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Title
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Permalink
https://escholarship.org/uc/item/41677683

Journal
New England Journal of Medicine, 387(4)

ISSN
0028-4793

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Publication Date
2022-07-28

DOI
10.1056/nejmoa2202106

Peer reviewed

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HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2022 December 02.

Published in final edited form as:

N Engl J Med. 2022 July 28; 387(4): 299–309. doi:10.1056/NEJMoa2202106.

Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

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Abstract

BACKGROUND—Vitamin D supplements are widely recommended for bone health in the general population, but data on whether they prevent fractures have been inconsistent.

METHODS—In an ancillary study of the Vitamin D and Omega-3 Trial (VITAL), we tested whether supplemental vitamin D_3 would result in a lower risk of fractures than placebo. VITAL was a two-by-two factorial, randomized, controlled trial that investigated whether supplemental vitamin D_3 (2000 IU per day), n–3 fatty acids (1 g per day), or both would prevent cancer and cardiovascular disease in men 50 years of age or older and women 55 years of age or older in

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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the United States. Participants were not recruited on the basis of vitamin D deficiency, low bone mass, or osteoporosis. Incident fractures were reported by participants on annual questionnaires and adjudicated by centralized medical-record review. The primary end points were incident total, nonvertebral, and hip fractures. Proportional-hazards models were used to estimate the treatment effect in intention-to-treat analyses.

RESULTS—Among 25,871 participants (50.6% women [13,085 of 25,871] and 20.2% Black [5106 of 25,304]), we confirmed 1991 incident fractures in 1551 participants over a median follow-up of 5.3 years. Supplemental vitamin D_3, as compared with placebo, did not have a significant effect on total fractures (which occurred in 769 of 12,927 participants in the vitamin D group and in 782 of 12,944 participants in the placebo group; hazard ratio, 0.98; 95% confidence interval [CI], 0.89 to 1.08; P = 0.70), nonvertebral fractures (hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P = 0.50), or hip fractures (hazard ratio, 1.01; 95% CI, 0.70 to 1.47; P = 0.96). There was no modification of the treatment effect according to baseline characteristics, including age, sex, race or ethnic group, body-mass index, or serum 25-hydroxyvitamin D levels. There were no substantial between-group differences in adverse events as assessed in the parent trial.

CONCLUSIONS—Vitamin D_3 supplementation did not result in a significantly lower risk of fractures than placebo among generally healthy midlife and older adults who were not selected for vitamin D deficiency, low bone mass, or osteoporosis. (Funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases; VITAL ClinicalTrials.gov number, NCT01704859.)

Fractures are major public health problems, especially among older adults. An estimated 53.6 million Americans have osteoporosis, low bone mass, or both,[1] and in the United States, 2 million osteoporotic fractures occur annually, a number projected to exceed 3 million fractures per year by 2040, with related costs of more than $95 billion per year.[2–4] Vitamin D supplements are widely recommended to the general population as a means to promote bone health. Between 1999 and 2012, use of vitamin D supplements increased from 5.1% to 19% among U.S. adults.[5] However, data on whether these supplements prevent fractures are conflicting.[6–10]

Vitamin D may support skeletal health and improve bone mineralization by increasing intestinal calcium absorption, reducing secondary hyperparathyroidism, and decreasing bone turnover.[11] Furthermore, in bone, vitamin D receptors and extrarenal activation of 1,25-dihydroxyvitamin D have been identified and linked to the formation of osteoblast progenitors, which suggests a role in bone formation.[12,13]

In 2011, the Institute of Medicine (IOM) established recommended dietary allowances for vitamin D of 600 to 800 IU per day, corresponding to a total 25-hydroxyvitamin D level of at least 20 ng per milliliter, in order to meet the bone health needs for 97.5% of the population.[8] Other societies or foundations recommend vitamin D intakes of at least 800 to 2000 IU per day for adults 50 years of age or older to attain 25-hydroxyvitamin D levels of at least 30 ng per milliliter.[8,14]

Results from randomized, controlled trials investigating the effects of supplemental vitamin D on fracture outcomes have been inconsistent, with trials finding evidence for benefit,

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no effect, or harm.[4,15–17] Differences to explain the divergent results across these trials include the use of bolus dosing,[17,18] coadministration of vitamin D with calcium,[19,20] and small sample sizes.[15] No large randomized, controlled trials have tested the effects of daily supplemental vitamin D alone (without coadministered calcium) in preventing fractures in the U.S. population.

