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ORIGINAL ARTICLE

Serum 25-hydroxyvitamin D levels and incident falls in older women

K. Uusi-Rasi[1] · R. Patil[1,2] · S. Karinkanta[1] · K. Tokola[1] · P. Kannus[1,3,4] · C. Lamberg-Allardt[5] · H. Sievänen[1]

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Abstract

Summary Three hundred eighty-seven home-dwelling older women were divided into quartiles based on mean serum 25-hydroxyvitamin D (S-25(OH)D) levels. The rates of falls and fallers were about 40% lower in the highest S-25(OH)D quartile compared to the lowest despite no differences in physical functioning, suggesting that S-25(OH)D levels may modulate individual fall risk.

Introduction Vitamin D supplementation of 800 IU did not reduce falls in our previous 2-year vitamin D and exercise RCT in 70–80 year old women. Given large individual variation in individual responses, we assessed here effects of S-25(OH)D levels on fall incidence.

Methods Irrespective of original group allocation, data from 387 women were explored in quartiles by mean S-25(OH)D levels over 6–24 months; means (SD) were 59.3 (7.2), 74.5 (3.3), 85.7 (3.5), and 105.3 (10.9) nmol/L. Falls were recorded monthly with diaries. Physical functioning and bone density were assessed annually. Negative binomial regression was used to assess incidence rate ratios (IRRs) for falls and Cox-regression to assess hazard ratios (HR) for fallers. Generalized linear models were used to test between-quartile differences in physical functioning and bone density with the lowest quartile as reference.

Results There were 37% fewer falls in the highest quartile, while the two middle quartiles did not differ from reference. The respective IRRs (95% CI) for falls were 0.63 (0.44 to 0.90), 0.78 (0.55 to 1.10), and 0.87 (0.62 to 1.22), indicating lower falls incidence with increasing mean S-25(OH)D levels. There were 42% fewer fallers (HR 0.58; 040 to 0.83) in the highest quartile compared to reference. Physical functioning did not differ between quartiles.

Conclusions Falls and faller rates were about 40% lower in the highest S-25(OH)D quartile despite similar physical functioning in all quartiles. Prevalent S-25(OH)D levels may influence individual fall risk. Individual responses to vitamin D treatment should be considered in falls prevention.

Keywords Bone density · Falls prevention · Older women · Physical functioning · Vitamin D

Introduction

Fragility fractures are a serious health problem among aging populations, and vitamin D has been thought to be beneficial in fracture prevention. Vitamin D has been proposed to mitigate fracture risk through its beneficial effects on bone mineral density (BMD) and bone strength and by reducing the risk of falling via improvement in neuromuscular function [1, 2].

Evidence has shown that vitamin D is important for health in general and is essential for skeletal development and maintenance. Serum 25-hydroxyvitamin D (S-25(OH)D) is commonly used as a marker of vitamin D status. However, despite substantial research, there is neither a consensus on the optimal dose of vitamin D supplements, nor a universally

✉ K. Uusi-Rasi
kirsti.uusi-rasi@uta.fi

1 The UKK Institute for Health Promotion Research, P.O. Box 30, 33501 Tampere, Finland

2 Department of Physiotherapy, Jehangir Hospital, Pune, Maharashtra 411001, India

3 Medical School, University of Tampere, Tampere, Finland

4 Department of Orthopedics and Trauma Surgery, Tampere University Central Hospital, Tampere, Finland

5 Department of Food and Environmental Sciences, University of Helsinki, Helsinki, Finland

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accepted threshold for desirable S-25(OH)D levels, or definition for vitamin D deficiency [3]. One suggested approach is to divide vitamin D status into four groups indicating severe deficiency (< 25 nmol/L), deficiency (< 50 nmol/L), insufficiency (< 75 nmol/L), and sufficiency (> 75 nmol/L) [4, 5].

There is also lack of information about the dose of vitamin D supplementation needed to reach a sufficient level. Mainly, daily doses of at least 800 IU are recommended for reducing falls and fractures [6]. Furthermore, substantial individual differences exist in the S-25(OH)D response even with the same dose of supplementation [7], and it is also likely that there are large inter-individual differences in the requirement of optimal vitamin D intake [8].

