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Full Length Article

The effect of vitamin D_3 supplementation on fracture incidence in an aging population — The Finnish vitamin D trial

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Article

Highlights

- Five-year vitamin D_3 supplementation of 1600 or 3200IU/day did not reduce fractures.
- An increased fracture incidence was observed in the 1600IU/day arm.
- Age, sex, or BMI did not modify the effects of supplementation on fracture incidence.

Abstract

Background

ffectiveness of vitamin D supplementation for fracture ntion at the population level remains a matter of debate. In this study, we evaluated the impact of vitamin D_3

Outline

supplementation on fracture risk among an aging population in Finland.

Methods

The study included 2495 participants, men ≥60 years and women ≥65 years, who were randomized for 5 years into three groups: 1600 IU/day or 3200 IU/day of vitamin D_3, or placebo. Fracture diagnoses were retrieved from two national care notification registers.

Results

During the mean 4.1-year supplementation period, there were 49, 73 and 52 fractures in the placebo, 1600 IU/day (compared to placebo: HR = 1.52, 95% CI = 1.06–2.18) and 3200 IU/day (HR = 1.07, 95% CI = 0.72–1.58) arms, respectively. During the extended 7.3-year follow-up, 104, 139 and 111 fractures occurred in the placebo, 1600 IU/day (HR = 1.40, 95% CI = 1.08–1.80) and 3200 IU/day (HR = 1.08, 95% CI = 0.83–1.41) arms, respectively. No statistically significant differences were observed in fracture subtypes. Age, sex, BMI, history of fracture or fall, osteoporosis diagnosis, or calcium supplement use did not modify the effects. In the sub-cohort of 550 participants, the mean±SD baseline serum 25-hydroxyvitamin D concentration was 74.8±18.2 nmol/L. After 12 months, the concentrations were 73.0±17.8, 99.7±21.1 and 120.4±21.8 nmol/L in the placebo, 1600 IU/day and 3200 IU/day arms, respectively (P<0.001).

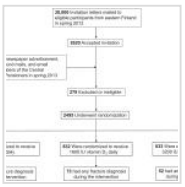
Conclusions

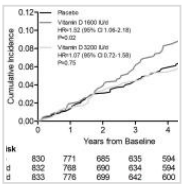
The 5-year vitamin D_3 supplementation of 1600 IU/day or 3200 IU/day did not reduce the risk of fractures among a largely vitamin D-sufficient aging population. The findings do not support use of high vitamin D doses for fracture prevention in such populations.

Clinical trial registry number

ClinicalTrials.gov: NCT01463813 ↗, https://clinicaltrials.gov/ct2/show/NCT01463813 ↗

Figures (2)





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Keywords

Fracture; Vitamin D; Supplementation; Elderly

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1. Introduction

Fractures significantly reduce quality of life and impose a socioeconomic burden on healthcare systems, with incidence rising worldwide [1], [2], [3]. Severe injuries, such as fractures of the hip, proximal humerus, pelvis, and vertebrae, are frequently associated with prolonged recovery periods, extended care, and increased mortality, even among relatively healthy older adults [4], [5]. The global population aged over 60 is projected to nearly double from 12% to 22% between 2015 and 2050 [6], and as life expectancy increases, the cumulative incidence of fragility fractures continues to grow. At the patient level, this translates to prolonged hospital stays, more frequent transitions to long-term care, higher fracture-related mortality, and increased healthcare costs, even after adjusting for age, comorbidities, education, and body mass index (BMI) [7].

Novel strategies for prevention of fractures are warranted for the aging population. Vitamin D supplementation is widely considered a supporting element in the treatment of osteoporosis and fracture prevention, often administered in combination with calcium. The primary role of vitamin D is to regulate calcium homeostasis and bone metabolism. Severe vitamin D deficiency is a well-established risk factor for rickets, osteomalacia and a potential modifiable risk factor for frailty in older adults [8]. Evidence from the 1990s demonstrated that supplementation with vitamin D_3 (800IU/day) combined with calcium supplementation (1200mg/day) for 18months reduced fracture risk among elderly individuals with marked vitamin D deficiency [9]. Subsequent meta-analyses have largely supported these findings, indicating that vitamin D supplementation in conjunction with calcium may reduce fracture risk, but mainly

among institutionalized individuals or those with severe vitamin D deficiency [10].

In contrast, studies evaluating vitamin D supplementation alone without added calcium have shown inconsistent results. A 5-year trial conducted in the early 2000s among community-dwelling older adults demonstrated a reduced fracture risk with 100,000IU of vitamin D_3 administered every four months [11]. However, more recent trials with community-dwelling populations have failed to demonstrate fracture prevention using dosing regimens ranging from 2000IU/day to 500,000IU once per year [12], [13], [14], [15], [16].

