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Effect of vitamin D on risk of falls and fractures – The contribution of recent mega-trials

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ABSTRACT

Three recently-completed, large clinical trials in the U.S, New Zealand, and Australia, referred to herein as the 'mega-trials', were conducted to determine the impact of supplemental vitamin D on a variety of outcomes including falls and fractures. The trials were similar in design and collectively included over 50,000 generally vitamin D replete, older men and women. The mega-trials established that vitamin D supplementation with the equivalent of 2000 to 3300 IU/d of vitamin D_3 had no favorable effect on risk of falls or fractures. This review focuses on specific design elements of the trials and how they likely influenced these trial findings. While these trials were in progress, evidence emerged that circulating 25-hydroxyvitamin D levels have a U-shaped association with risk of falling, raising concern about a potential untoward effect of high dose supplementation. There is compelling evidence that in older, vitamin D- and calcium-insufficient nursing home residents, the combination of vitamin D and calcium in modest replacement doses dramatically reduces the risk of hip and other fractures. Community-dwelling older adults in many populous countries around the globe have widespread vitamin D and calcium insufficiency. It is time to follow the evidence trail and determine the effect of vitamin D and calcium replacement on their risk of falls and fractures.

1. Introduction

The long-awaited vitamin D supplementation mega-trial results have now been published. These trials have contributed evidence related to the potential value of supplemental vitamin D in reducing falls and fractures. The objective of this review is to consider what these trials have and have not answered in the longstanding question of the role of vitamin D in bone and muscle health. The specific objectives are: 1) to review the impact of vitamin D supplementation on risk of falls and fractures in the 3 mega-trials, 2) to discuss the strengths and limitations of the mega-trial designs with respect to fall and fracture assessments and outcomes, 3) to consider how the mega-trials extend knowledge beyond that attained from earlier randomized controlled trials, and 4) to consider next steps in assessing the role of vitamin D in minimizing falls and fractures. The VITAL study [1] will be used as the main example and supporting information will be cited from two other mega-trials, the VIDA [2] and D-Health studies [3]. The terms deficient, insufficient, and replete used herein refer to the National Academy of Medicine definitions: <12 ng/ml (<30 nmol/L) – deficient, 12–20 ng/ml - insufficient, and ≥20 ng/ml – sufficient [4]. This is not a systematic or comprehensive review of the published literature, but rather an analysis of how specific design features of the mega-trials influenced their outcomes. It also considers the available evidence that might productively guide our next research efforts.

2. Summary of the mega-trial findings related to fractures and falls

VITAL This was a randomized, placebo-controlled trial carried out in the United States in 25,871 men and postmenopausal women, mean age 67 yrs. Participants were treated with 2000 IU of vitamin D_3 vs placebo and 1 g of omega-3 fatty acids vs placebo, in a two-by-two factorial design, for a mean of 5.3 years. An ancillary study to VITAL was performed to assess the effect of supplementation on falls and fractures [1]. The mean 25(OH)D level at baseline in this study was 30.2 ng/ml. Fractures were initially reported on the annual questionnaires. With participant consent, they were then verified by medical record reviews. There was no significant effect of supplementation with vitamin D on total fractures (HR 0.98 [95%CI 0.89, 1.08] or hip fractures (HR 1.01 [0.70, 1.47]).

Falls were assessed by an annual mail-out questionnaire [5]. The two designated fall–related outcomes were having: 1) two or more falls and 2) falls resulting in a doctor or hospital visit. Over the 5.3 year treatment

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Abbreviations:

25(OH)D	25-hydroxyvitamin D
BMD	bone mineral density
BMI	body mass index
D-Health	a vitamin D trial in Australia
FGF-23	fibroblast growth factor 23
RECORD	Randomized evaluation of calcium or vitamin D
STOP/IT study	Sites Testing Osteoporosis Prevention/ Intervention Treatment
STURDY	Study to Understand Fall Reduction and Vitamin D in You
ViDA	The Vitamin D Assessment Study
VITAL	Vitamin D and Omega-3 Trial

period, the odds ratio of having 2 or more falls did not differ significantly in the vitamin D and no vitamin D groups (OR = 0.97 [0.90, 1.05]) in the group as a whole or in subsets with baseline 25(OH)D levels <12 ng/ml, 12–20 ng/ml, or ≥20 ng/ml. Similarly, the odds ratio of injurious falls resulting in either a doctor or hospital visit did not differ in the two treatment groups.