Systematic reviews and meta-analyses of randomized, controlled trials have raised questions about whether supplemental vitamin D has beneficial effects for primary prevention of fractures.[21,22] In 2021, the U.S. Preventive Services Task Force found no effect of supplemental vitamin D on fracture incidence among community-dwelling adults with low 25-hydroxyvitamin D levels.[10] The IOM identified an increased risk of fractures at both low and high 25-hydroxyvitamin D levels and emphasized the need for more research from large randomized, controlled trials.[8] To address these knowledge gaps, we investigated whether supplemental vitamin D_3 would result in a lower risk of incident fractures than placebo among generally healthy U.S. adults in an ancillary study of the large Vitamin D and Omega-3 Trial (VITAL).[23]

METHODS

TRIAL DESIGN AND OVERSIGHT

VITAL was a randomized, controlled trial that investigated the effects of supplemental vitamin D_3 (cholecalciferol, 2000 IU per day), n–3 fatty acids (Omacor [Pronova BioPharma and BASF], 1 g per day), or both on the primary prevention of cancer and cardiovascular disease in a two-by-two factorial design. The rationale for this vitamin D_3 dose was that it would achieve a mean 25-hydroxyvitamin D level of approximately 40 ng per milliliter in the vitamin D group and a favorable balance of safety and efficacy.[23]

The trial protocol has been described previously[23,24] and is available with the full text of this article at NEJM.org. Among the exclusion criteria was a history of cancer, cardiovascular disease, or hypercalcemia (Fig. 1). Participants were not recruited on the basis of vitamin D deficiency, low bone mineral density, or fracture history. After a 3-month placebo run-in phase, participants who took at least two thirds of the trial pills underwent randomization. Participants agreed to limit any nontrial supplements of vitamin D to 800 IU per day and of calcium to 1200 mg per day.[8,23]

In this ancillary study, we examined the effects of supplemental vitamin D_3 as compared with placebo on incident fractures in 25,871 U.S. men (age, ≥50 years) and women (age, ≥55 years), including 5106 Black participants, who were enrolled from all 50 states and followed for a median of 5.3 years. During the run-in phase, participants completed detailed questionnaires to assess baseline demographic characteristics, medical history, medication use, and supplement use (e.g., calcium, vitamin D, and fish oil). Annual questionnaires assessed adherence to trial regimens, side effects, use of nontrial supplements (e.g., calcium and vitamin D) and medications, the development of major illnesses, osteoporosis or related risk factors,[19,25] physical activity, falls, and fractures.[24]

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Baseline and follow-up blood samples were provided by 16,956 and approximately 6,000 participants, respectively. Quest Diagnostics measured total 25-hydroxyvitamin D levels using liquid chromatography–tandem mass spectrometry; assays were calibrated to Centers for Disease Control and Prevention (CDC) standards.[23] This protocol was approved by the Mass General Brigham institutional review board, and participants gave written informed consent.

TRIAL END POINTS

The primary end points were first incident total, nonvertebral, and hip fractures. Fractures were initially reported by the participants on annual questionnaires. Participants who reported a fracture were sent an authorization form to obtain their medical records and a fracture questionnaire, in which they recorded date, fracture location, any association with cancer or prosthesis (e.g., joint replacement), and circumstances of the fracture. Requests for medical records were then sent to health care professionals or medical facilities that provided fracture care, including radiologic reports, orthopedic notes, other hospital records, and operative or procedure reports. For participants who reported hip or femur fractures, radiologic images were also requested. All incident fractures were centrally adjudicated by investigators and study staff who were unaware of the trial-group assignments. Fractures were coded according to anatomical location and level of trauma. We included fractures regardless of the level of trauma for all end-point analyses, because even high-trauma fractures are associated with an increased risk of subsequent fractures.[26,27]

Secondary end points were incident total, nonvertebral, and hip fractures, with the exclusion of toe, finger, skull, periprosthetic, and pathologic fractures. We identified 42 periprosthetic and 29 pathologic fractures (e.g., tumors and Paget's disease). For hip or femur fractures, a musculoskeletal radiologist (the fifth author) reviewed radiographs and determined whether fractures were periprosthetic or atypical femur fractures using criteria from an American Society for Bone and Mineral Research task force.[28] Three female participants had a total of 4 atypical femur fractures; two were taking alendronate and had pathologic fractures. In exploratory analyses, we examined major osteoporotic fractures (defined as hip, wrist, humerus, or clinical spine fractures), pelvic fractures, and wrist fractures.

STATISTICAL ANALYSIS

The primary aim was to assess the main effects of vitamin D supplementation as compared with placebo on first incident total, nonvertebral, and hip fractures in intention-to-treat analyses; secondary end points excluded toe, finger, skull, periprosthetic, and pathologic fractures. To ensure balance, we compared baseline characteristics according to randomized trial-group assignment. We used t-tests and analysis of variance to compare continuous variables across randomized groups and used chi-square tests to compare proportions. We used Cox proportional-hazards models to allow for variable follow-up lengths and estimated the cause-specific hazard ratio for fracture incidence for each intervention using indicators for treatment exposure, controlling for n–3 fatty acid randomization group, age, sex, and race or ethnic group. In a post hoc analysis, we applied the Andersen–Gill model allowing for multiple events per person with different time between events. We also assessed for effects of adherence by censoring data from participants who were taking fewer than two

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thirds of the assigned trial pills and for latency by excluding the first 1 and 2 years of follow-up.