In this study, we report findings from the Finnish Vitamin D Trial regarding the effects of 5-year vitamin D_3 supplementation at doses of 1600IU/day or 3200IU/day compared with placebo on the incidence of fractures during the intervention period and across three subsequent years of post-supplementation follow-up. The study population comprised generally healthy (no history of cardiovascular disease or cancer), community-dwelling older adults in Finland who were not recruited or selected based on their vitamin D status, osteoporosis diagnosis, prior fractures, or other indicators of elevated fracture risk at study entry.

2. Methods

2.1. Study population

The FIND study, spanning from September 2012 to October 2018, was a double-blind, placebo-controlled randomized trial with generally healthy men and women from the general population in Finland [17]. It was aimed at investigating the impact of 5-year vitamin D_3 supplementation on the prevalence of major chronic diseases, with cardiovascular disease and cancer as the primary endpoints. Fracture incidence was an ancillary outcome.

The inclusion criteria were male participants aged ≥60 y and postmenopausal female participants aged ≥65 y without a history of cardiovascular disease or cancer (except non-melanoma skin cancer). The exclusion criteria were: history of kidney stones, renal failure or dialysis, hypercalcemia, hypo- or

hyperparathyroidism, severe liver disease (cirrhosis), or sarcoidosis or other granulomatous diseases such as active chronic tuberculosis or granulomatosis with polyangiitis (previously known as Wegener's granulomatosis); use of vitamin D>800IU/d or calcium >1200mg/d from all supplemental sources combined (or if taking, willing to decrease or forego such use during the trial).

The recruitment process yielded a total of 2495 participants, who were subsequently randomized into three groups: 1) 1600IU/d of vitamin D_3, 2) 3200IU/d of vitamin D_3, or 3) placebo (Fig. 1). Within this cohort, a random subgroup of 551 participants underwent more detailed baseline examinations. Subsequent follow-up visits at 6, 12, and 24months involved 512, 533, and 496 participants, respectively [17]. Randomization into these groups occurred via sex-stratified simple randomization, with a 1:1:1 ratio, based on computerized random number generation. Sex was determined based on social security number, which in Finland indicates the biological sex of a person. The randomization was conducted by a statistician from outside of the study group.

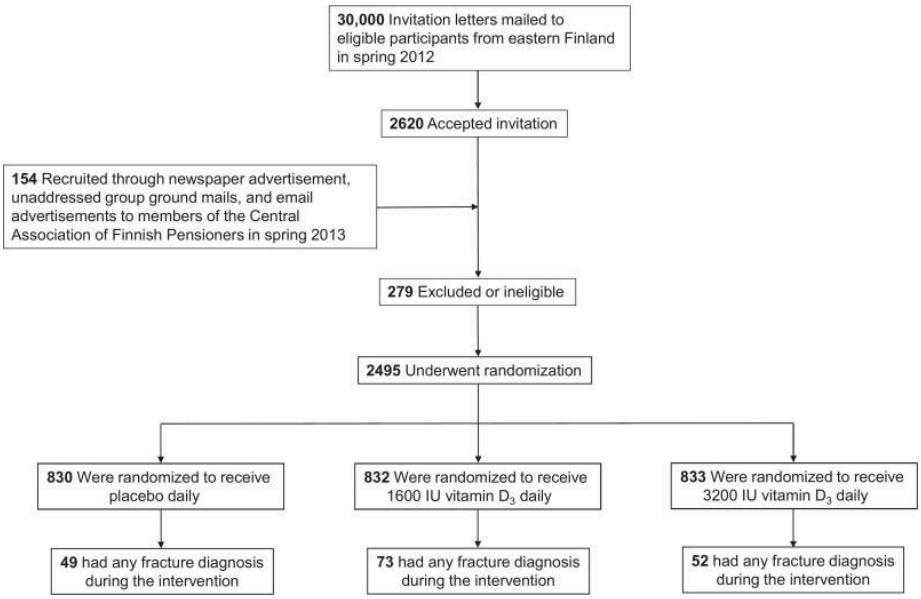

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Fig. 1. Flow-chart of the Finnish Vitamin D Trial.

The study pills were purchased from Galena Pharma Ltd. (Kuopio, Finland). One pill contained either 0, 1600IU or 3200IU of vitamin D_3. The pills were annually either mailed to the participants or

given at study visits. Double blinding was maintained throughout the study.