VIDA The VIDA study was a randomized, placebo-controlled trial conducted in New Zealand in 5108 men and postmenopausal women, mean age ~65 years [2]. Participants were treated monthly with 100,000 IU of D_3 (preceded by a single 200,000 IU dose) vs placebo for 3.3 yrs. The mean 25(OH)D level at baseline was 25.2 ng/ml. Non-vertebral fractures were counted based on hospital discharge records containing a primary or secondary diagnostic code for a non-vertebral fracture. Non-vertebral fractures were identified in 292 participants. The effect of vitamin D supplementation on non-vertebral fracture risk was not significant (HR 1.19 [95%CI 0.94, 1.50]).

Participants who fell were identified through a national governmental insurance organization that covers medical costs from injury; hence only injurious falls were counted. Vitamin D treatment had no significant impact on risk of an injurious fall (HR 0.99 [0.92, 1.07]).

D-Health This was a randomized, placebo-controlled trial carried out in a large group of randomly selected men and postmenopausal women in Australia, aged 60–84 years [3]. Participants were treated monthly with 60,000 IU of vitamin D_3 or placebo for an average of 5.1 years. Baseline 25(OH)D levels were not reported but the intra-trial mean predicted 25(OH)D level was 30.8 ng/ml in the placebo group and 46.0 ng/ml in the vitamin D group. Fractures were identified through linkage to two administrative databases, one containing hospital admission data and the other data on public and private medical services both inside and outside of hospitals. The 20,326 participants with linkage to these administrative datasets were included in the analysis. Vitamin D supplementation had no significant effect of fracture risk overall (HR 0.94 [0.84, 1.06]) or on hip fracture risk (HR 1.11 [0.86, 1.45]). Similarly, supplementation had no significant effect on major fractures (spine, radius, humerus, and hip) or on non-vertebral fractures.

A subset of 6000 participants were randomly selected for assessment of risk of falling [6]. Participants who reported falling in the month prior to the annual survey (by mail out questionnaire) were counted as fallers. A subset of 2400 of the 6000 participants also completed fall diaries. Vitamin D supplementation had no effect on falling in the last month (OR 1.02 [0.95, 1.10]). Analysis of fall diary data produced consistent results. There was no significant association between predicted 25(OH)D levels and risk of falling.

In the three mega-trials, there were no significant differences in falls or fractures based on gender, age, or BMI subgroups, with the single exception that falls differed by BMI subgroup in D-Health (see section *3.5* below for details) [6].

In summary, these three mega-trials, conducted concurrently in a total of more than 50,000 participants, demonstrated that supplementation with the equivalent of 2000 to 3300 IU of vitamin D_3 daily did not alter risk of falls or fractures in vitamin D-replete older adults.

3. The strengths and limitations of the mega-trial designs with respect to fall and fracture outcomes

Importantly, the mega-trials had primary outcomes *unrelated to falls or fractures*. The primary outcomes of the VITAL trial were cardiovascular disease and cancer; ancillary studies supported the assessment of falls and fractures. The primary outcome of the VIDA trial was cardiovascular disease; falls and fractures were secondary endpoints. The primary outcome of the D-Health trial was all-cause mortality; falls and fractures were tertiary endpoints. These trials demonstrated that vitamin D supplementation had no significant effect on their primary endpoints, incident cancer [7], cardiovascular disease [7,8], or all-cause mortality [9]. The trials were well designed and are considered to have a high level of internal and external validity related to their primary outcomes. With respect to *musculoskeletal endpoints*; however, they lacked such validity in several respects.

3.1. The mega-trials testing vitamin D alone did not build on important evidence that vitamin D in combination with calcium may reduce fracture risk

The scientific landscape when the mega-trials were designed was dominated by the landmark Chapuy trial [10]. This randomized, placebo-controlled trial was carried out in 3270 French female nursing home residents, mean age 84.6 years. At baseline, the participants were insufficient in vitamin D [mean 25(OH)D level = 16 ng/ml] and in calcium intake (mean intake 511 mg/d, or less than half of the recommended intake). Participants were randomly assigned to treatment for 18 months with modest daily doses of 800 IU of vitamin D_3 plus 1.2 g of calcium or with double placebo. Treatment resulted in a 43 % reduction in risk of hip fracture and a 32 % reduction in other non-vertebral fractures. Falls were not reported. The contributions of the individual components of the treatment, vitamin D and calcium, are not known.

