ΑΣΒΕΣΤΙΟ ΚΑΙ ΒΙΤΑΜΙΝΗ D

ΓΙΩΡΓΟΣ ΤΡΟΒΑΣ

ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ

ΕΡΓΑΣΤΗΡΙΟ ΕΡΕΥΝΑΣ ΠΑΘΗΣΕΩΝ ΤΟΥ ΜΥΟΣΚΕΛΕΤΙΚΟΥ ΣΥΣΤΗΜΑΤΟΣ «Θ.ΓΑΡΟΦΑΛΙΔΗΣ »

ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

Calcium and vitamin D for increasing bone mineral density in premenopausal women (Review)

Cochrane Database of Systematic Reviews 2023, Issue 1. Art. No.: CD012664

- **Objectives**
- To evaluate the benefits and harms of calcium and vitamin D supplementation, alone or in combination, to increase the BMD, reduce fractures, and report the potential adverse events in healthy premenopausal women compared to placebo.
- **Main results**
- We included seven RCTs with 941 participants.
- **Calcium versus placebo**
- Four studies compared calcium versus placebo (138 participants in the calcium group and 123 in the placebo group) with mean ages from 18.0 to 47.3 years.
- Calcium supplementation may have little to no effect on total hip or lumbar spine BMD after 12 months in three studies and after six months in one study.
- **Vitamin D versus placebo**
- Two studies compared vitamin D versus placebo (110 participants in the vitamin D group and 79 in the placebo group), with mean ages from 18.0 to 32.7 years.
- In the original studies, there were no differences in lumbar BMD between groups.
- **Calcium plus vitamin D versus placebo**
- Two studies compared calcium plus vitamin D versus placebo (271 participants in the calcium plus vitamin D group and 270 in the placebo group). The mean age range was 18.0 to 36 years.
- The individual studies found no difference between groups in percent of change on total hip BMD and lumbar spine BMD.
- **Main results**
- There was no difference in bone mineral density in any of the groups being supplemented with calcium, vitamin D, or calcium plus vitamin D compared with placebo. The studies did not report fractures (from any anatomical site), quality of life, or stopping the supplementation for side effects.

- **Authors' conclusions**
- Our results do not support the isolated or combined use of calcium and vitamin D supplementation in healthy premenopausal women as a public health intervention to improve BMD in the total hip or lumbar spine, and therefore it is unlikely to have a benefit for the prevention of fractures (vertebral and non-vertebral).
- The evidence found suggests that there is no need for future studies in the general population of premenopausal women; however, studies focused on populations with a predisposition to diseases related to bone metabolism, or with low bone mass or osteoporosis diagnosed BMD would be useful.

The NEW ENGLAND JOURNAL of MEDICINE

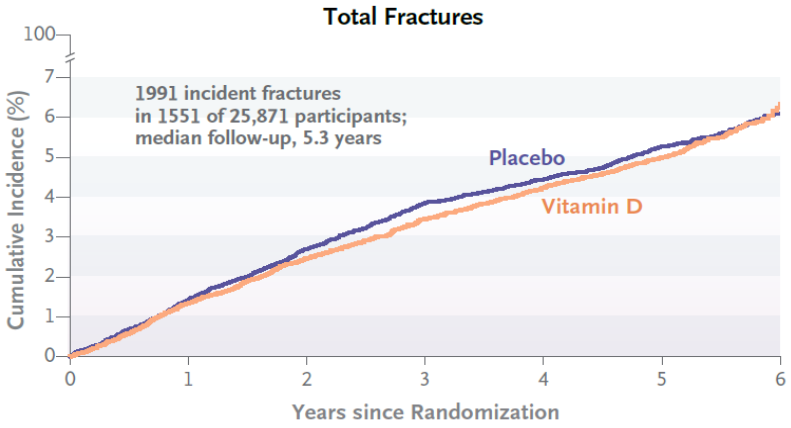
ESTABLISHED IN 1812 JULY 28, 2022 VOL. 387 NO. 4

Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

Meryl S. LeBoff, M.D., Sharon H. Chou, M.D., Kristin A. Ratliff, B.A., Nancy R. Cook, Sc.D., Bharti Khurana, M.D., Eunjung Kim, M.S., Peggy M. Cawthon, Ph.D., M.P.H., Douglas C. Bauer, M.D., Dennis Black, Ph.D., J. Chris Gallagher, M.D., I-Min Lee, M.B., B.S., Sc.D., Julie E. Buring, Sc.D., and JoAnn E. Manson, M.D., Dr.P.H.