Studies with vitamin D supplementation have shown improvements in physical functioning and reduction in fall rates, although not consistently [9–13]. Reasons behind these disparate results are multitude, such as the baseline S-25(OH)D levels, the administered supplement dose or dosage regimen, the dose-response of an individual, and the form of supplement, let alone the clinical characteristics of the target group. However, risk factors for falls are numerous, and it is improbable that vitamin D confers beneficial effects on all these.

Previously, we investigated the effects of vitamin D supplementation (800 IU/day) and multimodal supervised group-based exercise in reducing falls among older home-dwelling women in a 2-year randomized four-arm intervention trial (DEX). The trial showed that neither vitamin D nor exercise were effective in reducing the rate of falls, but there were less medically attended injurious falls among exercisers [14]. However, during the 2-year follow-up after the intervention, vitamin D without exercise was also associated with fewer injurious falls [15]. During the DEX RCT, individual S-25(OH)D levels varied substantially from 55 to 155 nmol/L among vitamin D-treated participants while large individual seasonal variations were also seen among women receiving placebo. It is important to know how these large individual variations relate to falls.

Therefore, in this exploratory reanalysis of the DEX trial data, we aimed to assess the relationship between mean S-25(OH)D levels and incident falls among the trial participants during the 2-year intervention period.

Methods

Trial design

The original DEX trial (NCT00986466) assessed the effects of exercise and vitamin D_3 on the risk of falls in 409 Finnish home-dwelling women aged 70 to 80 years living in the city of Tampere. Briefly, eligible women were randomly assigned to one of the four groups: (1) vitamin D 800 IU/day and exercise, (2) placebo and exercise, (3) vitamin D 800 IU/day without exercise, and (4) placebo without exercise. Eligibility criteria for the trial participants included a history of falling at least once during the previous 12 months, no use of vitamin D supplements, and no contraindications to exercise. The supervised, group-based exercise consisted of strength, balance, mobility, and agility training, administered twice weekly during the first year and once weekly during the second year. The exercise protocol is described in detail previously [16]. A total of 387 were included in the present study; women with only baseline S-25(OH)D level were excluded.

The study protocol was approved by the Ethics Committee of the Tampere University Hospital, Finland (R09090). Each participant provided her written informed consent prior to randomization.

Outcome measures

The primary outcome was an incident fall. Secondary outcomes included fallers, injurious falls, injured fallers, bone mineral density, and physical functioning (muscle strength, balance, and mobility). While the purpose of this post hoc analysis was to evaluate the influence of prevalent vitamin D supplementation on falls, the first 6 months were excluded as a wash-out period. At 6 months, vitamin D levels had increased from baseline levels and reached a steady state. It is possible that 6 months is an unnecessarily long duration, but we did not measure S-25(OH)D levels between baseline and 6 months.

The number of falls was obtained from prospective fall diaries returned monthly via mail, and details of each registered fall were ascertained by a telephone call. A fall was defined as "an unexpected event in which the participant comes to rest on the ground, floor or lower level" [17].

Injurious falls comprised both minor injuries (bruises, abrasions, contusions, and sprains) as well as moderate and severe injuries (fractures and head injuries). Injurious falls for which participants sought medical care (nurse, physician, or hospital) [18] were classified as medically attended injurious falls and were included in the analyses. Falls during the first 6 months were excluded from these analyses.

Data collection

All measurements were done at baseline and 12 and 24 months. Blood samples and physical functioning were also assessed at 6 and 18 months.

Body height and weight were measured with standard methods. Dietary intake of calcium and vitamin D were assessed with a validated food frequency questionnaire [19].

Body composition and areal bone mineral density of the left femoral neck were assessed using dual-energy x-ray absorptiometry (DXA) (Lunar Prodigy Advance, GE Lunar, Madison, WI, USA) [20]. Trabecular bone density (TrD) at the distal site (5%) and cortical density (CoD) at the middiaphysis (50%) of the tibia were assessed with peripheral quantitative computed tomography (pQCT) (Norland/Stratec XCT 3000, Pforzheim, Germany) [21].