Participants completed questionnaires at various time points throughout the trial: at baseline, after 12, 24, and 36 months, and at the conclusion of the 60-month study period [17]. The questionnaires included, for example, questions about history of fractures and falls or osteoporosis diagnosis before the baseline, and use of medications and supplements. The response options for supplement use were “I do not use”, “I use occasionally or seasonally” and “I use daily or almost daily”. The dose was not inquired for other supplements than vitamin D. The baseline, 36-month, and 60-month questionnaires included a validated 142-item food-frequency questionnaire. Additionally, the final questionnaire included an inquiry regarding adherence to the study regimen, specifically asking participants, “How many of the study pills did you take during the study?” Response options ranged from “<50%” to “100% or almost 100%”. BMI calculations were derived from the weight and height data provided in the baseline questionnaire.

Serum 25(OH)D_3 concentrations were measured with high-performance liquid chromatography using coulometric electrode array detection [17], [18]. Samples were collected from the subgroup at baseline (n=550), and after 6 (n=511) and 12 (n=532) months [17]. In a smaller subgroup of 60 participants, a direct competitive chemiluminescence immunoassay (Liaison 25 OH Vitamin D Total Assay, DiaSorin, Stillwater, MN, USA) was also used for serum 25(OH)D3 measurement from samples collected at months 0, 6, 12, 24 and 52 [17]. The serum 25(OH)D3 results were standardized against National Institute of Standards and Technology (NIST) reference values [17].

All participants were volunteer adults who were entitled to withdraw from the study at any time without explanation. All participants signed a written informed consent. The appropriate study approvals were obtained from the Ethics committee of the Kuopio University Hospital (#30/2010) and from the Finnish Institute for Health and Welfare.

2.2. Assessment of fracture diagnoses

Fracture diagnoses were retrieved from two national care notification registers, Hilmo for specialized health care and Avohilmo for primary health care (Finnish Institute for Health and Welfare, data agreement THL/523/5.05.00/2020), and from the Causes of Death Register (Statistics Finland, TK/1007/07.03.00/2022). The following International Classification of Diseases, 10th Revision (ICD-10) codes were considered as fractures: S02 (skull and facial bones, excluding S02.5 tooth), S12 (neck), S22 (ribs, sternum, and thoracic spine), S32 (lumbar spine and pelvis), S42 (shoulder and upper arm), S52 (forearm), S62 (wrist and hand), S72 (femur), S82 (lower leg, including ankle), S92 (foot and toe), T02 (multiple body regions), T08 (spine, level unspecified), T10 (upper limb, level unspecified), T12 (lower limb, level unspecified), and T14.2 (unspecified body region). The following ICD-10 codes were considered as osteoporotic fractures: M48.4–5 (fatigue fracture of vertebra or collapsed vertebra), M49.5 (collapsed vertebra in diseases classified elsewhere), M80 (osteoporosis with pathological fracture), S12, S22.0–1, S42.2–4, S52.5–6, S72.0–2, S82.3–8, T02.1, T08, and T91.1 (sequelae of fracture of spine). Fractures resulting from high-energy trauma, operative complications, or pathological causes were excluded. The first date when the ICD-10 code appeared in any of the registers was considered the date of the fracture in question.

2.3. Statistical analysis

Baseline characteristics were compared across study arms using ANOVA and Pearson's chi-square test. According to the pre-specified protocol, Cox proportional hazards regression models were used to predict the hazard of fracture in the two vitamin D_3 supplementation arms vs. the placebo arm. Kaplan-Meier curves and the log rank (Mantel-Cox) test were used to detect trends. In the non-prespecified analyses, we also analyzed the effects against the placebo group after combining the two vitamin D arms. In the analyses, two follow-up scenarios with respect to the use of registers were applied: the 5-year intervention period, in which follow-up ended at first occurrence of fracture diagnosis, a FIND primary endpoint (major cardiovascular disease or cancer), withdrawal, death, or completion of the 5-year supplementation period; and the extended period through December 31, 2021, censoring at fracture diagnosis, withdrawal, death, or the end of

the extended follow-up period. The models were adjusted for age and sex. Effect modification by age, sex, BMI, calcium supplement , osteoporosis diagnosis, and history of fracture or fall was explored using multiplicative interaction modeling. IBM® SPSS® version 29 was used for analyses. Two-sided $P<0.05$ was used to determine statistical significance.