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.)



EDITORIAL

VITAL Findings — A Decisive Verdict on Vitamin D Supplementation

Steven R. Cummings, M.D., and Clifford Rosen, M.D.

For the general population

ΠΕΡΙΟΡΙΣΜΟΙ

- Άτομα χωρίς υποβιταμίνωση D (87%ατομων της μελέτης VITAL είχαν επίπεδα 25OHD3 >20ng/ml.)
- Τα άτομα που συμμετείχαν στη μελέτη δεν στρατολογήθηκαν βάσει χαμηλής Οστικής Πυκνότητας η αυξημένου κινδύνου κατάγματος.

Table 1 | Overview of the large vitamin D supplementation clinical trials 2017–2020

Study	Country	Number of patients	Age (years, mean ± SD)	Ethnicity[a] (% white ethnicity)	Serum 25OHD (ng/ml)		Duration of follow-up (years)	Intervention (vitamin D vs placebo)	Primary outcome(s)
					Baseline	Final[b]			
VITAL[c]	USA	25,874	67 ± 7	71	30.8 ± 10	42 ± 10	5.3	2,000 IU per day	Cancer and cardiovascular disease
ViDA	New Zealand	5,110	66 ± 8	83	26.5 ± 9[d]	54 ± 16	3.3	One dose of 200,000 IU and 100,000 IU per month	Cardiovascular events and mortality
D2d	USA	2,423	60 ± 10	67	28.0 ± 10.2	54 ± 15	2.5	4,000 IU per day	T2DM
DO-HEALTH	Europe	2,157	74.9 ± 4.4	NM	22.4 ± 8.4	37.6 ± 11.3	3	2,000 IU per day[e]	Six health outcomes[f]
Calgary	Canada	373	62 ± 4	94	31 ± 8	80 ± 16[g]	3	400, 4,000 or 10,000 IU per day	BMD

Chakhtoura et al. (JCEM2022)
Umbrella review of meta-Analyses
25 RCTs

Vit D+calcium
13SR/MAs

↓Risk of hip fracture in 8/12SR/MAs(RR 0.61-0.84)

↓Risk of any fracrure in 7/11SR/MAs(RR 0.74-0.95)

Vit D alone
19SR/MAs

No fracture risk reduction in SR/MAs EXCLUSIVELY EVALUATING COMMUNITY –DWELLING INDIVIDUALS

OR IN THOSE ON VIT.D ALONE COMPARED TO PLACEBO/CONTROL

6 SR/MAs included 1 trial providing a high dose of 300,000 IU once
Mean age between 62 and 85 years
Trials extended from 1 to 7 years
5 SRs/MAs reported on baseline 25(OH)D(20.9–83.8 nmol/L)
Calcium dose was 500–1200 mg/day