Physical functioning was assessed by the short physical performance battery (SPPB) [22], which comprised static balance, four-meter normal walking speed, and five-time chair stand tests, and by the timed-up and go (TUG) test [23]. Dynamic balance was assessed with the backwards walking test [24]. Maximal isometric leg-extensor strength at a knee angle 110° was measured by a strain gauge dynamometer (Tamtron, Tampere, Finland). All tests are regularly used in our laboratory and have good reproducibility.

In addition, activities of daily living (ADL: eating, getting into and out of bed, dressing, bathing, clipping toenails, and using the toilet) were assessed for calculating an ADL disability score (range 6–36), and the Leipad questionnaire (range 0–87) was used to assess quality of life) [25, 26]. In these questionnaires, lower scores indicated better functioning. Cognitive functioning was assessed with the mini-mental state examination (MMSE range 0–30), lower scores indicating worse functioning.

Analysis of serum 25-hydroxy-vitamin D

Fasting S-25(OH)D levels were measured as a marker of vitamin D metabolism with OCTEIA immunoenzymometric assay (IDS, Bolton, UK). Reproducibility was ensured by adhering to the Vitamin D External Quality Assessment Scheme, DEQAS (deqas.kpmd.co.uk). Interassay variation was avoided by measuring all samples from the same participant in the same series. Blood samples were taken five times at 6-month intervals. Two samples were taken in summer and two in winter when S-25(OH)D concentrations are expected to be at their highest and lowest levels, respectively.

Statistical analysis

All women with at least one S-25(OH)D measurement after the baseline were included in these post hoc analyses, regardless of their compliance to the trial program. Follow-up time for falls, fallers, and injurious falls was determined from the 6-month time point to the end of the 24-month intervention, unless the participant withdrew from the study or died. The first 6 months of the trial were excluded from the present analysis to disregard the potentially confounding effect of the transient response to vitamin D treatment could be disregarded. The participants were divided into quartiles (D1–D4) based on the mean S-25(OH)D levels between 6 and 24 months. The mean levels (range) in the quartiles were 59.3 (36.2–68.5), 74.5 (68.6–80.5), 85.7 (80.6–92.5), and 105.3 (92.6–143.1) nmol/L, respectively.

Quartile-wise falls incidence rates were calculated as the total number of falls divided by the time over which falls were monitored (in 100 person-years) in each quartile. Negative binomial regression was used to estimate the incidence rate ratios (IRR) for falls and injurious falls. Cox-regression models were used to calculate hazard ratios (HR) for fallers and injured fallers in each quartile, with the lowest S-25(OH)D quartile (D1) as reference. Analyses were adjusted for age, height, weight, and exercise group.

Baseline between-quartile differences were evaluated with analyses of covariance, using age, height, and weight as covariates. For physical functioning and bone traits, between-quartile differences from baseline to 24 months were tested by generalized linear models using age, height, weight, and exercise group as covariates and the lowest S-25(OH)D quartile (D1) as reference. All statistical analyses were conducted using IBM SPSS statistics software version 24 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp.).

Results

Group characteristics in different S-25(OH)D quartiles are shown in Table 1. The two lowest quartiles were heavier than the two higher quartiles, but were otherwise similar. Mean dietary calcium intake was sufficient in all quartiles, and dietary vitamin D intake was about 10 μg/day and did not differ significantly between the quartiles. A greater proportion of vitamin D-supplemented women belonged to the highest quartiles (D3 and D4). Exercisers were equally distributed across the quartiles; only the D3 quartile had a few more exercisers compared to other quartiles. The two lowest S-25(OH)D quartiles (D1 and D2) showed small seasonal mean changes in S-25(OH)D between 5 and 10 nmol/L, while the mean increase from the baseline was nearly 20 nmol/L in quartile D3 and nearly 30 nmol/L in quartile D4 over the study period (Fig. 1). During the 6- to 24-month period, seasonal variation was small but similar between the quartiles; only the mean levels differed.

There were no statistically significant between-quartile differences at baseline in bone density or physical functioning. Also, changes in bone density and physical functioning were similar in all quartiles and none differed statistically significantly from the lowest quartile D1 (Table 2).