Following the Chapuy report, several randomized, placebo-controlled clinical trials were designed to determine the effect of vitamin D plus calcium on bone mineral density (BMD) and/or fracture risk in community-dwelling older adults. In one, the Boston STOP IT trial, 389 men and women age 65 years and older were treated for 3 years with 700 IU of vitamin D_3 plus 500 mg of calcium [11]. The baseline mean 25(OH)D level was 33 ng/ml in the men and 26 ng/ml in the women, and calcium intake was about 700 mg per day. In this relatively small trial, the supplemented group, when compared with placebo, had significant increases in BMD of the spine, femoral neck, and total body (the primary endpoints); they also had fewer fractures than the placebo group (11 vs 26, P = 0.02).

In a larger pragmatic, secondary fracture prevention trial in the UK, the RECORD Group trial [12], 5292 men and women age 70 years and older with a recent fragility fracture were randomized in a factorial-design to treatment with vitamin D_3 (800 IU per day), calcium (1000 mg per day), vitamin D_3 plus calcium, or placebo. They were followed for between 24 and 62 months. Serum 25(OH)D levels were assessed in a small subset of 60 participants enrolled at two of the 21 clinical sites. In this subset, serum 25(OH)D, initially 15.2 ng/ml, rose by 9 ng/ml in both vitamin D groups and rose by 3.1 in the placebo group, for a difference in change of about 6 ng/ml after 24 months of treatment. New fragility fractures, the primary endpoint of the trial, were ascertained by mail out questionnaire every 4 months and verified by hospital records when possible. Return of questionnaires and pill compliance declined over time. At 24 months, 3765 participants (71 %) returned questionnaires and, of these, fewer than half (46.8 %) reported taking study pills at least 80 % of the time. The outcome of the trial was that fracture risk was not significantly altered by vitamin D alone (HR

1.02 [0.88, 1.19]), by calcium alone (HR 0.94 [0.81, 1.09]), or by the combination (HR 1.01 [0.75, 1.36]).

To summarize, there is clear and convincing evidence that nursing home residents with vitamin D and calcium insufficiency/deficiency had dramatic fracture risk reduction within 18 months of treatment with vitamin D plus calcium supplementation in replacement doses. Evidence for dual (vitamin D + calcium) and single (vitamin D or calcium alone) supplementation in vitamin D insufficient community-dwelling older adults is inconsistent. The mega-trials did not address this outstanding question.

3.2. The mega-trials were conducted in populations with adequate vitamin D status

Vitamin D insufficiency was not an entry criterion in the mega-trials. Additionally, the vitamin D environment was changing when these mega-trials were being conducted. During that period, there was a surge in vitamin D publications. Fig. 1 shows the results of a PubMed search of vitamin D publications between 1990 and 2023. The arrow at 2009 indicates the year that recruitment for VITAL began.

In concert with the increase in vitamin D publications, vitamin D supplement usage in the U.S. rose dramatically [13,14]. As a result, participants in the VITAL trial at enrollment had a mean 25(OH)D level of 30.3 ng/ml [1], a level that was well within the sufficient range. Baseline 25(OH)D levels were also in the optimal range in ViDA (25.6 ng/ml) [2], and in D-Health, in which 80 % of participants had a predicted 25(OH)D level >20 ng/ml [3].

3.3. Quality of fracture and falls ascertainments

Fracture ascertainment was of high quality in the mega-trials. In VITAL, participants who reported a fracture were sent a medical release form. Upon return of the signed release, fractures were verified by review of their medical record. All incident fractures were centrally adjudicated [1]. Similarly, in ViDA, non-vertebral fracture information was obtained from hospital admissions records that contained ICD-10 codes [2]. In D-Health, the first fracture at any skeletal site was identified through linkage with in-hospital and out-patient administrative datasets [3].