We examined modification of the treatment effect in prespecified subgroups, defined by sex, race or ethnic group, body-mass index (BMI; the weight in kilograms divided by the square of the height in meters), baseline use of calcium or vitamin D supplements, baseline serum total 25-hydroxyvitamin D levels (above or below the median and according to quartiles), and trial group. In addition, we explored whether treatment effect varied according to history of fragility fractures or baseline use of osteoporosis medications. The primary aims were to examine the effects of vitamin D and n–3 fatty acids in this two-by-two factorial trial. Here, we present the main effects of vitamin D as compared with placebo, because there was no interaction between vitamin D and n–3 fatty acids in the analysis of fracture outcomes. There was no control for multiple hypothesis testing, and no adjustment was made to the P values or confidence intervals. Thus, results regarding secondary and exploratory end points, as well as those regarding subgroups, should be interpreted with caution.

This study was designed by the first author in conjunction with the last author. The first four authors had full access to trial data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The manuscript was written by the first author with contributions from all the authors.

Results

TRIAL PARTICIPANTS

Participants were randomly assigned to one of four groups: vitamin D plus n–3 fatty acids, vitamin D plus placebo, n–3 fatty acids plus placebo, or double placebo. Baseline characteristics (Table 1, and Table S2 in the Supplementary Appendix, available at NEJM.org) were balanced between the trial groups. The mean (±SD) age of the participants was 67.1±7.1 years, 50.6% (13,085 of 25,871) were women, and 20.2% (5106 of 25,304) were Black. The mean BMI was 28.1±5.7. Only 4.8% of the participants (1240 of 25,690) were taking osteoporosis medications at baseline, yet 10.3% (2578 of 25,023) had a history of fragility fracture. At baseline, a total of 42.6% (11,030 of 25,871) took nontrial vitamin D supplements limited to 800 IU per day, and 20.0% (5166 of 25,871) took calcium supplements limited to 1200 mg per day. Table S1 shows the representativeness of VITAL participants to the general U.S. population.

The mean baseline 25-hydroxyvitamin D level (16,757 participants) was 30.7±10.0 ng per milliliter. At baseline, 401 (2.4%) had 25-hydroxyvitamin D levels of less than 12 ng per milliliter and 2161 (12.9%) had levels of less than 20 ng per milliliter. Among participants who provided 2-year blood samples, mean 25-hydroxyvitamin D levels increased from 29.2 ng per milliliter to 41.2 ng per milliliter in the vitamin D group (P<0.001, 1347 participants) and decreased slightly from 30.0 ng per milliliter to 29.4 ng per milliliter in the placebo group (P = 0.01, 1308 participants). Mean parathyroid hormone levels decreased in the vitamin D group from 40.8 ng per milliliter to 37.2 ng per milliliter (P<0.001, 1396 participants), with no changes in the placebo group. There were no 2-year changes in

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calcium levels in either group. Adherence to trial pills was 87.3% at 2 years and 85.4% at 5 years.

FRACTURE INCIDENCE

A total of 87.0% of the participants who reported a fracture consented to medical-record review, and documentation was obtained for 91.3% of these participants. We adjudicated 2133 total fractures and confirmed 1991 fractures (93.3%) in 1551 participants during the intervention period, with a median follow-up of 5.3 years. Supplemental vitamin D_3, as compared with placebo, did not have a significant effect on first incident total fractures (which occurred in 769 of 12,927 participants in the vitamin D group and in 782 of 12,944 participants in the placebo group; hazard ratio, 0.98; 95% confidence interval [CI], 0.89 to 1.08; P = 0.70), nonvertebral fractures (in 721 participants in the vitamin D group and in 744 in the placebo group; hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P = 0.50), or hip fractures (in 57 participants in the vitamin D group and in 56 in the placebo group; hazard ratio, 1.01; 95% CI, 0.70 to 1.47; P = 0.96), with adjustment for age, sex, race or ethnic group, and n–3 fatty acid randomization group (Table 2 and Fig. 2).

There was no effect modification according to baseline age, sex, race or ethnic group, BMI, or personal use of supplemental calcium or vitamin D (Tables 3, S3, and S4). Baseline 25-hydroxyvitamin D levels, when stratified above or below the median (31 ng per milliliter) or in quartiles (≤24.0, 24.1 to 30.0, 30.1 to 36.9, or ≥37.0 ng per milliliter), as prespecified, did not modify the effects of supplemental vitamin D_3 as compared with placebo on incident total, nonvertebral, or hip fractures. In exploratory analyses, there was no significant effect modification on fracture incidence between the vitamin D and placebo groups according to baseline clinically relevant 25-hydroxyvitamin D thresholds (<12, <20, <30, or ≥50 ng per milliliter), serum calcium levels (15,884 participants), or parathyroid hormone levels (16,803 participants). There were no significant differences in fracture incidence among participants using osteoporosis medications or among those with a history of fragility fracture. In sensitivity analyses, results did not change among participants adherent to trial pills, and no latency effect was found. Supplemental vitamin D_3 also did not result in a lower risk of recurrent fractures than placebo.