In the highest D4 quartile, there were fewer falls and fallers than in the lowest quartile D1, while the D2 and D3 quartiles did not differ statistically significantly from D1. The IRRs (95% CI) for all falls were 0.87 (0.62 to 1.22), 0.78 (0.55 to 1.10), and 0.63 (0.44 to 0.90) in the D2–D4 quartiles, respectively, when compared with D1. There were also 42% fewer fallers (HR 0.58; 040 to 0.83) in D4 compared to D1 (Fig. 2). There also were fewer injurious falls and fallers in D4 compared to D1, while other quartiles did not differ from D1. Differences in medically attended falls or fallers did not reach statistical difference between the quartiles (Table 3).

Table 1 Baseline characteristics of the S-25(OH)D quartiles, mean (SD)

Characteristic	D1 $N = 96$	D2 $N = 97$	D3 $N = 97$	D4 $N = 97$
Age, year	74.3 (3.0)	74.7 (3.1)	74.0 (3.0)	73.6 (2.8)
Height, cm	160.0 (5.7)	159.6 (6.5)	159.4 (6.2)	160.0 (5.2)
Weight, kg	73.9 (12.0)	73.9 (11.6)	70.3 (11.4)	70.8 (11.8)
Fat mass, kg	30.2 (8.7)	31.1 (8.3)	28.3 (8.6)	28.3 (8.7)
Lean mass, kg	40.6 (4.6)	40.0 (4.4)	39.2 (3.8)	39.4 (4.5)
Change in weight, kg	0.11 (3.25)	− 0.68 (3.35)	− 0.37 (3.11)	− 0.96 (3.14)
Body fat%	41.9 (6.4)	43.2 (6.3)	41.1 (6.4)	41.0 (6.8)
Dietary calcium intake, mg/day	1105 (296)	1167 (297)	1211 (288)	1199 (314)
Dietary vitamin D intake, μg/day	9.2 (3.0)	10.4 (2.6)	11.2 (3.0)	10.6 (3.7)
S-25(OH)D, nmol/L	57.1 (13.4)	65.2 (13.4)	68.6 (14.8)	78.1 (21.9)
Health status, *N*				
Good to excellent	41	41	48	41
Satisfactory	52	53	46	53
Bad	3	3	3	3
Diagnosed illness, no/yes	15/81	8/89	17/80	10/87
Medication, no/yes	21/75	11/86	16/81	17/80
MMSE (0–30)[a]	28.6 (1.6)	28.2 (1.6)	28.2 (1.5)	28.4 (1.3)
ADL (6–36)[b]	6.7 (1.7)	7.1 (2.2)	6.6 (1.5)	6.8 (1.9)
Quality of life (total Leipad score 0–87)[b]	16.0 (7.4)	16.3 (7.1)	15.0 (8.4)	15.5 (8.2)
Waist circumference, cm	93.4 (11.1)	93.2 (11.3)	89.8 (10.8)	89.7 (11.6)
RR, syst, mmHg	145.5 (16.7)	146.7 (14.4)	149.7 (17.1)	147.6 (18.2)
RR, diast, mmHg	80.7 (9.0)	80.8 (8.3)	81.9 (9.4)	81.3 (8.6)
Exercise intervention, *N*, no/yes	53/43	54/43	35/62	51/46
Placebo /vitamin D supplement (800 IU/d), n	85/11	61/36	35/62	15/82

D1 = 36.2–68.5, D2 = 68.6–80.5, D3 = 80.6–92.5, D4 = (92.6–143.1) nmol/L

[a] Higher scores indicate better functioning

[b] Lower scores indicate better functioning

Discussion

Previously, the original DEX trial showed that women in the exercise groups experienced over 50% fewer injurious falls compared to women with no exercise, while vitamin D supplementation (800 IU/day) did not have that benefit [14]. However, results of the current exploratory reanalysis showed that the highest S-25(OH)D levels were related to fewer falls and fallers compared with the lowest S-25(OH)D levels. This observation gives rise to the question whether vitamin D can, after all, effectively reduce the risk of falls. Exercisers were quite evenly distributed across quartiles based on vitamin D levels, which can partly explain why there was no corresponding difference in changes in physical functioning after the intervention. There is some evidence that calcium and vitamin D deficiency alters muscle function [27], and vitamin D supplementation has been proposed as a possible mean in delaying functional decline through its direct effect on muscle strength and functioning [28, 29]. While the participants in the present study were basically replete in vitamin D, it is possible that vitamin D supplementation, even at adequate baseline levels, may alter muscle function. However, the used methods of assessing physical functioning in our trial were not sensitive