Falls assessments in the mega-trials were not of the highest quality, understandably given the size of the trials and the limited interaction between study staff and participants. Falls assessment was based on annual mail out questionnaires in VITAL and D-Health and on more frequent mail out questionnaires (every 1 or 4 months) in ViDA. More rigorous assessment is recommended for high quality fall information. The assessment ideally includes a) use of prospective daily recording and a notification system to inform study staff when a participant had fallen (e.g., by postcard, text, or phone call) and b) staff follow up with monthly phone calls to rectify missing data and to ascertain further details of falls and injuries [15]. An even more intense assessment is recommended for adults with impaired memory [16]. The detailed approach reduces the number of forgotten falls and the double reporting of falls (identified by similar fall circumstances).

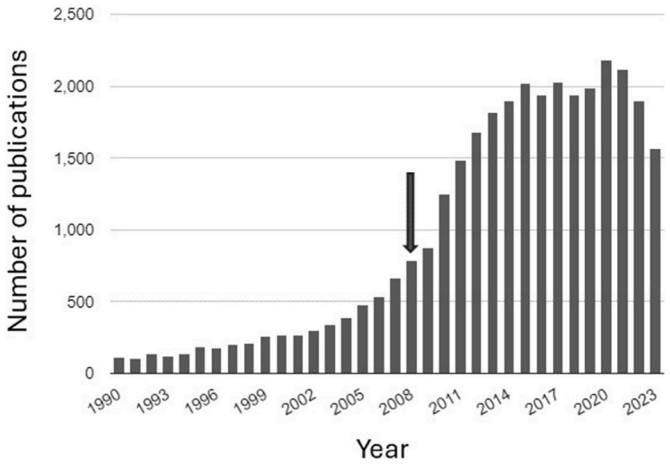

Fig. 1. Number of vitamin D publications (identified in a Pub Med search), by year. The arrow indicates the year when the VITAL study started recruiting participants.

3.4. Calcium intake was not assessed or administered in the mega-trials

Calcium intake was not assessed in the mega-trials, presumably because calcium intake was not considered to be important for their primary outcomes, cardiovascular disease, cancer, and mortality. Additionally, calcium was not administered, for the same reason. In a global assessment of calcium intake in 2017 [17], the average calcium intakes in adults residing where the mega-trials were conducted were: 934 mg per day in the U.S., 807 mg per day in New Zealand, and 805 mg per day in Australia. Based on these national average intakes, it seems unlikely that large numbers of mega-trial participants were calcium deficient, although specific information is lacking. Calcium intake in the mega-trial participants was likely far higher than 512 mg per day, the mean intake of the French nursing home participants in the Chapuy trial [10].

3.5. A potential nonlinear impact of vitamin D supplementation on risk of falling

The classical association of nutrients with physiologic function appears to apply to vitamin D. In this model, both inadequate and excessive intake of a nutrient are associated with suboptimal physiological function [18]. There is evidence that more falls occur in individuals with low and also with high 25(OH)D levels. In a one-year dose-finding vitamin D intervention trial in postmenopausal women, Smith and Gallagher reported a U-shaped association of the intra-trial mean 25(OH)D level with risk of falling [19]. The nadir of fall risk in this study was in the 25 (OH)D concentration range of 35–41 ng/ml. Similarly, in the STOP IT study in men and women aged 65 years and older who were treated daily for 3 years with 700 IU of vitamin D_3 together with 500 mg of calcium or double placebo, there was a U-shaped association between risk of falling and the intra-trial mean 25(OH)D level [20]. The nadir region in this cohort was 20–40 ng/ml. Fall risk was recently assessed in a secondary analysis of an earlier 4-year vitamin D plus calcium cancer prevention trial in 2303 postmenopausal women [21]. In this trial, postmenopausal women were treated for 4 years with 2000 IU of vitamin D_3 plus 1500 mg of calcium vs double placebo daily. The mean 25(OH)D level at entry into the trial was 32.6 ng/ml. There was no association of 25(OH)D with all falls at 25(OH)D levels below 60 ng/ml; however participants with intra-trial 25(OH)D levels >60 ng/ml had significantly greater risk of having 2 or more falls than participants with 25(OH)D levels in the range of 30–40 ng/ml (OR = 1.99 [95 % CI 1.2, 3.3]) [22]. In the STURDY study, a trial testing the effect of 1000 IU vs 200 IU of vitamin D_3 daily on fall risk in 647 older adults with a history of falling, the higher dose did not lower fall risk [23]. However in the higher dose group, there were more serious falls and more falls requiring hospitalization than in the lower dose group.Finally, in a clinical trial in 200 older adults with baseline 25(OH)D levels <20 ng/ml, participants were supplemented with 60,000 IU of vitamn D_3 per month, 24,000 IU per month (equivalent to 2000 and 800 IU daily), or 24,000 IU of vitamin D_3 plus 300 μg of calcifediol [24]. The investigators found no group difference in muscle performance, the primary outcome, but the incidence of falling, a secondary endpoint, was higher in the two higher dose groups than in the group taking 2400 IU of vitamin D_3 per month. These studies support a nonlinear association of serum 25(OH)D with fall risk. The precise range of the nadir region for falls is not yet clear, but the