Meta-Analysis

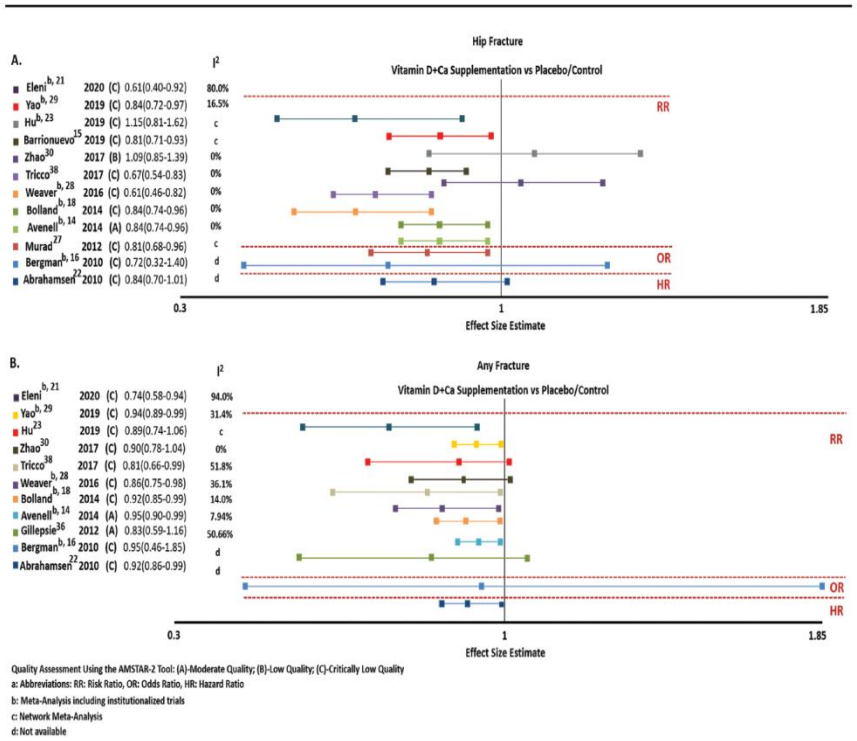
Vitamin D Supplementation and Fractures in Adults: A Systematic Umbrella Review of Meta-Analyses of Controlled Trials

Marlene Chakhtoura,[1] Dania S. Bacha,[1] Charbel Gharios,[1] Sara Ajjour,[1] Mariam Assaad,[1] Yara Jabbour,[1] Francesca Kahale,[1] Aya Bassatne,[1] Stephanie Antoun,[1] Elie A. Akl,[2,3] Roger Bouillon,[4] Paul Lips,[5] Peter R. Ebeling,[6] and Ghada El-Hajj Fuleihan[1]

The Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 3

Conclusions

- Ca/D reduces the risk of hip and any fracture in analyses combining institutionalized and community-dwelling individuals.
- High-risk individuals, such as those older, institutionalized, or with low vitamin D status, may benefit most, although this could not be unequivocally demonstrated in the few SRs/MAs that evaluated such predictors, most likely because of low power.



We used A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR-2) for quality assessment

Role of vitamin D supplementation in the management of musculoskeletal diseases: update from an European Society of Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group

Thierry Chevalley · Maria Luisa Brandi · Kevin D. Cashman · Etienne Cavalier· Nicholas C. Harvey· Stefania Maggi · Cyrus Cooper · Nasser Al-Daghri · Oliver Bock · Olivier Bruyre · Mario Miguel Rosa· Bernard Cortet · Alfonso J. Cruz-Jentoft · Antonio Cherubini · Bess Dawson-Hughes · Roger Fielding · Nicholas Fuggle · Philippe Halbout· John A. Kanis · Jean-Marc Kaufman· Olivier Lamy · Andrea Laslop· Maria Concepcion Prieto Yerro · Rıgis Radermecker · Jotheeswaran Amuthavalli Thiyagarajan · Thierry Thomas · Nicola Veronese · Marten de Wit · Jean-Yves Reginster · Rene Rizzoli Aging Clinical and Experimental Research (2022) 34:2603–2623

Vitamin D and fracture risk

- In summary, intervention studies in elderly subjects with vitamin D deficiency, as demonstrated by low serum 25(OH)D, have shown a beneficial effect of vitamin D (800–1000 IU/day) and calcium supplementation on any and hip fractures.
- Vitamin D-deficient adults with 25(OH) D levels below 50 nmol/L(20ng.ml) could benefit from vitamin D and calcium supplementation that brings them into a 25(OH)D range of 50–100 nmol/L(20-40 ng/ml)
- On the other hand, vitamin D-replete adults with 25(OH)D levels in the range of 50–100 nmol/L(20-40ng/ml) are unlikely to benefit from vitamin D supplementation.
- Furthermore, vitamin D supplementation resulting in 25(OH)D levels above 100 nmol/L(40ng/ml) probably increases the risk of fractures.

Vitamin D and falls

- In summary, vitamin D3 supplementation with doses less than 800 IU/day does not seem to reduce falls while doses between 800 and 1000 IU/day reduce falls and large bolus doses increase falls.
- Unfortunately, the recent 2017–2020 megatrials did not address the question of vitamin D and falls in vitamin D deplete populations.

