaptation of the Cox proportional hazards model for multiple events in survival analysis²¹ was used to verify the central results. Nominal significance was defined using a two-sided *P*-value < .05. Numbers-needed-to-treat analyses were performed based on the inverse of the difference in absolute risk of a person falling for the duration of the study between the two groups and also on the difference in the incidence rates of falling between the two groups.

RESULTS

Figure 1 illustrates the number of subjects participating at each stage of establishment of the trial groups and during follow-up. For the measured variables, there were no apparent differences between the two randomized groups, except that there was an excess number of subjects with a history of hip fracture in the vitamin D treatment group (Table 1). Institutional staff returned 95% of the falls diaries.

On an intention-to-treat basis, there were 665 falls observed in 486 person-years in the vitamin D supplement group, compared with 890 falls observed in 478 person-years in the placebo group. Using the negative binomial model that accounts for all falls, the incident rate ratio for the vitamin D supplement group compared with the control group was 0.73 (95% confidence interval (CI) = 0.57–0.95). There was also a trend favoring vitamin D supplementation for the odds of ever sustaining a fracture or fall, but this did not reach nominal statistical significance (Table 2). Using the Cox proportional hazards model, the hazard ratio (HR) for time to first fall was 0.86 (95% CI = 0.70–1.06).

Further preplanned analyses were performed excluding 85 subjects (14% of the total, 41 in the placebo group and 44 subjects in the D treatment group) whose vitamin D compliance was 50% or less (Table 3). This low-compliance group represented a total of 59 person-years of observation (median follow-up of 133 days), among whom 123 falls were observed in 27 subjects. The remaining 540 subjects contributed 904 person-years (median follow-up of 730 days), among whom 1,432 falls were observed in 328 subjects. There were 570 falls observed in 451 person-years in the vitamin D supplement group, compared with 862 falls observed in 453 person-years in the placebo group. The negative binomial model revealed a moderate reduction in the incident rate ratio for falls with vitamin D treatment (0.63, 95% CI = 0.48–0.82). There was also a moderately lower risk of sustaining a fall in subjects who received vitamin D supplementation than in subjects who received placebo supplementation (odds ratio = 0.70, 95% CI = 0.50–0.99). There was also a trend to a reduction in fractures and a protective effect for time to first fall of 0.80 (95% CI = 0.64–1.00).

Table 1. Comparison of Baseline Variables and Tablet Compliance of Groups Randomized to Vitamin D Supplementation and Placebo

Characteristic	Placebo (n = 312)	Vitamin D (n = 313)
Sex, n (%)		
Female	296 (95)	297 (95)
Male	16 (5)	16 (5)
Institution, n (%)		
Nursing home	168 (54)	165 (53)
Hostel	144 (46)	148 (47)
Age, mean ± SD	83.3 ± 8.8	83.6 ± 7.8
Weight, kg, mean ± SD	59.4 ± 11.6	60.5 ± 12.8
Tibial length, cm, mean ± SD	32.4 ± 3.8	32.4 ± 4.2
Abbreviated Mental Test score, n (%)		
0–4	85 (27)	87 (28)
5–7	55 (18)	71 (23)
8–10	140 (45)	129 (41)
Not recorded	32 (10)	26 (8)
Walking score, n (%)		
1	41 (13)	43 (14)
2–4	60 (19)	60 (19)
5–7	209 (67)	209 (67)
Not recorded	2 (1)	1 (0)
Outside exposure, n (%)		
Never	13 (4)	18 (6)
< Monthly	37 (12)	45 (14)
< Weekly	77 (25)	79 (25)
≥ Weekly	183 (59)	170 (54)
Unknown	2 (1)	1 (0)
25D level, nmol/L, n (%)		
25–40	169 (54)	190 (61)
41–60	109 (35)	88 (28)
61–90	34 (11)	35 (11)
Previous fracture, n (%)		
Hip	36 (12)	54 (17)*
Colles	17 (5)	8 (3)
Recorded vertebral	19 (6)	13 (4)
Other	22 (7)	29 (9)
Any	75 (24)	83 (27)
Calcium supplements, n (%)	15 (5)	14 (4)
Previous estrogen use, n (%)	8 (3)	13 (4)
Previous bisphosphonate use, n (%)	2 (1)	1 (0)
Percentage compliance, n (%)		
0–25	15 (5)	12 (4)
26–50	23 (7)	23 (7)
51–75	64 (21)	56 (18)
76–100	207 (66)	213 (68)
Unknown	3 (1)	9 (3)

* *P* = .05; otherwise *P* > .05 for all comparisons between groups.