lower 25(OH)D boundary appears to be about 20 ng/ml. The upper boundary is less certain, but may be between 40 and 60 ng/ml. Refinement of this estimate will require additional data and also the use of standardized 25(OH)D values, in alignment with the Vitamin D Standardization Program guidance [25].

The mega-trials provide little information about the lower boundary of the optimal 25(OH)D range for minimal falls likely because few insufficient participants were enrolled. They do add some information about fall risk at higher 25(OH)D levels, notwithstanding the fact that falls assessments, as indicated in section *3.3* above, were not optimal. VITAL demonstrated no difference in the proportion of participants with two or more falls in the vitamin D vs no vitamin D group and no association between the baseline 25(OH)D level and risk of falling. They did note in an exploratory analysis that participants in the vitamin D-treated group who achieved a free 25(OH)D level above the median had an increase in hospitalizations due to a fall when compared with the placebo group [5]. The D-Health trial identified no significant impact of vitamin D treatment on risk of falling in the month prior to completing the annual falls questionnaire in the group as a whole. However, in the subset of 2385 participants with baseline body mass index (BMI) < 25 kg/m^2, supplementation resulted in a 25 % *increase* in risk of falling (OR 1.25 [95%CI 1.09, 1.43]) [6]. As expected, the participants with BMI <25 kg/m^2 had higher baseline 25(OH)D levels than did participants with BMI ≥ 25.

This section has focused on evidence that the association of 25(OH)D with risk of falling is likely U-shaped. It is notable that a U-shaped association has also been reported for fractures. In an observational study in Australia, the baseline 25(OH)D level was positively associated with risk of fracture over the following 4.3 years. The nadir region for fracture was in the fourth 25(OH)D quintile which included levels ranging from 24 to 29 ng/ml, thus overlapping the apparent nadir region for falls [26].

The mechanism(s) underlying the adverse effect of high 25(OH)D levels on fall/fracture risk are not fully understood but may be related to changes in circulating levels of FGF-23 [27,28]. High 25(OH)D levels stimulate release of FGF-23 from osteocytes. FGF-23 downregulates 1α-hydroxylase (CYP27B1) and upregulates 24-hydroxylase (CYP24A1) [29], effectively lowering the circulating $1,25(OH)_2D$ level. Higher FGF-23 levels are associated with frailty [30], a strong risk factor for falls. Increased fracture risk would be expected based on impairment of bone mineralization resulting from lower circulating $1,25(OH)_2D$ levels and on the aforementioned increase in frailty [30].

4. Moving forward – follow the evidence trail

Insufficiency and deficiency of vitamin D and calcium have become uncommon in countries where the mega-trials were conducted; however, that is not the case in much of the global population. A global assessment of vitamin D status published in 2012 revealed vitamin D deficiency was widespread in adults in China, much of Southeast Asia, India, the Middle East and North Africa, and in selected locations in South America [31]. In many regions, particularly in Africa, reliable data on vitamin D status were not available [31]. Updated information in selected large countries has shown little change. For instance, the mean 25(OH)D level in adults in China was estimated to be 17.7 ng/ml in 2021(32). The mean level in India was 14.2 ng/ml in 2017(33), and it ranged from 13 to 17 ng/ml by region, with the lowest level in Northern India. In Saudi Arabia, the mean 25(OH)D level in adults was reported to be 13 ng/ml in 2018; this level is also seen in other parts of the Middle East and North Africa [34].