Vitamin D safety and therapeutic window

BONE

- Deleterious effects of high dose vitamin D supplementation with 4000 or 10,000 IU, compared with 400 IU daily, resulted in greater losses of total volumetric BMD in healthy vitamin D-sufficient females, but not in males.
- a mean age of 62 years and a baseline 25(OH)D level of 79 nmol/L (31ng/ml) 3 years duration.

MUSCLE

- In a 12-month double-blind randomized controlled trial, elderly women with a mean age of 66 years and relatively low baseline 25(OH)D of 38 nmol/L.(15ng/ml)
- .The maximum decrease in falls was obtained with serum 25(OH)D of 75–100 nmol/L (30-40ng/ml)and median doses 1600–3200 IU while fall rates increase as serum 25(OH)D exceeded 100 to 112.5 nmol/L (40-45ng/ml)suggesting a biphasic effect (U-shape curve) of vitamin D effect.
- in a one-year double blind randomized controlled trial, community-dwelling men and women aged 70 years and older amongst whom 58% were vitamin D insufficient (< 50 nmol/L), received 24,000 IU vs60,000 IU vitamin D3 vs 24,000 IU vitamin D3 and 300 ug calcifediol . Although higher monthly doses of vitamin D were effective in reaching a 25(OH)D threshold of at least75 nmol/L, participants had no benefit on lower extremity function, but an increased risk of falls was even observed in the highest quartile of achieved 25(OH)D of 125 nmol/L(50ng/ml) as compared to the lowest quartile with 25(OH)D at 67 nmol/L(27ng/ml)
- In the Australian D-Health trial, a monthly dose of 60,000 IU of cholecalciferol given to 21,315 participants aged 60–84 years for a maximum of 5 years with mean achieved serum 25(OH)D concentrations of 114.8 nmol/L(46ng/ml)did not reduce the risk of falling, but even was associated with a higher risk in a sub-group with BMI < 25 kg/m2 [91].

The health effects of vitamin Dsupplementation: evidence from human studies

Roger Bouillon , Despoina Manousaki, Cliff Rosen , Katerina Trajanoska, Fernando Rivadeneira and J. Brent Richards

Nature Revlews Endocrinology volume 18 | February 2022

- ≥4,000 IU of vitamin D convey some risks other than simple hypercalcaemia or hypercalciuria.
- Such doses, or the equivalent of serum 25OHD concentrations well above 112 nmol/l or 45 ng/ml bring no benefits, but might be harmful in some people (for example, in causing loss of BMD or increasing the risk of falls). The same is true for intermittent high-dose boluses of vitamin D.

Role of vitamin D supplementation in the managementof musculoskeletal diseases: update from an European Society of Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group

In some European countries, 25,000 IU monthly(corresponding thereby to 800 IU/day) is commonly prescribed.

There is no evidence to recommend or to discourage this regimen.

The choice may be left to the patient's preference for ensuring optimal adherence to vitamin D supplementation.

Indications for vitamin D supplementation

- **Daily vitamin D (800–1000 IU**)
- Subjects at risk of osteoporosis
- Patients on concurrent osteoporosis treatment
- Patients with fragility fracture
- Elderly people at risk of falling
- Obese patients
- Subjects with pigmented skin
- Subjects with limited sun exposure
- Subjects with insufficient vitamin D intake
- Patients with malabsorption[1]
- Patients after bariatric surgery[1]
- Patients on anticonvulsants
- Patients on glucocorticoids
- **Loading dose (25,000 or 50,000 IU/week for 4–6 weeks)**
- Low 25-hydroxyvitamin D levels
- Need for a rapid correction of vitamin D deficiency
- After bariatric surgery
- Malabsorption
- Severe obesity

- 1 Higher doses (2000 IU/daily) may be needed

Vitamin D and osteoarthritis

- In summary, observational and intervention studies provide little evidence for a protective effect of vitamin D on cartilage volume loss or radiologic OA worsening, although it may have a favorable effect on joint pain.
- Indeed, subset analyses and one pilot randomized controlled trial suggest that patients with 25(OH)D below 50 nmol/L(20ng.ml) may experience less joint pain with vitamin D supplementation.
- Trials assessing radiologic OA and cartilage loss did not demonstrate an effect of vitamin D supplementation in patients with 25(OH)D levels above 50 nmol/L(20ng/ml).
- No trials have been performed in patients with low 25(OH)D levels.