Findings for vitamin D as compared with placebo were similar with respect to secondary end points, excluding toe, finger, skull, periprosthetic, and pathologic fractures: total fractures (hazard ratio, 0.99; 95% CI, 0.89 to 1.10), nonvertebral fractures (hazard ratio, 0.97; 95% CI, 0.87 to 1.08), and hip fractures (hazard ratio, 1.03; 95% CI, 0.70 to 1.52) (Tables 2 and S5). Findings were also similar for exploratory end points: major osteoporotic fractures (hazard ratio, 0.99; 95% CI, 0.83 to 1.17), pelvic fractures (hazard ratio, 1.08; 95% CI, 0.64 to 1.80), and wrist fractures (hazard ratio, 0.89; 95% CI, 0.69 to 1.15), excluding periprosthetic and pathologic fractures (Tables 2 and S6).

ADVERSE EVENTS

There were no substantial differences in the incidence of hypercalcemia and kidney stones between the vitamin D and placebo groups as assessed by the VITAL data and safety monitoring board.[23]

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DISCUSSION

In this large randomized, controlled trial, supplemental vitamin D_3 (2000 IU per day) without coadministered calcium did not result in a lower risk of fractures than placebo (with adjustment for age, sex, race or ethnic group, and n–3 fatty acid randomization group) among U.S. adults who were not selected on the basis of vitamin D deficiency, low bone mass, or osteoporosis. Findings were similar for secondary end points, which excluded toe, finger, skull, periprosthetic, and pathologic fractures. We also found no effect of supplemental vitamin D_3 as compared with placebo on major osteoporotic fractures and other exploratory end points, including pelvic and wrist fractures. No latency effect was found. Data are presented as supplemental vitamin D_3 as compared with placebo because there was no interaction between vitamin D and n–3 fatty acids in the analysis of fracture outcomes.

It has been suggested that the effects of supplemental vitamin D_3 might be limited to those with low 25-hydroxyvitamin D levels. Higher prevalences of vitamin D deficiency have been reported among Black adults (from reduced cutaneous vitamin D synthesis and other mechanisms),[29] persons with obesity[30] (from vitamin D sequestration and increased volume in fat), post-menopausal women, older men, and older persons with hip fractures.[31–33] However, our results did not suggest any differences in the effects of supplemental vitamin D_3 on fracture outcomes according to race or ethnic group, BMI, or age. Although most participants in our cohort may have already reached the 25-hydroxyvitamin D level needed for bone health (mean baseline 25-hydroxyvitamin D level, 30.7±10.0 ng per milliliter), VITAL was large enough to stratify participants according to baseline 25-hydroxyvitamin D levels. We found no significant differences in fracture incidence between trial groups according to various 25-hydroxyvitamin D thresholds. In post hoc analyses, we found no benefit for supplementation in the relatively small number of participants with baseline 25-hydroxyvitamin D levels of less than 12 ng per milliliter (401 participants). Similarly, a study conducted in the Netherlands showed that supplemental vitamin D (400 IU per day) had no effect on hip or peripheral fractures in elderly adults with very low vitamin D levels.[34] In post hoc analyses, we also found no substantial between-group differences in fracture incidence among participants who were at high fracture risk (i.e., those taking osteoporosis medications [1240 participants] or with a history of fragility fractures [2578 participants]). Other randomized, controlled trials[19,20] and meta-analyses[35] have shown that vitamin D and calcium coadministration reduce fracture risk modestly. However, in post hoc analyses, we found no substantial differences in the 20.0% of the participants who took supplemental calcium.

Previous randomized, controlled trials from around the world that investigated the effects of supplemental vitamin D on fracture outcomes have shown conflicting results. In a British trial, supplemental vitamin D_3 (100,000 IU every 4 months) as compared with placebo for 5 years resulted in a marginal reduction in the relative risk of first hip, wrist, forearm, or spine fracture in men and women.[18] A trial in Australia, however, showed that very high oral doses of vitamin D (500,000 IU per year) resulted in an increased fracture risk among older women, who were found to have reached a 25-hydroxyvitamin D level of 48 ng per milliliter 1 month after bolus dosing.[16] However, we did not find any evidence of increased

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fracture risk among participants with baseline 25-hydroxyvitamin D levels of 50 ng or more per milliliter in exploratory analyses. The Vitamin D Assessment Study involving 5110 older men and women in New Zealand investigated supplemental vitamin D (100,000 IU per month) as compared with placebo and showed no effect on incident nonvertebral fractures over a period of 3.3 years.[17] Bolus dosing, however, has been shown to result in nonphysiologic variability in blood 25-hydroxyvitamin D levels.[36] The DO-HEALTH trial examining the effect of supplemental vitamin D (2000 IU per day) on nonvertebral fractures in 2157 older European adults also had null findings of vitamin D supplementation on fracture risk.[15]