3. Results

Women comprised 42.5% of the participants. The mean±SD age of the participants was 68.2±4.5 years (66.4±3.9 years in men, 70.6±4.0 in women). The mean±SD dietary calcium intake was 1369±739 mg/d (1353±697 mg/day in men and 1389±791 mg/day in women). Regular use of calcium supplements was reported by 79 men (5.8%) and 302 women (29.6%). Thirty-six females (2.7%) and one male (0.2%) used osteoporosis medications, and 142 females (13.2%) used estrogen medication. The baseline characteristics were in balance between the three supplementation arms (Table 1). In the sub-cohort, the mean±SD serum 25(OH)D concentration at baseline was 74.8±18.2 nmol/L (29.9±7.3 ng/mL) (P-difference between the arms=0.72). Among these, 9.1% (n=50) had concentrations below 50 nmol/L (20 ng/mL) and 50.0% (n=275) had concentrations of at least 75 nmol/L (30 ng/mL). After 12 months, the mean±SD concentrations were 73.0±17.8 nmol/L (29.3±7.2 ng/mL), 99.7±21.1 nmol/L (40.0±8.5 ng/mL) and 120.4±21.8 nmol/L (48.3±8.7 ng/mL) in the placebo, 1600 IU/day, and 3200 IU/day arms, respectively ($P<0.001$). The measurements in the sub-cohort of 60 participants with data from the months 0, 6, 12, 24 and 52 indicated that the differences between the study arms were maintained throughout the 5-year supplementation period [17]. Among the 1609 participants with data from the final questionnaire, 74.8% (n=1203) reported complete adherence in using the study pills (P-difference between the arms=0.39), while 95.3% (n=1533) reported using at least 80% of the pills (P-difference=0.82).

Table 1. Baseline characteristics of the participants.

Characteristic	Overall (*n*=2495)	Placebo arm (*n*=830)
Female sex, n (%)	1069 (42.8)	372 (44.8)
Age, mean (SD), y	68.2 (4.5)	68.2 (4.5)
Age group, n (%)		
60–64 y[a]	620 (24.8)	202 (24.3)
65–69 y	1089 (43.6)	373 (44.9)
70–74 y	589 (23.6)	186 (22.4)
≥75 y	197 (7.9)	69 (8.3)
Employment status, n (%)	*n*=2469	*n*=823
Full-time work	201 (8.1)	76 (9.2)
Part-time work	95 (3.8)	27 (3.3)
Unemployed	61 (2.5)	14 (1.7)
Retired	2097 (84.9)	703 (85.4)
Not working for other reasons	15 (0.6)	3 (0.4)
Leisure-time physical activity, mean (SD), h/week[b]		
Light	13.1 (10.8) (*n*=2172)	13.1 (10.9) (*n*=7
Heavy	5.7 (6.5) (*n*=1601)	5.6 (6.3) (*n*=52
Smoking regularly[c], n (%)	885 (35.7) (*n*=2477)	292 (35.4) (*n*=8
At least a high school diploma, n (%)	417 (16.8) (*n*=2483)	135 (16.3) (*n*=8
Married, n (%)	1849 (74.7) (*n*=2476)	620 (75.2) (*n*=8
Body mass index, mean (SD), kg/m^2	27.1 (4.3) (*n*=2491)	27.2 (4.3) (*n*=828)
Alcohol intake, mean (SD), g/day	7 (13) (*n*=2464)	8 (16) (*n*=824)
Vitamin D intake from diet, mean (SD), IU/d	428 (312) (n=2464)	416 (260) (n=824)
The major vitamin D sources in the diet		

Characteristic	Overall (*n*=2495)	Placebo arm (*n*=830)
Liquid dairy products, mean (SD), g/d	488 (409)	473 (387)
Fish, mean (SD), g/d	76 (96)	71 (74)
Vegetable fat spreads, mean (SD), g/d	13 (9)	12 (9)
Use of own vitamin D supplements, n (%)		
Not at all	1670 (66.9)	535 (64.5)
200–400IU/day	361 (14.5)	133 (16.0)
>400 - <800IU/day	74 (3.0)	27 (3.3)
800IU/day	390 (15.6)	135 (16.3)
Calcium intake from diet, mean (SD), mg/d	1369 (739) (*n*=2463)	1344 (708) (*n*=
Daily calcium supplement use, n (%)	381 (16.0) (*n*=2387)	143 (18.1) (*n*=7
History of fracture, n (%)	716 (29.1) (*n*=2459)	229 (27.9) (*n*=820)
At least 1 fall during previous year, n (%)	934 (37.6) (*n*=2481)	330 (40.0) (*n*=824)
Osteoporosis diagnosis, n (%)	91 (3.7) (*n*=2484)	33 (4.0) (*n*=828)
Osteoporosis medication[d], n (%)	37 (1.5)	11 (1.3)
Osteoporosis medication at end of trial, n (%)	16 (1.0) (*n*=1611)	6 (1.1) (*n*=543)
Corticosteroid medication, n (%)	26 (1.0)	11 (1.3)
Diabetes medication, n (%)	222 (9.0)	68 (8.2)
Estrogen medication[e], n (%)	142 (5.7)	49 (5.9)
Self-rated health good or excellent, n (%)	1460 (59.2) (*n*=2467)	460 (56.0) (*n*=8
Use of personal anti-slip device		