Kaplan-Meier survival curves for the outcomes for falls and fractures are shown in Figures 2 and 3, respectively. Using the Anderson-Gill adaptation of the Cox proportional hazards model yielded similar results to the negative binomial model (HR = 0.74, 95% CI = 0.54–1.02) for all subjects and 0.67, 95% CI = 0.48–0.93 for subjects whose compliance was 50% or greater.

Table 2. Falls and Fractures in 625 People in Residential Care According to Vitamin D Treatment Allocation

Falls and Fractures	Placebo (n = 312)	Vitamin D (n = 313)	Incident Rate Ratio	Odds Ratio	95% Confidence Interval
Falls, n	890	665	0.73		0.57–0.95
Fell, n (%)				0.82	0.59–1.12
Yes	185 (59)	170 (54)			
No	127 (41)	143 (46)			
Fracture, n (%)				0.69	0.40–1.18
Yes	35 (11)	25 (8)			
No	277 (89)	288 (92)			

All estimates were almost identical after further adjustment for baseline serum 25D level. Removing subjects who had poor compliance with the calcium (as opposed to the vitamin D) supplements or who were nonambulatory did not alter the effect estimates. There was no apparent effect of vitamin D supplements on total mortality (OR = 1.20, 95% CI = 0.84–1.71) for all subjects, and limiting analyses to subjects with 50% compliance or greater, the OR for mortality was not substantially different (1.16, 95% CI = 0.78–1.72). Similarly, adjusting for weight, cognitive function, psychotropic use, wandering, and level of accommodation, which were found previously to influence the risk of falls,² did not substantially alter the effect of vitamin D supplementation. Limiting the analysis to the 468 subjects who were not bedbound and had compliance with D supplements of 50% or greater did not substantially alter the effect estimates (HR for falls = 0.79, 95% CI = 0.63–0.99; incident rate ratio for falls = 0.63, 95% CI = 0.48–0.82). Including subjects who had no record of ever having any study medications delivered to them but had any usable falls diary (an additional 38 subjects, n = 663), produced a HR for falls of 0.87 (95% CI = 0.71–1.07) and an incident rate ratio for falls of 0.75 (95% CI = 0.58–0.97).

Number-needed-to-treat analyses, based on the absolute risk differences in people who fell while receiving treatment versus control suggest that 12 people needed to be treated to prevent one of those people falling during the time of the study, or that eight people needed to be treated for 1 year to prevent a fall occurring. Institution staff did

not report any adverse events with vitamin D intervention to the investigators.

DISCUSSION

This is the first long-term trial of vitamin D supplementation that has demonstrated a significant reduction in the rate of falls. The population sampled was at high risk of falls and the deleterious consequences of these events. Although only a small proportion of older people are frail and need to be housed in residential care facilities, they are an important group that is at risk of falls and fractures and their morbid consequences. Any measures that can prevent falls and fractures are thus of considerable public health importance. This is particularly valuable if the intervention is cheap and without major side effects, which is the case for vitamin D supplementation, as demonstrated by the lack of significant adverse events.

What have other intervention studies revealed as to benefits of vitamin D supplementation? A randomized intervention study of 800 IU vitamin D and calcium supplementation in institutionalized older women demonstrated a reduction of 43% in hip fractures rates,⁵ and a confirmatory study found similar effects on hip fracture rates but no effect on the proportion of people who fell during the study—greater than 60% in both groups.²² A Dutch trial, which studied a healthier, more-independent, older population failed to find an effect on fracture rates with 400 IU of vitamin D supplementation (without calcium supplementation).²³ A North American study that used a

Table 3. Falls and Fractures in 540 People in Residential Care Who Had Greater than 50% Compliance with Vitamin D Treatment

Falls and Fractures	Placebo (n = 271)	Vitamin D (n = 269)	Incident Rate Ratio	Odds Ratio	95% Confidence Interval
Falls, n	862	570	0.63		0.48–0.82
Fell, n (%)				0.70	0.50–0.99
Yes	176 (65)	152 (56)			
No	95 (35)	117 (43)			
Fracture, n (%)				0.68	0.38–1.22
Yes	30 (11)	21 (8)			
No	241 (89)	248 (92)			