In VITAL, we previously found that vitamin D supplementation did not affect incident fall risk or changes in bone mineral density or structure.[37,38] We did find that in participants with baseline free 25-hydroxyvitamin D levels below the median, supplemental vitamin D_3 had a slight benefit on spine and total hip bone mineral density.[38] Ongoing studies in VITAL are assessing whether baseline measured free 25-hydroxyvitamin D levels or genetic variation in vitamin D absorption, metabolism, or receptor function may identify a subgroup of patients who may benefit from vitamin D supplementation with respect to fracture outcomes.

Strengths of this study include the large, diverse sample size and high adherence. Incident fractures were adjudicated and confirmed. Levels of 25-hydroxyvitamin D were measured and calibrated according to standards set by the CDC. This study also has limitations. We evaluated only one vitamin D dose, and the trial was not designed to test the effects of vitamin D supplementation in those who are vitamin D deficient. Only a small percentage of participants (2.4%) had vitamin D levels of less than 12 ng per milliliter. It would not have been feasible or ethical to study the effects of vitamin D as compared with placebo on incident fractures in a population preselected for vitamin D deficiency. No adjustment was made for multiplicity for secondary, exploratory, or parent trial end points. In addition, results may not be generalizable to adults with osteoporosis or osteomalacia or older institutionalized persons.

In this randomized, controlled trial, supplemental vitamin D_3 did not result in a lower risk of incident total, nonvertebral, or hip fractures than placebo among generally healthy midlife and older adults who were not selected for vitamin D deficiency, low bone mass, or osteoporosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by grants (R01 AR060574, R01 AR070854, and R01 AR059775, to Dr. LeBoff) from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The VITAL parent trial is supported by grants (U01 CA138962, R01 CA138962, and R01AT011729, to Drs. Manson and Buring) from the National Cancer Institute, the National Heart, Lung, and Blood Institute, the Office of Dietary Supplements, the National Institute of Neurological Disorders and Stroke, and the National Center for Complementary and Integrative Health.

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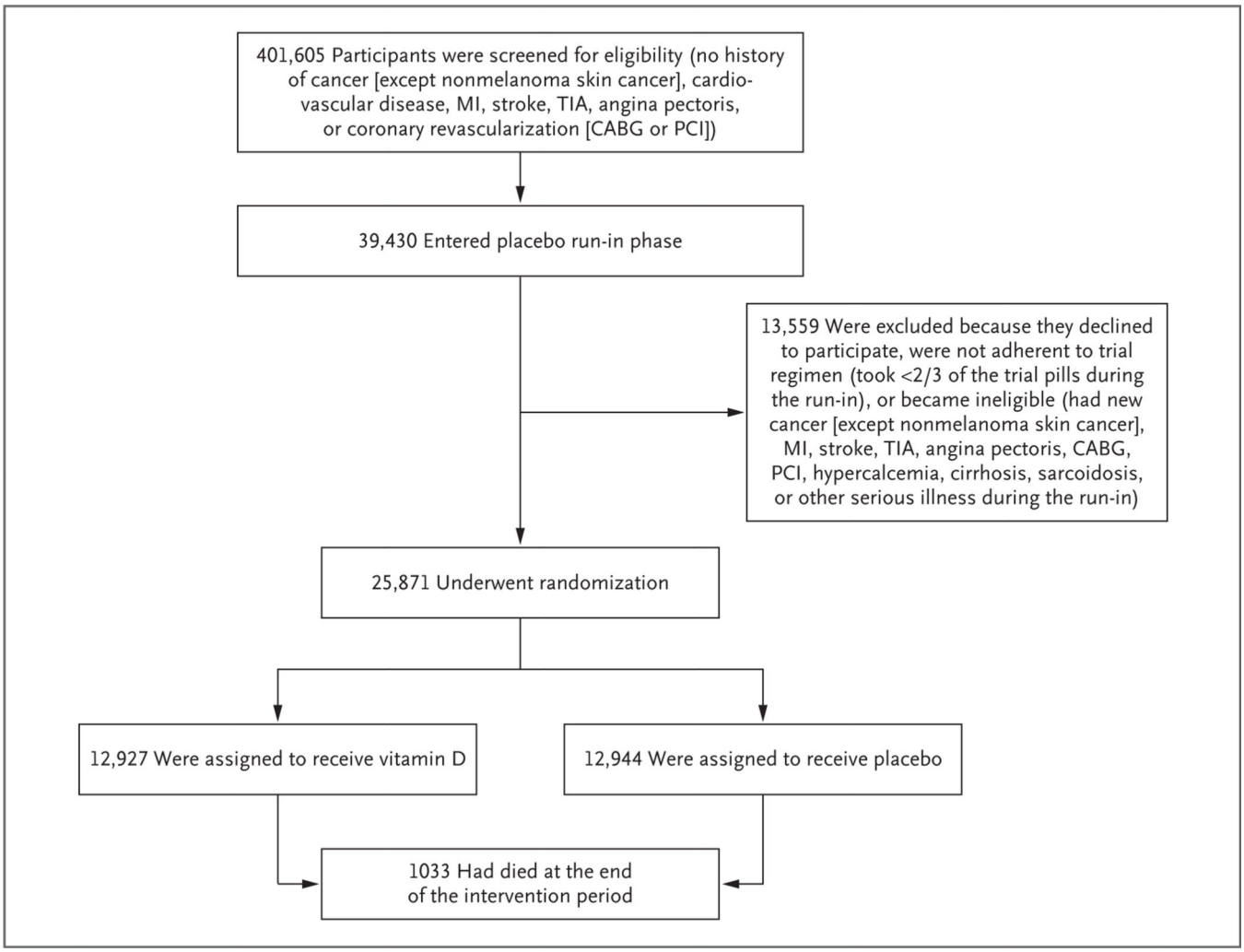