Characteristic	Overall (*n*=2495)	Placebo arm (*n*=830)
Hip protectors, n (%)	2 (0.1) (*n*=2376)	0 (*n*=788)
Anti-slip device for shoes, n (%)	499 (21.0) (*n*=2373)	177 (22.5) (*n*=786)
Walking stick(s), n (%)	279 (11.8) (*n*=2371)	99 (12.6) (*n*=785)
Rollator or kicksled, n (%)	41 (1.7) (*n*=2368)	17 (2.2) (*n*=785)

a
All are men in this age group.

b
Light activity is defined as gardening and other light outdoor activities, etc., heavy activity is defined as physical exercise that causes sweating or heavy breathing.

c
Smoking regularly is defined as smoking almost every day during the last year.

d
Osteoporosis medication includes ATC codes A12CD – Fluoride, H05BA – Calcitonins, M05B - Drugs affecting bone structure and mineralization. Of the 37 users, only one was male (in the placebo arm).

e
All estrogen (ATC code G03) users are female.

3.1. Incidence of fracture during the 5-year supplementation period

During the mean 4.1-year follow-up, 174 participants (7.0%) reported at least one fracture. There were 49, 73 and 52 fractures in the placebo, 1600IU/day and 3200IU/day arms, respectively. Compared to the placebo arm, the risk of any fracture in the

1600IU/day arm was increased by 51.9% (95% CI 5.7–118.1%), whereas no increase in risk was observed in the 3200IU/day arm (Table 2, Fig. 2). No statistically significant differences between the arms were observed in any fracture subtype or in site-specific fractures (Table 2) or when the two vitamin D arms were combined and compared to the placebo arm. In the stratified analyses, the increased risk in the 1600IU/day arm was statistically significant in men, in older participants, in participants with lower BMI, in participants not using calcium supplements, in participants with history of falling, and in participants without osteoporosis diagnosis, although the interactions were not statistically significant (Table 3). There were no statistically significant effects in the stratified analyses based on fracture history (Table 3).

Table 2. Incidence of fractures during the 5-year supplementation period according to randomization arm[a].

Event	**Placebo (*n*=830)**	**1600IU/day (*n*=832)**	***P* value**
PY, *n*	3480.0	3558.2	
All fractures			
Events, *n*	49	73	
Rate per 100 PY (95% CI)	1.40 (1.07–1.86)	2.05 (1.63–2.57)	
Hazard ratio (95% CI)	1	1.52 (1.06–2.18)	0.024
Fractures from low energy falls[b]			
Events, *n*	11	15	
Rate per 100 PY (95% CI)	0.32 (0.18–0.57)	0.42 (0.25–0.70)	
Hazard ratio (95% CI)	1	1.37 (0.63–2.99)	0.426
Osteoporotic fractures[c]			
Events, *n*	35	47	
Rate per 100 PY (95% CI)	1.01 (0.72–1.40)	1.32 (0.99–1.75)	

Event	Placebo (*n*=830)	1600IU/day (*n*=832)	*P* value
Hazard ratio (95% CI)	1	1.37 (0.88–2.12)	0.162
Fractures in forearms (ICD-10: S52)			
Events, *n*	15	17	
Rate per 100 PY (95% CI)	0.43 (0.26–0.71)	0.48 (0.30–0.77)	
Hazard ratio (95% CI)	1	1.16 (0.58–2.33)	0.672
Fractures in ribs(s), sternum, and thoracic spine (ICD-10: S22)			
Events, *n*	11	13	
Rate per 100 PY (95% CI)	0.32 (0.18–0.57)	0.37 (0.21–0.63)	
Hazard ratio (95% CI)	1	1.17 (0.52–2.60)	0.710
Fractures in the lower leg, including ankle (ICD-10: S82)			
Events, *n*	9	15	
Rate per 100 PY (95% CI)	0.26 (0.13–0.50)	0.42 (0.25–0.70)	
Hazard ratio (95% CI)	1	1.67 (0.73–3.81)	0.225
Fractures in wrist and hand level (ICD-10: S62)			
Events, *n*	5	6	
Rate per 100 PY (95% CI)	0.14 (0.06–0.34)	0.17 (0.08–0.38)	
Hazard ratio (95% CI)	1	1.19 (0.36–3.91)	0.772
Fractures in the shoulder and upper arm (ICD-10: S42)			
Events, *n*	5	5	
Rate per 100 PY (95% CI)	0.14 (0.06–0.34)	0.14 (0.06–0.34)	
Hazard ratio (95% CI)	1	1.01 (0.29–3.48)	0.990