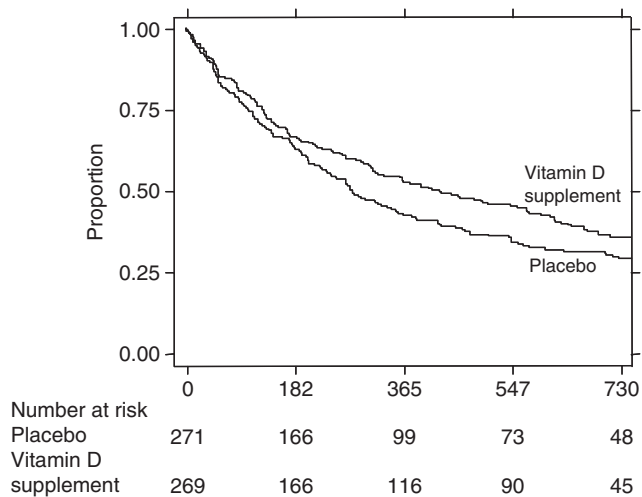


Figure 2. Kaplan-Meier estimates of cumulative hazard for falls for subjects whose compliance was 50% or greater. Vitamin D supplements were given for 2 years (730 days).

combination of vitamin D and calcium supplementation found benefits for fractures in independent older people, but again, unfortunately, falls were not measured.²⁴ A recent British study examining community-dwelling older adults found a 22% reduction in the risk of fracture but no significant effect on fall rate,²⁵ although in this study, the self-reported data on falls were collected only after the 5-year study had been completed. A 1-year unblinded, randomized study of vitamin D and calcium supplementation of 150 older women who had recently had a fractured neck of femur demonstrated a reduction in the rates of falls, but 70% of the subjects were severely deficient in vitamin D at baseline.²⁶ Two short-term vitamin D supplementation studies reported a beneficial effect on body sway and fall rates in community-dwelling older women with low vitamin D levels and on fall rates in residents in a long-stay geriatric ward.^{27,28} Two recently completed studies of vitamin D and calcium supplementation for community-dwelling subjects failed to find any benefits in terms of

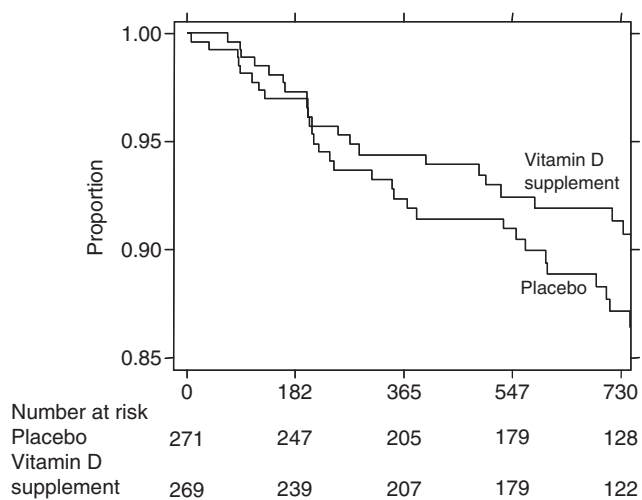


Figure 3. Kaplan-Meier estimates of cumulative hazard for fractures for subjects whose compliance was 50% or greater. Vitamin D supplements were given for 2 years (730 days).

fracture rates and falls.^{29,30} Besides targeting a nonresidential care population, both of these studies had relatively low rates of adherence to treatment (63% and 55%) and measured falls inadequately (by 1-week recall of falls three times per year²⁹ and by a single question at 6 monthly intervals³⁰).

Two systematic reviews^{1,11} concluded that there was insufficient evidence to support the hypothesis that vitamin D supplements prevent falls, but one meta-analysis,¹² which was largely based on long-term studies of calcitriol, claimed some support for this hypothesis. The latter study did not have sufficient evidence to recommend conventional vitamin D supplements. Conclusions from these previous studies and the current one are that vitamin D supplementation has the greatest effect in decreasing falls in older people who are frail and have low or suboptimal preexisting vitamin D levels and that additional calcium supplementation may be necessary to maximize this effect. The precise preexisting 25D level at which vitamin D supplementation is beneficial requires further investigation, but it now seems clear that it is well above the level of frank vitamin D deficiency (25 nmol/L).