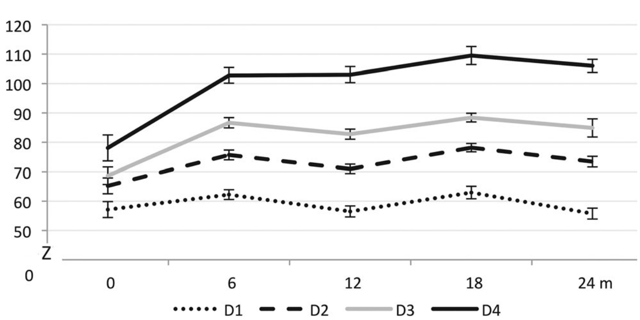

Fig. 1 Mean S-25(OH)D (95% CI) levels in vitamin D quartiles during the 2-year intervention. D1 = 36–68, D2 = 69–80, D3 = 81–92, and D4 = 93–143 nmol/L

Table 2 Baseline values (SD) and mean %-changes (95% CI) in bone density and physical functioning in each S-25(OH)D quartile

Outcome	Absolute value, mean (SD)	At 24 m,	Change at 24 m	*P* compared with quartile D1
Normal walking speed, m/s				
D1	1.00 (0.20)	1.00 (0.19)	− 0.8 (− 3.9 to 2.3)	
D2	0.99 (0.20)	0.99 (0.20)	− 0.3 (− 3.5 to 3.0)	0.99
D3	1.05 (0.19)	1.02 (0.18)	− 3.2 (− 6.9 to 0.5)	0.70
D4	1.06 (0.20)	1.01 (0.18)	− 5.5 (− 8.6 to − 2.3)	0.14
Chair stand time, s				
D1	12.44 (2.44)	11.52 (2.15)	− 7.0 (− 10.3 to − 3.8)	
D2	12.70 (2.87)	12.13 (2.56)	− 3.0 (− 5.8 to − 0.3)	0.13
D3	12.55 (3.14)	11.35 (2.28)	− 7.8 (− 12.5 to 1.5)	0.86
D4	12.29 (2.43)	11.85 (3.56)	− 2.7 (− 6.9 to 1.5)	0.09
TUG time, s				
D1	9.20 (2.08)	9.12 (2.08)	− 1.0 (− 4.6 to 2.6)	
D2	9.44 (2.24)	9.53 (2.78)	1.6 (− 2.6 to 5.8)	0.21
D3	8.79 (1.59)	8.75 (1.56)	0.4 (− 3.0 to 3.8)	0.90
D4	8.72 (1.69)	8.77 (2.00)	1.4 (− 2.0 to 4.7)	0.53
Backwards walking, proportion of those able to do 6.1 m, %				
D1	38.5	61.4	19.3 (9.3 to 29.3)	
D2	35.1	48.3	11.5 (2.1 to 20.9)	0.12
D3	48.5	66.7	17.2 (7.4 to 27.1)	0.92
D4	46.4	65.6	17.2 (7.8 to 26.6)	0.94
Leg extensors muscle strength, *N*/kg				
D1	23.7 (6.1)	26.0 (7.8)	9.1 (3.0 to 15.1)	
D2	22.3 (6.8)	24.4 (6.4)	9.5 (4.2 to 14.8)	0.65
D3	23.4 (6.3)	26.9 (7.4)	13.2 (8.8 to 17.6)	0.31
D4	23.1 (7.3)	24.9 (8.0)	7.1 (3.2 to 10.9)	0.33
Femoral neck BMD, g/cm^2				
D1	0.86 (0.13)	0.85 (0.13)	− 1.3 (− 2.1 to − 0.6)	
D2	0.87 (0.14)	0.87 (0.13)	− 0.6 (− 1.3 to 0.2)	0.12
D3	0.84 (0.12)	0.82 (0.12)	− 1.5 (− 2.2 to − 0.8)	0.76
D4	0.87 (0.12)	0.86 (0.13)	− 1.2 (− 1.8 to − 0.5)	0.67
Distal tibia TrD, mg/cm^3				
D1	221.8 (33.5)	222.0 (33.6)	− 0.2 (− 0.5 to 0.1)	
D2	223.3 (27.8)	223.2 (29.0)	− 0.1 (− 0.5 to 0.2)	0.90
D3	219.3 (30.8)	218.1 (31.2)	− 0.2 (− 0.6 to 0.2)	0.81
D4	223.8 (30.4)	223.5 (31.6)	− 0.2 (− 0.5 to 0.2)	0.85
Tibial shaft CoD, mg/cm^3				
D1	1106.1 (38.0)	1104.8 (37.3)	− 0.1 (− 0.3 to 0.1)	
D2	1107.3 (36.3)	1107.6 (37.0)	0.0 (− 0.2 to 0.2)	0.44
D3	1109.2 (29.7)	1106.9 (31.0)	− 0.1 (− 0.4 to 0.1)	0.73
D4	1112.8 (39.2)	1112.4 (41.2)	0.0 (− 0.2 to 0.1)	0.80