Calcium intake follows a similar pattern. It is generally adequate in the countries where the mega-trials were conducted. However, in many locations, calcium intake is very low. Moreover, adults in regions with low mean 25(OH)D levels also frequently have low calcum intake. For instance, mean calcium intake in adults in China is < 400 mg/d, mean intake in adults in India is 429 mg/d, and mean intake in adults in Saudi Arabia is 445 mg/d [17]. Thus serum 25(OH)D levels and calcium intake in these populous regions are far below recommended levels and, as shown in Table 1, are even below the levels reported in the French nursing home residents [10].

5. Summary and conclusions

Supplementation with vitamin D in replete older adults offers no evident musculoskeletal benefit. There is mounting evidence that achieving 25(OH)D levels >40–60 ng/ml may increase risk of falling. Since the majority of fractures and many other injuries result from falls, minimizing fall risk is a high priority.

Modest replacement levels of vitamin D and calcium (800 IU of vitamin D_3 and 1200 mg of calcium daily) dramatically lowered hip fracture and all fracture risk in vitamin D and calcium-insufficient and deficient French nursing home residents [10]. Notably, these doses are consistent with recommendations of the National Academy of Medicine for older adults [4]. It is unfortunate that we do not know what benefit might result from similar doses of vitamin D and calcium in multiple heavily-populated countries and regions with almost universal inadequacy in both vitamin D and calcium. The current low vitamin D and calcium status has been in place for many generations in these regions. It is possible that adaptations have occurred to accommodate these intake levels, but this is speculation.

Determining the impact of supplementation with modest doses of both vitamin D and calcium on risk of falls and fractures in China, India, and the Middle East and other dual-deficiency regions is a high priority. Evidence of benefit of vitamin D and calcium supplementation in these regions is needed to provide the incentive for these regions to institute new policies, such as food fortification, in order to optimize vitamin D status and calcium intake for musculoskeletal health.

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CRediT authorship contribution statement

Bess Dawson-Hughes: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial

Table 1
Mean serum 25(OH)D levels and calcium intake in community-dwelling adults in China, India, and Saudi Arabia compared with baseline (pre-treatment) levels in the French nursing home trial.

	25(OH)D, ng/ml (ref)	Ca intake, mg/d (ref)	Hip fracture risk (ref)
French nursing home trial	**16** [10]	**511** [10]	**↓ 43 %**
China	18 [32]	<400 [17]	?
India	14 [33]	429 [17]	?
Saudi Arabia	13 [34]	445 [17]	?

interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] LeBoff MS, Chou SH, Ratliff KA, Cook NR, Khurana B, Kim E, et al. Supplemental vitamin D and incident fractures in midlife and older adults. N Engl J Med 2022; 387(4):299–309.

[2] Khaw KT, Stewart AW, Waayer D, Lawes CMM, Toop L, Camargo Jr CA, et al. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol 2017;5(6):438–47.

[3] Waterhouse M, Ebeling PR, McLeod DSA, English D, Romero BD, Baxter C, et al. The effect of monthly vitamin D supplementation on fractures: a tertiary outcome from the population-based, double-blind, randomised, placebo-controlled D-Health trial. Lancet Diabetes Endocrinol 2023;11(5):324–32.

[4] IOM. Dietary reference intakes for calcium and vitamin. Washington, DC: D; 2011.

[5] LeBoff MS, Murata EM, Cook NR, Cawthon P, Chou SH, Kotler G, et al. VITamin D and OmegA-3 TriaL (VITAL): Effects of vitamin D supplements on risk of falls in the US population. J Clin Endocrinol Metab 2020;105(9):2929–38.

[6] Waterhouse M, Sanguineti E, Baxter C, Duarte Romero B, McLeod DSA, English DR, et al. Vitamin D supplementation and risk of falling: outcomes from the randomized, placebo-controlled D-Health Trial. Journal of cachexia, sarcopenia and muscle 2021;12:1428–39.

[7] Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med 2019;380(1):33–44.

[8] Scragg R, Stewart AW, Waayer D, Lawes CM, Toop L, Sluyter J, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study : a randomized clinical trial. JAMA cardiology 2017;2: 608–16.

[9] Neale RE, Baxter C, Romero BD, McLeod DSA, English DR, Armstrong BK, et al. The D-Health Trial: a randomised controlled trial of the effect of vitamin D on mortality. Lancet Diabetes Endocrinol 2022;10(2):120–8.

[10] Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992;327 (23):1637–42.

[11] Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337(10):670–6 [see comment].

[12] Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005;365(9471): 1621–8.