Event	Placebo (*n*=830)	1600IU/day (*n*=832)	*P* value
Fractures in the femur (ICD-10: S72)			
Events, *n*	5	6	
Rate per 100 PY (95% CI)	0.14 (0.06–0.34)	0.17 (0.08–0.38)	
Hazard ratio (95% CI)	1	1.22 (0.37–4.01)	0.739
Fractures in the foot (except ankle) (ICD-10: S92)			
Events, *n*	3	10	
Rate per 100 PY (95% CI)	0.09 (0.03–0.27)	0.28 (0.15–0.52)	
Hazard ratio (95% CI)	1	3.37 (0.93–12.3)	0.065
Fractures in lumbar spine and pelvis (ICD-10: S32)			
Events, *n*	3	4	
Rate per 100 PY (95% CI)	0.09 (0.03–0.27)	0.11 (0.04–0.30)	
Hazard ratio (95% CI)	1	1.39 (0.31–6.22)	0.667
Other fractures[d]			
Events, *n*	1	3	
Rate per 100 PY (95% CI)	0.03 (0.00–0.20)	0.08 (0.03–0.26)	
Hazard ratio (95% CI)	1	2.88 (0.30–27.7)	0.360

PY, person-years. ICD-10, International Classification of Diseases 10th Revision.

a Adjusted for age and sex in the Cox proportional hazards regression model.

b Fractures related to the following ICD-10 codes: W00, W01, W10, and W19.

c

Composite endpoint of the following ICD-10 codes: M48.4–5, M49.5, M80, S12, S22.0–1, S42.2–4, S52.5–6, S72.0–2, S82.3–8, T02.1, T08, and T91.1.

d

Composite endpoint of skull and facial bone fractures (n=2, ICD-10: S02, excluding tooth fractures S02.5), neck fractures (n=4, ICD-10: S12), and a fracture in an unspecified body region (n=0, ICD-10: T14.2).

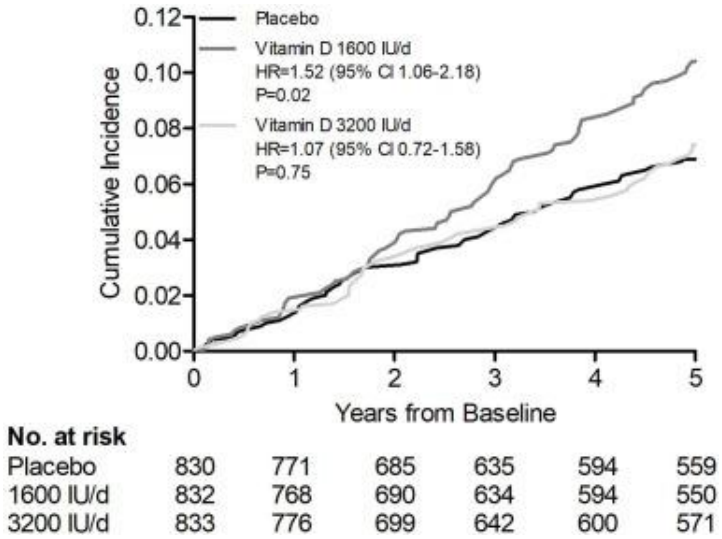

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Fig. 2. Cumulative incidence of any fracture in the three study arms during the 5-year supplementation period. Hazard ratio is from Cox proportional hazards regression models adjusted for age and sex.

Table 3. Incidence of any fractures during the 5-year supplementation period according to subgroup and randomization arm.

	No. of participants	Placebo	1600IU/
Men (events, n)	1426	14	36
		1	2.44 (1.3
Women (events, n)	1069	35	37

	No. of participants	Placebo	1600IU/
		1	1.14 (0.7
Age<median 67.4yr (events, *n*)	1247	20	26
		1	1.28 (0.7
Age≥median 67.4yr (events, *n*)	1248	29	47
		1	1.70 (1.0
BMI<median 26.4kg/m^2 (events, *n*)	1250	22	38
		1	1.77 (1.0
BMI≥median 26.4kg/m^2 (events, *n*)	1245	27	35
		1	1.32 (0.8
BMI <25kg/m^2 (events, *n*)	850	14	25
		1	1.70 (0.8
BMI 25–30kg/m^2 (events, *n*)	1136	20	36
		1	1.95 (1.1
BMI ≥30kg/m^2 (events, *n*)	509	15	12
		1	0.81 (0.3
Regular use of calcium supplements[a]			
Yes (events, n)	381	13	11
		1	1.06 (0.4
No (events, *n*)	2006	35	55
		1	1.54 (1.0
History of fracture[a]			
Yes (events, n)	716	23	34
		1	1.43 (0.8
No (events, n)	1743	26	37
		1	1.47 (0.8
At least 1 fall during previous year at baseline[a]			

	No. of participants	Placebo	1600IU/
(events, n)	934	25	37
		1	1.67 (1.0
No (events, n)	1547	24	36
		1	1.42 (0.8
Osteoporosis diagnosis[a]			
Yes (events, n)	91	5	4
		1	0.88 (0.2
No (events, n)	2393	44	69
		1	1.59 (1.0

Values are hazard ratios (95% confidence intervals) adjusted for age and sex in the Cox proportional hazards regression model.

a Data on supplement use missing for 108 participants, on fracture history for 36 participants, on fall history for 14 participants, and on osteoporosis diagnosis on 11 participants.