D1 = 36.2–68.5, D2 = 68.6–80.5, D3 = 80.6–92.5, D4 = (92.6–143.1) nmol/L

Analyses were adjusted for age, height, weight, and exercise group

enough to capture improvements in muscle performance or functioning corresponding to the decline seen in falls. Obviously, further research is needed to reveal exact mechanisms of action.

In their recent systematic review including seven trials with vitamin D supplementation in falls prevention, Guirguis-Blake et al. reported mixed results; one trial of annual high dose of cholecalciferol showed an increase, one trial of

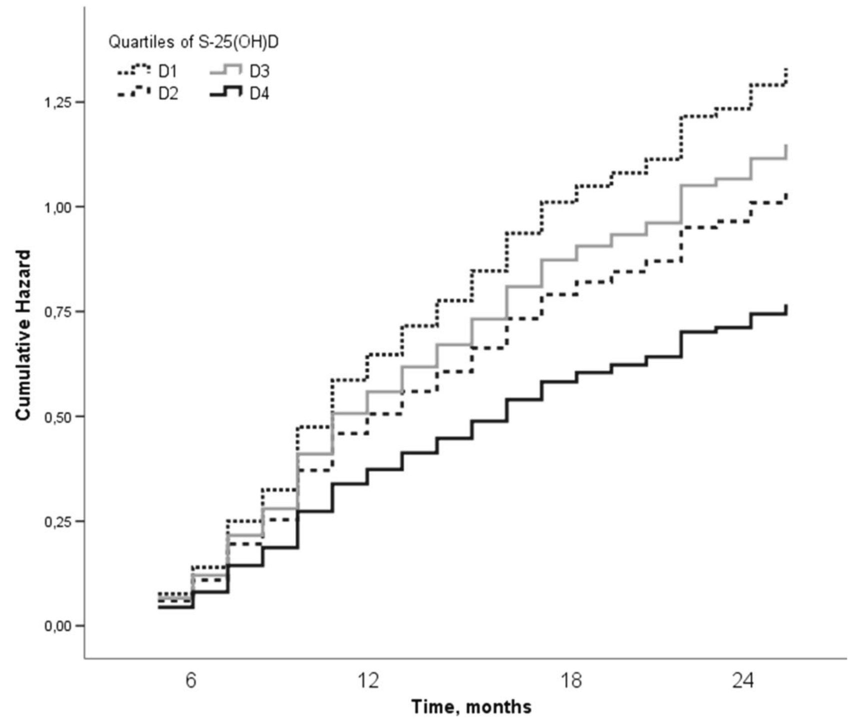

Fig. 2 Hazard ratios for fallers in vitamin D quartiles. Note that the first 6 months were excluded from the analyses. D1 = 36–68, D2 = 69–80, D3 = 81–92, and D4 = 93–143 nmol/L. Analyses were adjusted for age, height, weight, and exercise group

calcitriol showed a reduction, and the five remaining trials showed no difference in falls [30]. However, several studies have shown the association of increased falls with serum S-25(OH)D levels greater than 100–112 nmol/L [31–33]. Smith et al. found a U-shaped response curve in the incidence of fallers, with a significant reduction with medium doses of vitamin D (1600–3200 IU) compared to both low doses (400–800 IU) and high doses (4000–4800 IU) of vitamin D. When dividing the participants into quintiles by S-25(OH)D levels, faller rates were lowest in the middle quintile (S-25(OH)D between 80 and 100 nmol/L), but increased as S-25(OH)D exceeded 100 nmol/L. This middle quintile is about the same