Original Investigation | Nutrition, Obesity, and Exercise

Association of Body Weight With Response to Vitamin D Supplementation and Metabolism

Deirdre K. Tobias, ScD; Heike Luttmann-Gibson, PhD; Samia Mora, MD, MHS; Jacqueline Danik, MD, DrPH; Vadim Bubes, PhD; Trisha Copeland, MS, RD;Meryl S. LeBoff, MD; Nancy R. Cook, ScD; I-Min Lee, MD, ScD; Julie E. Buring, ScD; JoAnn E. Manson, MD,

JAMA Network Open. **2023;6(1):e2250681**

- In the original VITAL published in 2019, vitamin D(cholecalciferol), 2000 IU/d, supplementation did not reduce the incidence of cardiovascular disease or cancer in the group as a whole.
- However, prespecified secondary analyses in VITAL indicated a statistical interaction by baseline body weight, whereby randomization to vitamin D supplementation vs placebo was associated with
- a significant 24%lower cancer incidence,
- 42%lower cancer mortality and
- 22%lower incidence of autoimmune disease among participants with normal body weight [BMI] <25.0 ,
- but no reductions among those with overweight or obesity.
- the present post hoc analysis by Tobias and colleagues is the largest study to date examining whether a health outcome may differ in individuals with obesity due to differential effects by BMI of vitamin D supplementation on circulating vitamin D activity.
- The authors have conducted a very thorough analysis including multiple biomarkers of vitamin D metabolism, including total, bioavailable, and free 25-hydroxyvitamin D (25-OHD), as well as vitamin D binding protein.

- Thanks to its very large sample size and detailed biomarker analyses, the current study is able to provide novel evidence that responses to vitamin D supplementation may be attenuated in individuals with overweight and obesity, and that this may contribute to the differential outcomes by BMI noted in the original VITAL.

Vitamin D and Risk for Type 2 Diabetes in People With Prediabetes
A Systematic Review and Meta-analysis of Individual Participant Data From 3 Randomized Clinical Trials

Anastassios G. Pittas, MD, MS; Tetsuya Kawahara, MD, PhD; Rolf Jorde, MD, PhD; Bess Dawson-Hughes, MD; Ellen M. Vickery, MS; Edith Angellotti, MD; Jason Nelson, MPH; Thomas A. Trikalinos, MD; and Ethan M. Balk, MD, MPH

Ann Intern Med 7 February 2023.

- The three eligible trials tested three oral formulations of Vitamin D: cholecalciferol, 20,000 IU (500 mcg) weekly; cholecalciferol, 4,000 IU (100 mcg) daily; or eldecalcitol, 0.75 mcg daily, against placebos.
- Vitamin D reduced the risk for diabetes in people with prediabetes by a statistically significant 15% in adjusted analyses. The 3-year absolute risk reduction was 3.3%.

- “The present study does not reach an opposite conclusion from the D2d study.
- In D2d and two other similar vitamin D and diabetes prevention trials (one in Norway and one in Japan), vitamin D reduced the rate of progression to diabetes in adults with prediabetes, but the observed differences were not statistically significant because the reported relative risk reductions (10%-13%) were smaller than each trial was powered to detect (25%-36%).”
- “Individual participant data meta-analyses increase the statistical power to detect an effect. After combining data, we found that vitamin D reduced the risk of progression from prediabetes to diabetes by 15% and this result was statistically significant. So, the conclusion of the meta-analysis is essentially the same conclusion as in D2d and the other two trials. The difference is that the result is now statistically significant.

- The authors acknowledged that the absolute risk reduction number is small, especially when compared with the risk reduction seen with intensive lifestyle changes (58%) and metformin (31%)
- But “extrapolating to the more than 374 million adults worldwide who have prediabetes suggests that inexpensive vitamin D supplementation could delay the development of diabetes in more than 10 million people,” they said.

Review

Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS)

Nutrients **2022**, 14, 4148

How Should the Patient with Chronic Kidney Disease (CKD) Be Supplemented with Vitamin D?

Table 8. Recommendations regarding the supplementation of vitamin D metabolites in patients with impaired renal function, and in relation to their stage of renal failure.