Figure 1. Screening, Randomization, and Follow-up of the Participants.

CABG denotes coronary-artery bypass grafting, MI myocardial infarction, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

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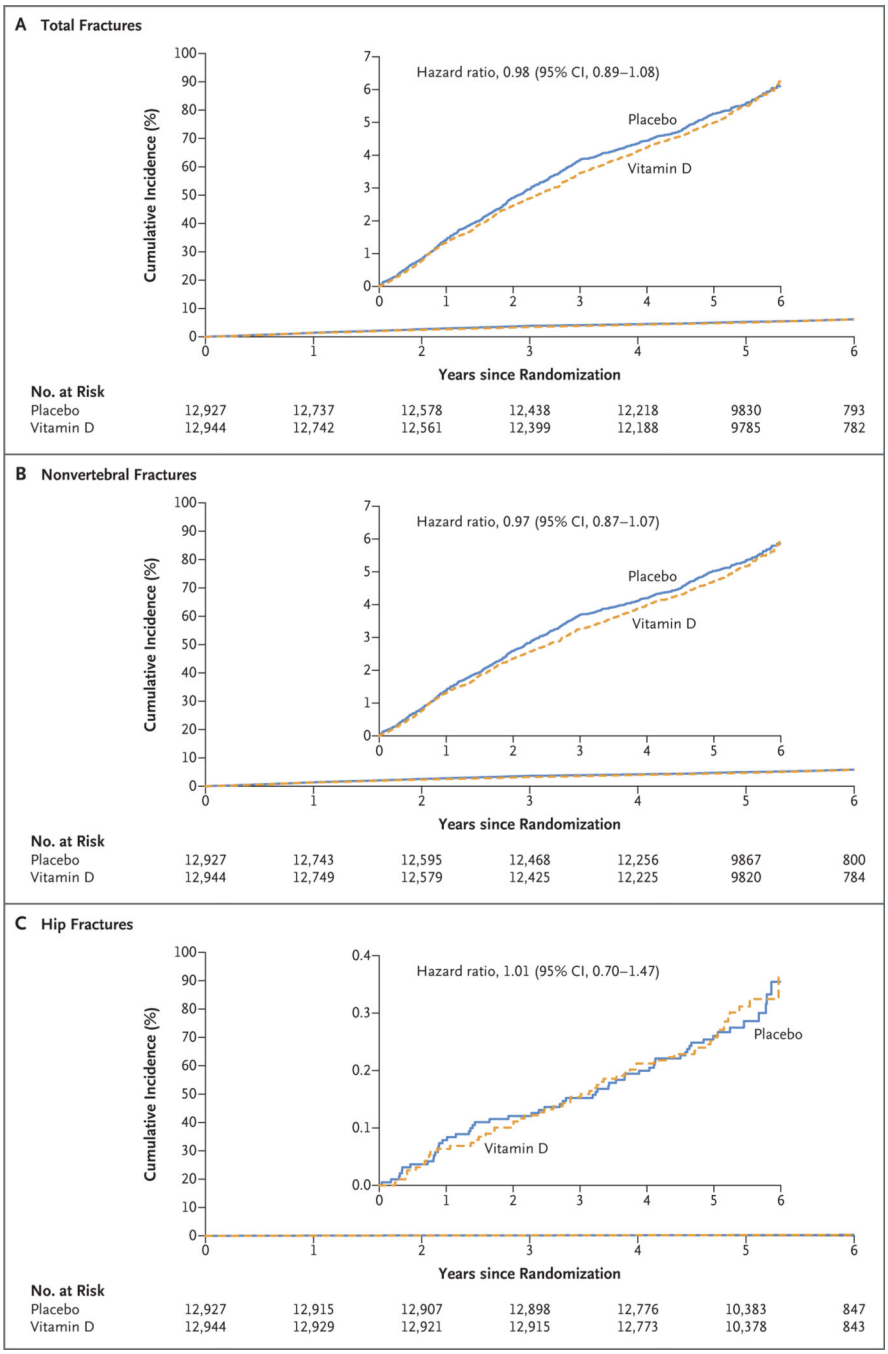

Figure 2. Cumulative Incident Fractures in the Vitamin D and Placebo Groups.