Table 3 Mean of S-25(OH)D levels (SD) and rate of falls per 100 person-years in each study group, and incidence rate ratios (IRR) (95% CI) for falls and injurious falls

Outcome	D1 *N* = 96	D2 *N* = 97	D3 *N* = 97	D4 *N* = 97
S-25OHD, nmol/L	59.5 (7.3)	74.7 (3.4)	86.0 (3.7)	105.9 (10.9)
Rate of falls				
Falls, all	137.2	115.5	104.6	85.0
Falls with any injury	71.7	59.4	53.6	45.4
Falls with medically attended injuries	9.6	14.2	8.0	7.2
Falls with fractures	4.1	2.7	3.4	2.0
IRR				
Falls, all	1	0.87 (0.62–1.22)	0.78 (0.55–1.10)	0.63 (0.44–0.90)
Falls with any injury	1	0.84 (0.62–1.14)	0.75 (0.55–1.03)	0.65 (0.65–0.90)
Medically attended injurious falls	1	1.54 (0.77–3.08)	0.90 (0.41–2.00)	0.73 (0.33–1.65)
HR				
All fallers	1	0.78 (0.55–1.11)	0.86 (0.61–1.22)	0.58 (0.40–0.83)
All injured fallers	1	0.89 (0.61–1.31)	0.94 (0.64–1.38)	0.61 (0.40–0.92)
Medically attended injured fallers	1	1.53 (0.73–3.21)	1.03 (0.46–2.33)	0.68 (0.28–1.62)

D1 = 36–68, D2 = 69–80, D3 = 81–93, D4 = 94–143 nmol/L

S-25(OH)D is a mean of 6–24 months

Analyses were adjusted for age, height, weight, and exercise group

S-25(OH)D level we had in the highest quartile (mean 105 nmol/L) which was associated with decreased rate of falls and fallers. It may be possible that bolus dosing monthly or annually is more harmful than daily doses, even when equivalent to daily doses of 800 IU.

In our study, changes in bone density between quartiles were similar, suggesting a negligible effect of prevalent vitamin D levels on bone mineral status. Many studies have shown that increased bone loss is only associated with S-25(OH)D levels less than 50 nmol/L [34, 35], which is lower than the mean level in our lowest quartile.

Besides the loss of bone density with aging, there also is loss of muscle strength and power, leading to increased risk of falls and related injuries. Thus, minimizing the decline in muscular performance is essential in the prevention of frailty. Exercise can be expected to be effective in retarding and even maintaining muscle function and balance [36]. Previously, we found no effect of vitamin D on physical functioning in the original 2 × 2 factorial RCT design of the DEX trial [14]; and in these current reanalysis, changes were similar across the quartiles and independent of vitamin D levels. At baseline, the two lowest quartiles had a trend for somewhat poorer mobility (slower gait speed and TUG time) but no differences in lower leg muscle strength were seen. These results do not clarify the relationship between vitamin D and physical functioning. However, the curve describing physical functioning in relation to S-25(OH)D may level off at about 50 nmol [37, 38] and even the lowest quartile in this present study was above that level. Thus, the mean S-25(OH))D levels seemed to be sufficient regarding physical functioning.

Many observational studies have found an association between low vitamin D levels and low physical functioning, although not consistently [10, 37, 39]. Cross-sectional studies are especially prone to confounding factors, and it may be questioned whether hypovitaminosis is a cause or a consequence of low physical functioning. For instance, physically inactive people may not have outdoor exposure to sunlight, resulting in lower S-25(OH)D levels. However, RCTs also show contradictory results suggesting that vitamin D supplementation in persons with vitamin D deficiency may or may not have a positive effect on physical functioning [1, 2]. Furthermore, large doses of vitamin D do not seem to be efficient at improving physical functioning [31, 40].