	Evidence Level
It is recommended in the patient with CKD-MBD to correct hypovitaminosis D with cholecalciferol, with the same modalities used in the general population with normal renal function.	⊕⊕⊕⊕
It is recommended to limit the use of active vitamin D compounds (calcitriol or synthetic analogues) to subjects on dialysis or in G4-G5 CKD stage with severe and progressive hyperparathyroidism	⊕⊕⊕⊕

An increased risk of falling was described with:
(a) 100,000 IU cholecalciferol per
month towards lower doses in nursing home residents ;
(b) 500,000 IU cholecalciferol once a year vs. placebo in elderly women at high risk of falls/fracture not admitted to an institution ;
(c) 60,000 IU of cholecalciferol or 24,000 IU of cholecalciferol and 12,000 IU
of calcifediol per month towards a lower dose of cholecalciferol in elderly (>70 yrs), noninstitutionalized men and women with a personal history of fall ; and
(d) 4000 IU cholecalciferol per day to smaller doses in women aged >57 years and basal 25OHD3 values 20 ng/mL (50 nmol/L) .

Limitations of MEGA-TRIALS

(1) high-risk patients not included;
(2) low number of patients with inadequate 25(OH)D levels;
(3) lack of adequate dose of vitamin D supplementation and/or lack of adjustment for inadequate dietary calcium intake;
(4) lack of adequate 25(OH)D concentration during the whole study duration;
(5) a study duration not sufficient for a reliable evaluation of BMD changes and fracture incidence;
(6) the lack of the registration of all major comorbidities .

Consensus and Controversial Aspects of Vitamin D and COVID-19

Authors: John P Bilezikian, Neil Binkley, Hector F De Luca, Angelo Fassio, Anna Maria Formenti, Ghada El-Hajj Fuleihan, Annemieke C Heijboer, Andrea Giustina JCEM 2022

- **Participants:** The International Conferences "Controversies in Vitamin D" are a series of workshops that started in 2017 featuring international experts and leaders in vitamin D research and clinical practice. The 5th annual conference was held in Stresa, Italy, from 15 to 18 September 2021.
- **Conclusions:** There is quite consistent evidence for an association between low 25 OH vitamin D (25(OH)D) levels and poor COVID-19 outcomes, despite heterogeneous publications of variable quality.
- However, the low vitamin D status in COVID-19 patients might also reflect reverse causality.
- Vitamin D supplementation might have a positive role in COVID-19 prevention.
- The evidence supporting a beneficial effect of vitamin D treatment in decreasing the risk of COVID-19 complications is conflicting.
- Conclusive statement regarding the beneficial effect of vitamin D in this context await high-quality randomized controlled trials.

Original article EMAS position statement: Vitamin D and menopausal health Maturitas 169 (2023) 2–9

Panagiotis Anagnostis a,*, Sarantis Livadas b, Dimitrios G. Goulis a, Silvia Bretz c, Iuliana Ceausu d, Fatih Durmusoglu e, Risto Erkkola f, Ivan Fistonic g, Marco Gambacciani h, Marije Geukes i, Haitham Hamoda j, Caoimhe Hartley k, Angelica Lind´en Hirschberg l, Blazej Meczekalski m, Nicolas Mendoza n, Alfred Mueck o,p, Antonina Smetnik q, Petra Stute r, Mick van Trotsenburg s, Margaret Rees t, Irene Lambrinoudaki

- Concerning menopausal symptomatology, vitamin D deficiency may have a negative impact on some aspects, such as sleep disturbances, depression, sexual function and joint pains.
- However, vitamin D supplementation has no effect on these, except for vulvovaginal atrophy, at relatively high doses, i.e., 40,000–60,000 IU/week (1000–1500 IU/week) orally or 1000 IU/day (25 μg/day) as a vaginal suppository
- Vitamin D supplementation may have a modestly beneficial effect on lipid profile and glucose homeostasis, especially in obese individuals or those ≥60 years old and at doses of ≥2000 IU/day (≥50 μg/day). However, it has no effect on the incidence of cardiovascular events.
- Concerning skeletal health, vitamin D deficiency is associated with low bone mass and an increased risk of fractures. Vitamin D supplementation at maintenance doses of 800–2000 IU/day (20–50 μg/day), after repletion of vitamin D status with higher weekly or daily doses, may be of benefit only when co-administered with calcium (1000–1200 mg/day), especially in the elderly populations and those with severe vitamin D deficiency.

Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial

Jill Hahn,Nancy R Cook, Erik K Alexander,5 Sonia Friedman,Joseph Walter,
Vadim Bubes, Gregory Kotler, I-Min Lee, JoAnn E Manson, Karen H Costenbader **BMJ 2022;376:e066452**

- **PARTICIPANTS**
- 25 871 participants, consisting of 12 786 men ≥50years and 13 085 women ≥55 years at enrollment.
- **INTERVENTIONS**
- Vitamin D (2000 IU/day) or matched placebo, and omega 3 fatty acids (1000 mg/day) or matched placebo.
- Participants self-reported all incident autoimmune diseases from baseline to a median of 5.3 years of follow-up; these diseases were confirmed by extensive medical record review
- **MAIN OUTCOME MEASURES**
- The primary endpoint was all incident autoimmune diseases confirmed by medical record review:
- rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, psoriasis, inflammatory bowel disease.

- **CONCLUSIONS**
- Vitamin D supplementation for five years, with or without omega 3 fatty acids, reduced autoimmune disease by 22%,
- while omega 3 fatty acid supplementation with or without vitamin D reduced the autoimmune disease rate by 15% (not statistically significant).

Original Investigation | Geriatrics

Effect of Vitamin D3 and Omega-3 Fatty Acid Supplementation on Risk of Frailty
An Ancillary Study of a Randomized Clinical Trial

Ariela R. Orkaby, MD, MPH; Rimma Dushkes, PhD; RachelWard, PhD; Luc Djousse,MD, ScD; Julie E. Buring, ScD; I-Min Lee, MBBS, ScD; Nancy R. Cook, ScD; Meryl S. LeBoff, MD; Olivia I. Okereke, MD, SM; Trisha Copeland, MS, RD; JoAnn E. Manson, MD, DrPH ***JAMA Network Open.*** **2022;5(9):e2231206**

- Findings In this ancillary study of a randomized clinical trial including 25 871individuals aged 50 years or older, neither vitamin D3, 2000 IU/d, nor omega-3 fatty acid, 1 g/d, supplementation, compared with placebo, significantly affected change in frailty score during 5 years of treatment.

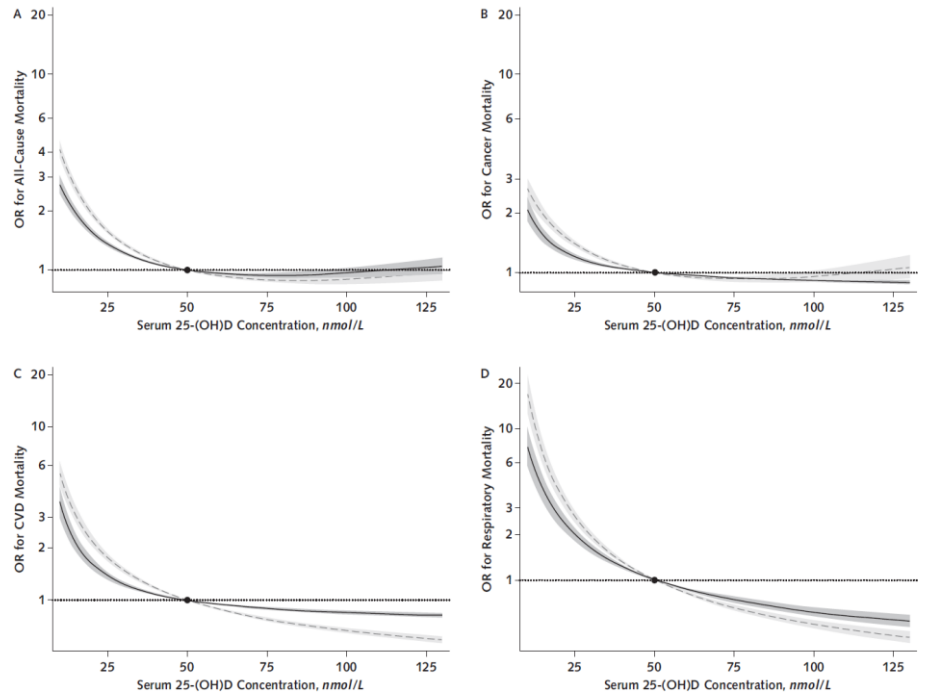
- Invited Commentary | Geriatrics
- There Is No Magic Pill to Prevent Frailty—You Still Have to Eat Your Vegetables
- Elizabeth Eckstrom, MD, MPH; Bryanna De Lima, MPH