The median follow-up was 5.3 years. Analyses were conducted with the use of Cox regression models that were controlled for age, sex, race or ethnic group, and n–3 fatty acid randomization group (intention-to-treat analyses). The insets show the same data on an enlarged y axis.

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Table 1.

Characteristics of the Participants at Baseline, According to Randomized Assignment to Vitamin D or Placebo.[*]

Characteristic	Total (N = 25,871)	Vitamin D Group (N = 12,927)	Placebo Group (N = 12,944)
Female sex — no. (%)	13,085 (50.6)	6,547 (50.6)	6,538 (50.5)
Age — yr	67.1±7.1	67.1±7.0	67.1±7.1
Race or ethnic group — no./total no. (%)[†]			
Non-Hispanic White	18,046/25,304 (71.3)	9,013/12,647 (71.3)	9,033/12,657 (71.4)
Black	5,106/25,304 (20.2)	2,553/12,647 (20.2)	2,553/12,657 (20.2)
Non-Black Hispanic	1,013/25,304 (4.0)	516/12,647 (4.1)	497/12,657 (3.9)
Asian or Pacific Islander	388/25,304 (1.5)	188/12,647 (1.5)	200/12,657 (1.6)
American Indian or Alaskan Native	228/25,304 (0.9)	118/12,647 (0.9)	110/12,657 (0.9)
Other or unknown	523/25,304 (2.1)	259/12,647 (2.0)	264/12,657 (2.1)
Body-mass index[‡]	28.1±5.7	28.1±5.7	28.1±5.8
Diabetes — no./total no. (%)	3,537/25,824 (13.7)	1,804/12,900 (14.0)	1,733/12,924 (13.4)
Parental history of hip fracture — no./total no. (%)	3,704/23,979 (15.4)	1,809/11,970 (15.1)	1,895/12,009 (15.8)
Rheumatoid arthritis — no./total no. (%)	1,118/25,512 (4.4)	556/12,749 (4.4)	562/12,763 (4.4)
History of fragility fracture — no./total no. (%)	2,578/25,023 (10.3)	1,287/12,513 (10.3)	1,291/12,510 (10.3)
Unintentional fall in the past year — no./total no. (%)	6,921/25,715 (26.9)	3,521/12,848 (27.4)	3,400/12,867 (26.4)
Current use of osteoporosis medication — no./total no. (%)[§]	1,240/25,690 (4.8)	609/12,835 (4.7)	631/12,855 (4.9)
Current smoker — no./total no. (%)	1,835/25,488 (7.2)	921/12,732 (7.2)	914/12,756 (7.2)
Current use of supplemental vitamin D — no. (%)[¶]	11,030 (42.6)	5,497 (42.5)	5,533 (42.7)
Current use of glucocorticoids — no./total no. (%)	461/25,427 (1.8)	239/12,705 (1.9)	222/12,722 (1.7)
Servings of milk per day	0.71±0.91	0.71±0.89	0.72±0.92
Baseline 25-hydroxyvitamin D level — ng/ml[‖]	30.7±10.0	30.7±10.0	30.7±10.0
Baseline calcium level — mg/dl[**]	9.00±1.61	9.00±1.61	9.00±1.61

[*] Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.

[†] Race and ethnic group were reported by the participants.

[‡] A total of 30.1% of the participants had a normal body-mass index (18.5 to <25), 40.1% were overweight (25 to <30), and 28.9% were obese (≥30).

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[§] Osteoporosis medications included alendronate (Fosamax), raloxifene (Evista), risedronate (Actonel), zoledronate (Reclast), denosumab (Prolia), teriparatide injection (Forteo), salmon calcitonin (Miacalcin or Fortical), and other osteoporosis medications not listed above.

[¶] The mean 25-hydroxyvitamin D level at baseline was 34.9 ng per milliliter for participants taking vitamin D supplements (total, <800 IU per day) and 27.4 ng per milliliter for participants not taking vitamin D supplements.

[//] Data were available for 16,757 participants.

[**] Data were available for 15,884 participants.

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Table 2.