Despite Finland being located at northern latitudes (Tampere is at the 61.3° N latitude), and the limited amount of exposure to natural UVB radiation for synthesizing vitamin D on the skin during winter, the baseline mean S-25(OH)D level in the pooled group was 67.1 (17.9) nmol/L [41]. Although the levels varied between individuals, none of the participants were severely vitamin D-deficient; only 11 women had mean S-25(OH)D levels below 50 nmol/L. Several studies have shown that similar supplement doses can produce substantially different changes in S-25(OH)D levels, with a stronger response to vitamin D supplements among people with lower baseline levels [8, 42].

About one quarter, or precisely, 47 of 191 supplemented women belonged to the two lowest quartiles in spite of receiving 800 IU vitamin D supplements daily, and 11 (5.7%) were in the lowest quartile. On the other hand, 50 (25.8%) women receiving placebo were in the two highest quartiles. There are several possible explanations for non-response, including malabsorption, content of vitamin D supplements, or low compliance. At baseline, disorders of the gastrointestinal tract were inquired and all vitamin D supplements were supplied from the same batch. Compliance was systematically checked by counting remaining pills every 6 months, when a new batch of pills was given to the participants. Only nine (2%) women had a compliance of below 80%. It is also possible that women receiving placebo had other supplements besides the study preparation, resulting in high levels of S-25(OH)D, although the use of all nutrient supplements was checked regularly and use of vitamin D supplements was repeatedly forbidden. Furthermore, it must also be taken into account that the absorption and metabolism of vitamin D may largely be under genetic regulation. However, assessing genetic polymorphisms for vitamin D metabolism was beyond the scope of this study. Instead of recommending a universal dosage for vitamin D dose for all, its effects could be elaborated and the doses adjusted individually. Sufficiency of vitamin D intake is reliably diagnosed with measuring S-25(OH)D.

Differences in S-25(OH)D levels may also be due to differences in body composition. Some evidence suggests that obese persons require more vitamin D compared with their lean or normal weight counterparts because of sequestration in adipose tissue [43, 44], although not consistently [45, 46]. In this current study, the two lower quartiles had greater body mass and higher fat mass than the two higher quartiles, but individual response seemed to be independent of fat mass. Instead, the response was associated with baseline S-25(OH)D levels.

Major strength of the current study was the large sample size, prospective 18-month follow-up, and a wide variation in S-25(OH)D levels. To eliminate the transient phase in response to vitamin D supplementation, and to focus on a steady state-situation, we excluded the first 6 months at the beginning of the study to attain comparability between the quartiles. A previous vitamin D supplementation study S-25(OH)D of older Finnish women found that the S-25(OH)D levels plateaued after 6 weeks [47]. We also excluded falls during the first 6 months from the analyses with the reasoning that vitamin D may not have had enough time to affect falls during the first 6 months. This approach allowed us to assess the associations of prevalent S-25(OH)D levels with incident falls.

A major limitation of this study was that it is exploratory by nature and based on post hoc analyses of the data from a previous RCT. Thus, direct causal inference is subject to bias. Also, all participants were community-dwelling women in good health and physical condition, and the results cannot be generalized to older population in general. In addition, mean S-25(OH)D levels were above the target level > 50 nmol/L even in the lowest quartile. Only 51 (23%) women had baseline vitamin D levels lower than 50 nmol/L, and none were severely deficient. There is evidence that the effect of vitamin D on physical functioning and fall risk is more prominent among frail people [10, 48]. Nevertheless, the beneficial influence of vitamin D on fall incidence became apparent.

In conclusion, while vitamin D supplementation was not found beneficial in reducing falls or injurious falls in the original RCT design, the current exploratory reanalysis of the same data showed that high S-25(OH)D levels were associated with fewer falls and fallers. These findings were evident despite no differences seen in changes in physical functioning between the S-25(OH)D quartiles. Thus, the present findings suggest that prevalent S-25(OH)D levels may partly modulate individual fall risk.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study. The study protocol was approved by the institutional ethics committee of the Tampere University Hospital, Tampere, Finland. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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