Vitamin D Deficiency Increases Mortality Risk in the UK Biobank
A Nonlinear Mendelian Randomization Study

Joshua P. Sutherland, BHSc Nut Med (Hons); Ang Zhou, PhD; and Elina Hyppönen, PhD

Ann Intern Med. 25 October 2022.

- **Participants**: 307 601 unrelated UK Biobank participants of White European ancestry (aged 37 to 73 years at recruitment) with available measurements of 25-hydroxyvitamin D (25-(OH)D) and genetic data.
- **Measurements:** Genetically predicted 25-(OH)D was estimated using 35 confirmed variants of 25-(OH)D. All-cause and cause specific mortality (cardiovascular disease [CVD], cancer, and respiratory) were recorded up to June 2020.



The D-Health Trial: a randomised controlled trial of the effect of vitamin D on mortality

Rachel E Neale, Catherine Baxter, Briony Duarte Romero, Donald S A McLeod, Dallas R English, Bruce K Armstrong, Peter R Ebeling, Gunter Hartel, Michael G Kimlin, Rachel O'Connell, Jolieke C van der Pols, Alison J Venn, Penelope M Webb, David C Whiteman, Mary Waterhouse

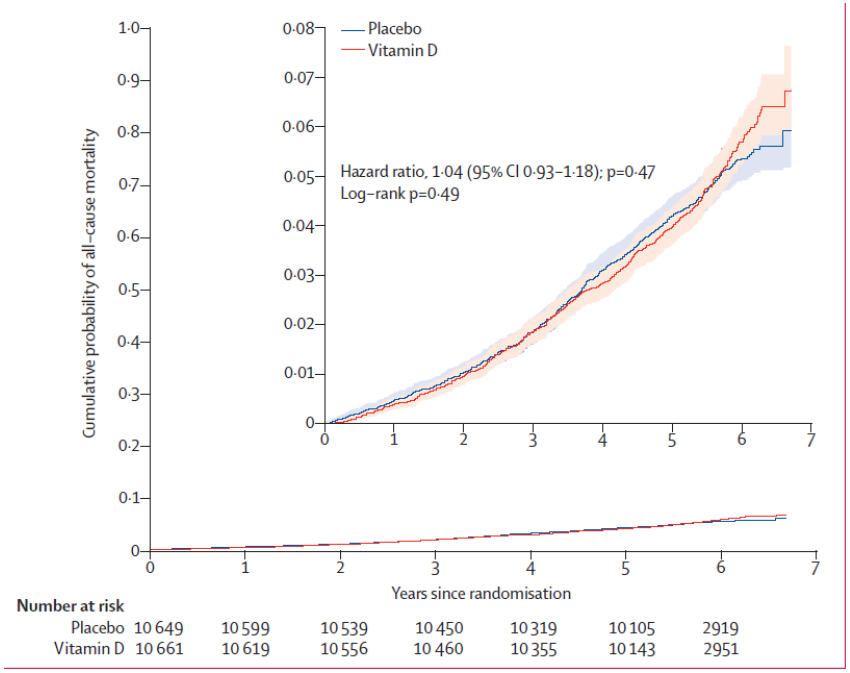
***Lancet Diabetes Endocrinol* 2022; 10: 120–28**

- # Methods

- We did a randomised, double-blind, placebo-controlled trial of oral vitamin D3 supplementation(60 000 IU per month) in Australians 60 years or older who were recruited across the country via the Commonwealth electoral roll.

- # Interpretation

- Administering vitamin D3 monthly to unscreened older people did not reduce all-cause mortality



ΕΥΧΑΡΙΣΤΩ