[13] Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999-2012. JAMA 2016;316(14):1464–74.

[14] Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL. Trends in use of high-dose vitamin D supplements exceeding 1000 or 4000 international units daily, 1999-2014. JAMA 2017;317(23):2448–50.

[15] Lamb SE, Jorstad-Stein EC, Hauer K, Becker C, Prevention of Falls Network E, Outcomes Consensus G. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. J Am Geriatr Soc 2005;53(9):1618–22.

[16] Adamczewska N, Vassallo M, Thomas PW, Thomas S, Barrado-Martin Y, Nyman SR. Feasibility and accuracy of different methods for collecting data on falls among older people with dementia. Alzheimer Dis Assoc Disord 2020;34(4):362–5.

[17] Balk EM, Adam GP, Langberg VN, Earley A, Clark P, Ebeling PR, et al. Global dietary calcium intake among adults: a systematic review. Osteoporos Int 2017;28 (12):3315–24.

[18] Morris MC, Tangney CC. A potential design flaw of randomized trials of vitamin supplements. JAMA 2011;305(13):1348–9.

[19] Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: a randomized clinical trial. J Steroid Biochem Mol Biol 2017;173:317–22.

[20] Dawson-Hughes B, Wang J, Barger K, Bischoff-Ferrari HA, Sempos CT, Durazo-Arvizu RA, et al. Intra-trial mean 25(OH)D and PTH levels and risk of falling in older men and women in the Boston STOP IT trial. J Clin Endocrinol Metab 2022; 107:e1932–7.

[21] Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 2007;85(6):1586–91.

[22] Binkley N, Borchardt G, Durazo-Arvizu R, Sempos C, Lappe J. Association of standardized serum 25-hydroxyvitamin D with falls in post-menopausal women. J Bone Miner Res 2023;38(Supp1). abstract 54.

[23] Appel LJ, Michos ED, Mitchell CM, Blackford AL, Sternberg AL, Miller 3rd ER, et al. The effects of four doses of vitamin D supplements on falls in older adults : a response-adaptive, randomized clinical trial. Ann Intern Med 2021;174(2):145–56.

[24] Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med 2016;176(2): 175–83.

[25] Sempos CT, Heijboer AC, Bikle DD, Bollerslev J, Bouillon R, Brannon PM, et al. Vitamin D assays and the definition of hypovitaminosis D: results from the first international conference on controversies in vitamin D. Br J Clin Pharmacol 2018; 84(10):2194–207.

[26] Bleicher K, Cumming RG, Naganathan V, Blyth FM, Le Couteur DG, Handelsman DJ, et al. U-shaped association between serum 25-hydroxyvitamin D and fracture risk in older men: results from the prospective population-based CHAMP study. J Bone Miner Res 2014;29(9):2024–31.

[27] Zittermann A, Berthold HK, Pilz S. The effect of vitamin D on fibroblast growth factor 23: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Nutr 2021;75(6):980–7.

[28] Zittermann A, Berthold HK, Pilz S. Correction: the effect of vitamin D on fibroblast growth factor 23: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Nutr 2022;76:488.

[29] Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest 2004;113(4):561–8.

[30] Beben T, Ix JH, Shlipak MG, Sarnak MJ, Fried LF, Hoofnagle AN, et al. Fibroblast growth factor-23 and frailty in elderly community-dwelling individuals: the cardiovascular health study. J Am Geriatr Soc 2016;64(2):270–6.

[31] Wahl DA, Cooper C, Ebeling PR, Eggersdorfer M, Hilger J, Hoffmann K, et al. A global representation of vitamin D status in healthy populations. Arch Osteoporos 2012;7:155–72.

[32] Liu W, Hu J, Fang Y, Wang P, Lu Y, Shen N. Vitamin D status in Mainland of China: a systematic review and meta-analysis. EClinicalMedicine 2021;38:101017.

[33] Selvarajan S, Gunaseelan V, Anandabaskar N, Xavier AS, Srinivasamurthy S, Kamalanathan SK, et al. Systematic review on vitamin D level in apparently healthy Indian population and analysis of its associated factors. Indian J Endocrinol Metab 2017;21(5):765–75.

[34] Chakhtoura M, Rahme M, Chamoun N, El-Hajj Fuleihan G. Vitamin D in the Middle East and North Africa. Bone Rep 2018;8:135–46.