Hazard Ratios for the Primary, Secondary, and Exploratory End Points, According to Randomized Assignment to Vitamin D or Placebo, in Intention-to-Treat Analyses.*

End Point	Vitamin D Group (N = 12,927)	Placebo Group (N = 12,944)	Hazard Ratio (95% CI)
	no. of participants with event		
Primary end points: confirmed incident fractures			
Total	769	782	0.98 (0.89–1.08)
Nonvertebral	721	744	0.97 (0.87–1.07)
Hip	57	56	1.01 (0.70–1.47)
Secondary end points: confirmed incident fractures excluding toe, finger, skull, periprosthetic, and pathologic fractures			
Total	678	685	0.99 (0.89–1.10)
Nonvertebral	630	649	0.97 (0.87–1.08)
Hip	54	52	1.03 (0.70–1.52)
Exploratory end points: confirmed incident fractures excluding periprosthetic and pathologic fractures			
Major osteoporotic fractures: hip, wrist, humerus, or clinical spine fractures	276	278	0.99 (0.83–1.17)
Pelvic	32	29	1.08 (0.64–1.80)
Wrist	118	132	0.89 (0.69–1.15)

*Analyses were performed with the use of Cox proportional-hazards models that were adjusted for age, sex, race or ethnic group, and n–3 fatty acid randomization group. Confidence intervals were not adjusted for multiple comparisons, and inferences drawn from them may not be reproducible.

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Table 3.

Hazard Ratios for Total Fractures with Vitamin D as Compared with Placebo, According to Subgroup.*

Subgroup	No. of Participants	Vitamin D Group (N = 12,927)	Placebo Group (N = 12,944)	Hazard Ratio (95% CI)
		no. of participants with event		
Age				
<Median of 66.7 yr	12,859	282	285	0.99 (0.84–1.18)
≥Median of 66.7 yr	13,012	487	497	0.97 (0.86–1.10)
Sex				
Male	12,786	265	250	1.07 (0.90–1.28)
Female	13,085	504	532	0.94 (0.83–1.06)
Race or ethnic group				
Non-Hispanic White	18,046	655	658	0.99 (0.89–1.11)
Black	5,106	53	59	0.89 (0.62–1.30)
Other	2,152	46	51	0.90 (0.61–1.35)
BMI category				
<25	7,849	300	327	0.93 (0.79–1.09)
25 to <30	10,127	254	271	0.93 (0.78–1.11)
≥30	7,294	198	165	1.17 (0.95–1.44)
BMI				
<Median of 27.1	12,589	435	456	0.95 (0.83–1.09)
≥Median of 27.1	12,681	317	307	1.03 (0.88–1.20)
Osteoporosis medication†				
Yes	1,240	62	79	0.74 (0.53–1.03)
No	24,450	704	697	1.01 (0.91–1.12)
History of fragility fractures†				
Yes	2,578	146	161	0.87 (0.69–1.09)
No	22,445	598	595	1.01 (0.90–1.14)
Baseline use of supplemental vitamin D				
Yes	11,030	393	399	0.97 (0.84–1.12)
No	14,841	376	383	0.99 (0.86–1.14)
Supplemental calcium				

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Subgroup	No. of Participants	Vitamin D Group (N = 12,927)	Placebo Group (N = 12,944)	Hazard Ratio (95% CI)
		no. of participants with event		
≤1200 mg/day	5,166	228	232	0.92 (0.77–1.11)
None	20,705	541	550	1.00 (0.89–1.13)
Baseline 25-hydroxyvitamin D level, according to median				
<Median of 31 ng/ml	8,430	239	241	1.02 (0.85–1.22)
≥Median of 31 ng/ml	8,327	329	344	0.93 (0.80–1.08)
Baseline 25-hydroxyvitamin D level in quartiles				
Quartile 1: ≤24.0 ng/ml	4,270	115	112	1.04 (0.80–1.36)
Quartile 2: 24.1–30.0 ng/ml	4,104	122	128	0.98 (0.77–1.26)
Quartile 3: 30.1–36.9 ng/ml	4,097	151	154	0.98 (0.78–1.23)
Quartile 4: ≥37.0 ng/ml	4,286	180	191	0.89 (0.73–1.10)
Baseline 25-hydroxyvitamin D level, according to threshold of 12 ng/ml[†]				
<12 ng/ml	401	7	8	1.03 (0.36–2.95)
≥12 ng/ml	16,356	561	577	0.97 (0.86–1.09)
Randomization in the n–3 fatty acids portion of the trial				
Placebo group	12,938	374	392	0.95 (0.82–1.09)
Active-agent group	12,933	395	390	1.02 (0.88–1.17)

[*] Analyses were conducted with the use of Cox proportional-hazards models that were adjusted for age, sex, race or ethnic group, and n–3 fatty acid randomization group (intention-to-treat analyses). Confidence intervals were not adjusted for multiple comparisons, and inferences drawn from them may not be reproducible.

[†] These subgroups were not prespecified, but a subgroup defined by a baseline 25-hydroxyvitamin D level of less than 10 ng per milliliter (201 participants) was prespecified.

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