3.2. Incidence of fracture during the extended follow-up period

During the mean post-supplementation period of 3.2 years, 180 additional fractures occurred, 83 in men and 97 in women. The increased risk of any fracture observed in the 1600IU/day arm during the 5-year supplementation period remained during the post-supplementation period follow-up, with 39.5% (95% CI 8.2–79.9%) increase in risk compared to the placebo arm (Supplemental Table 1, Supplemental Fig. 1). No increase in risk was observed in the 3200IU/day arm or in any fracture subtype. The increased risk in the 1600IU/day arm was again stronger in men, older participants and participants with lower BMI, and in those without osteoporosis diagnosis (Supplemental Table 2). In these analyses, there was also an increased risk of fracture in the 3200IU/day arm among the participants with BMI below the

median, although the HR did not differ from the 1600IU/day arm (Supplemental Table 2). However, none of the interactions reached statistical significance (Supplemental Table 2). There were no marked differences in the risk based on calcium supplement use or history of fracture or falls (Supplemental Table 2).

4. Discussion

This study examined the impact of five years of daily oral vitamin D_3 supplementation on fracture risk among an aging Finnish population who were not at increased risk of fractures, followed by an additional three-year post-supplementation fracture follow-up. The findings indicate that vitamin D_3 supplementation did not reduce overall fracture risk or the incidence within the fracture types of interest across the three randomization arms of placebo and 1600IU/day or 3200IU/day of vitamin D_3. In contrast, there was an increased risk of any fracture in the 1600IU/day arm.

Previous research on the association between vitamin D and fracture risk has yielded inconsistent findings, likely reflecting differences in study settings and methodologies. A systematic review and meta-analysis involving 69 trials with over 153,000 participants found little to no clinically meaningful evidence to support routine use of calcium, vitamin D, or combined supplementation to prevent fractures and falls in general population [19]. However, vitamin D plays a critical role in calcium absorption and the maintenance of skeletal health, with accumulating evidence indicating that severe vitamin D deficiency is associated with reduced muscle strength, impaired physical performance among community-dwelling older adults, and an elevated risk of fractures [20], [21]. Accordingly, combined supplementation with calcium and vitamin D, particularly among individuals with overt deficiency, may confer protective effects against fractures, with some evidence observed for hip fracture reduction in older, high-risk populations [10]. However, indiscriminate vitamin D supplementation is considered an unlikely strategy for preventing fractures in generally healthy older adults. On the contrary, some evidence suggests that such an approach may even increase hip fracture risk in certain subgroups, such as older women, when administered without concomitant calcium supplementation [22]. Similarly, an observational study in

men found a U-shaped association between serum 25(OH)D concentration and fracture risk, suggesting that men in both the lowest (<36 nmol/L, mean 28 nmol/L) and highest (>72 nmol/L, mean 89 nmol/L) serum 25(OH)D quintile had an increased fracture risk [23]. The increased risk of any fracture in the 1600 IU/day arm in our study could also be interpreted to indicate potential harm with vitamin D supplementation. However, as there was no difference in fracture risk between the placebo and 3200 IU/day arms despite the mean serum 25(OH)D concentrations of 120 nmol/L in the 3200 IU/day arm, the finding suggests that the association may not be attributable to high circulating 25(OH)D per se, and that the higher risk in the 1600 IU/day arm is unlikely a causal effect of vitamin D supplementation. To support this, there were no differences in the incidence of falls, a major risk factor for fractures, between the three arms in this study [24]. Within the extended follow-up analysis, we did find an increased fracture risk also in the 3200 IU/day arm among those with lower BMI. However, as there was no dose-response between vitamin D and risk, and given the large number of analyses, a random finding cannot be excluded.

Overall, our findings align with the current consensus that routine vitamin D testing and indiscriminate population-wide supplementation are not justified in generally healthy individuals. The main challenge lies in identifying individuals most likely to benefit from testing and targeted supplementation. A recent review of vitamin D guidelines highlights substantial variability, as roughly two-thirds recommend screening people deemed at risk for deficiency and about half support supplementation, yet “at risk” definitions vary widely. About one-third of guidelines recommend supplementation (400–1000 IU/day) for patients with osteoporosis and for older adults, using comparable doses but with inconsistent age thresholds [25]. Overall, this variability underscores the need for further international collaboration to harmonize the risk definitions to enable more consistent, evidence-based recommendations.