What are the implications for vitamin D supplementation in older people in residential care? For ethical reasons, those in the group who were markedly vitamin D deficient were not included in this study, and their attending medical practitioners were advised to supplement these patients. This was nearly half of residents in high care facilities and about one-fifth of those in low-care facilities. There is some evidence that the level of 25 nmol/L reflects a level of severe deficiency, as indicated by PTH levels.¹⁶ It could be postulated that vitamin D supplements may have even greater effects on falls and fracture rates in these subgroups deficient in vitamin D. The number of people who were not included because their vitamin D levels were greater than the midpoint of the reference range was only about 2% of the total population in residential care. The recommendation is that all older people in residential care should be considered for supplementation with vitamin D, but there may be rare individuals in the general population with high baseline vitamin D levels or specific disorders such as sarcoidosis who might be prone to adverse effects from near-physiological amounts of vitamin D as a supplement. Furthermore, number-needed-to-treat analyses suggest that it was necessary to treat 12 people to prevent one person falling during the time of the study or that eight people needed to be treated for 1 year to prevent a fall occurring. Nevertheless, it should be emphasized that care is required in the use of vitamin D supplements in individuals who may have specific medical conditions affecting bone and mineral metabolism, such as primary hyperparathyroidism, who were excluded from this study.

The use of vitamin D supplements was studied in subjects who were coadministered calcium supplements. The effect of vitamin D supplementation may not be present in individuals who do not have adequate availability of exogenous calcium from dietary sources or supplements. It has been previously demonstrated that average dietary calcium intake is low in this population—well below 500 mg per day³¹—whereas the recommended dietary intake for Australians for calcium intake in women of this age group is 1,000 mg per day.³²

This study shares a number of the limitations inherent in studies of frail older people in residential care. Dropouts

due to death and illnesses were unavoidably large in number. There was great heterogeneity in physical state and comorbid conditions. A large number of raters whose training in this assessment was minimal ascertained falls. A larger sample would be required to confirm antifracture efficacy in a study of this design. At no stage was vitamin D status checked after the introduction of vitamin D supplementation. The dose of vitamin D supplementation was reduced from 10,000 IU weekly to 1,000 IU daily because of the discontinuation of the larger dose, and this may have reduced the effect of the supplementation.

Nevertheless, this study supports the use of vitamin D supplements in older people in residential care. The demonstrated benefits in this study on the rates of falls for individuals with marginal vitamin D levels, even without frank vitamin D deficiency, highlights the potential benefits of vitamin D supplementation in this population.

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Author Contributions: Leon Flicker designed the study, approached some of the institutions, supervised the data collection, coordinated and interpreted the analyses, wrote the first draft, and coordinated the drafting of the manuscript. Robert MacInnis maintained and further developed the databases, supervised the data checking, performed the analyses, assisted in the interpretation of the analyses, and participated in drafting the manuscript. Mark Stein designed and performed the pilot studies; helped design the study; helped develop the methodology of subject recruitment, randomization, and data acquisition; assisted with and helped supervise the establishment of the database; assisted with supervision of data acquisition; reviewed the analyses; and participated in drafting the manuscript. Sam Scherer assisted in and helped develop the pilot studies; helped design the study, including the methodology of approaching institutions and subject recruitment and the methodology of data acquisition; assisted in subject recruitment; assisted in supervision of data acquisition; reviewed the analyses; and participated in drafting of the manuscript. Kate Mead was the nurse coordinator for most of the period of the study; helped develop the methodology of approaching the institutions and subject recruitment and the methodology of data acquisition; was responsible for a large part of recruitment and data acquisition; assisted with the establishment of the database; reviewed the analyses; and participated in drafting the manuscript. Caryl Nowson helped design the study, assisted in supervision of data acquisition, reviewed the analyses, and participated in drafting the manuscript. Jenny Thomas was the study coordinator for the Perth arm of the study, approached

the institutions, was responsible for Perth subject recruitment and data acquisition, reviewed the analyses, and participated in drafting the manuscript. Chris Lowndes was the nurse coordinator for the latter period of the study, supervised the completion of the study, assisted in data management and cleaning, reviewed the analyses, and participated in drafting the manuscript. John Hopper helped design the study, supervised the performance of the analyses, and participated in drafting the manuscript. John Wark supervised and assisted with the pilot studies, helped design the study, undertook substantial supervision of data acquisition and maintenance and subject recruitment, reviewed the analyses, and participated in drafting of the manuscript.

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