Mechanistically, the deficiency can lead to secondary hyperparathyroidism, increased bone turnover, muscle weakness, and heightened risk of falls, all of which contribute to fracture risk in older adults. However, the degree to which pre-existing vitamin

D deficiency influences the efficacy of vitamin D supplementation in reducing fracture risk remains less understood. This is partly because conducting a randomized controlled trial (RCT) that enrolls participants solely based on clinically significant vitamin D deficiency would not be ethically feasible. In a recent study by LeBoff et al., clinically relevant baseline serum 25-hydroxyvitamin D concentrations did not appear to modify the effect of vitamin D_3 supplementation, compared with placebo, on the incidence of total, nonvertebral, or hip fractures [14]. Nevertheless, further research is needed to better understand the benefits of screening and vitamin D supplementation in at-risk patients. Less devastating outcomes, such as non-hip fractures, are particularly challenging to evaluate due to substantial heterogeneity in fracture classifications and definitions across meta-analyses, which complicates cross-study comparisons and interpretation.

4.1. Strengths and limitations

A key strength of our study is its population-based design with two different vitamin D dosages. The use of standardized serum 25-hydroxyvitamin D measurements further enhanced the accuracy and comparability of the biochemical data. Moreover, all fracture outcomes were ascertained through national medical records, a source that has been demonstrated to provide reliable and comprehensive information on health disorders [26], [27]. A major limitation of the study is that the protocol was primarily designed to investigate cardiovascular disease and cancer incidence, not fractures, which were an ancillary outcome. In addition, vitamin D deficiency (<50 nmol/L) was very low (9%), preventing separate fracture risk analyses among individuals with initial vitamin D deficiency. This mainly reflects the successful vitamin D food fortification policy in Finland, together with the increased use of vitamin D supplements [28]. The study included only white elderly men and women, so the findings may not be generalizable to other ethnicities and age-groups.

5. Conclusions

This randomized controlled trial demonstrates that 5-year vitamin D_3 supplementation at doses of 1600 IU/day or 3200 IU/day did not reduce the overall risk of fractures, nor did it affect the incidence

of any major fracture subtype, when compared with placebo in a community-dwelling population of predominantly vitamin D–sufficient older Finnish adults. These findings provide no evidence to support high-dose vitamin D_3 supplementation for fracture prevention in the general aging population.

CRediT authorship contribution statement

Toni Rikkonen: Writing – original draft, Methodology, Investigation, Conceptualization. **Sari Hantunen:** Writing – review & editing, Project administration, Investigation, Funding acquisition, Conceptualization. **Heikki Kröger:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Christel Lamberg-Allardt:** Writing – review & editing, Funding acquisition, Conceptualization. **JoAnn E. Manson:** Writing – review & editing, Methodology, Conceptualization. **Tarja Nurmi:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Marjo Tuppurainen:** Writing – review & editing, Methodology, Conceptualization. **Ari Voutilainen:** Writing – review & editing, Formal analysis, Data curation. **Tomi-Pekka Tuomainen:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Jyrki K. Virtanen:** Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sari Hantunen reports financial support was provided by Research Council of Finland. Sari Hantunen reports financial support was provided by Juho Vainio Foundation. Toni Rikkonen reports financial support was provided by Paivikki and Sakari Sohlberg Foundation. Christel Lamberg-Allardt reports financial support was provided by Medicinska Understödsföreningen Livoch Hälsa. Tomi-Pekka Tuomainen reports financial support was provided by Finnish Foundation for Cardiovascular Research. Tomi-Pekka Tuomainen reports financial support was provided by Finnish Diabetes Research Foundation. Tomi-Pekka Tuomainen reports financial support was provided by Finnish Cultural Foundation. Jyrki K. Virtanen reports a relationship with Abiogen Pharma SpA that includes: travel reimbursement. Dr. Lamberg-Allardt reports involvement in the Nordic Nutrition recommendations 2023 as a member of the Systematic Review Centre, and in European Food Safety Authority, procurement, preparatory work for the update of the tolerable upper intake levels for vitamin D, 2023. Dr. Manson reports receiving grants from the National Institutes of Health during the conduct of the study, and grants from the National Institutes of Health and from Mars Edge outside the submitted work. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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Supplementary material

Data availability

The data will not be openly available because it contains sensitive personal information of the participants that cannot be completely anonymized. However, the analytical code used for the current study can be made available upon reasonable request, and the data is open for potential research collaboration by contacting the corresponding author.

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