

Vitamin D: Review of Current Evidence and Recommendations

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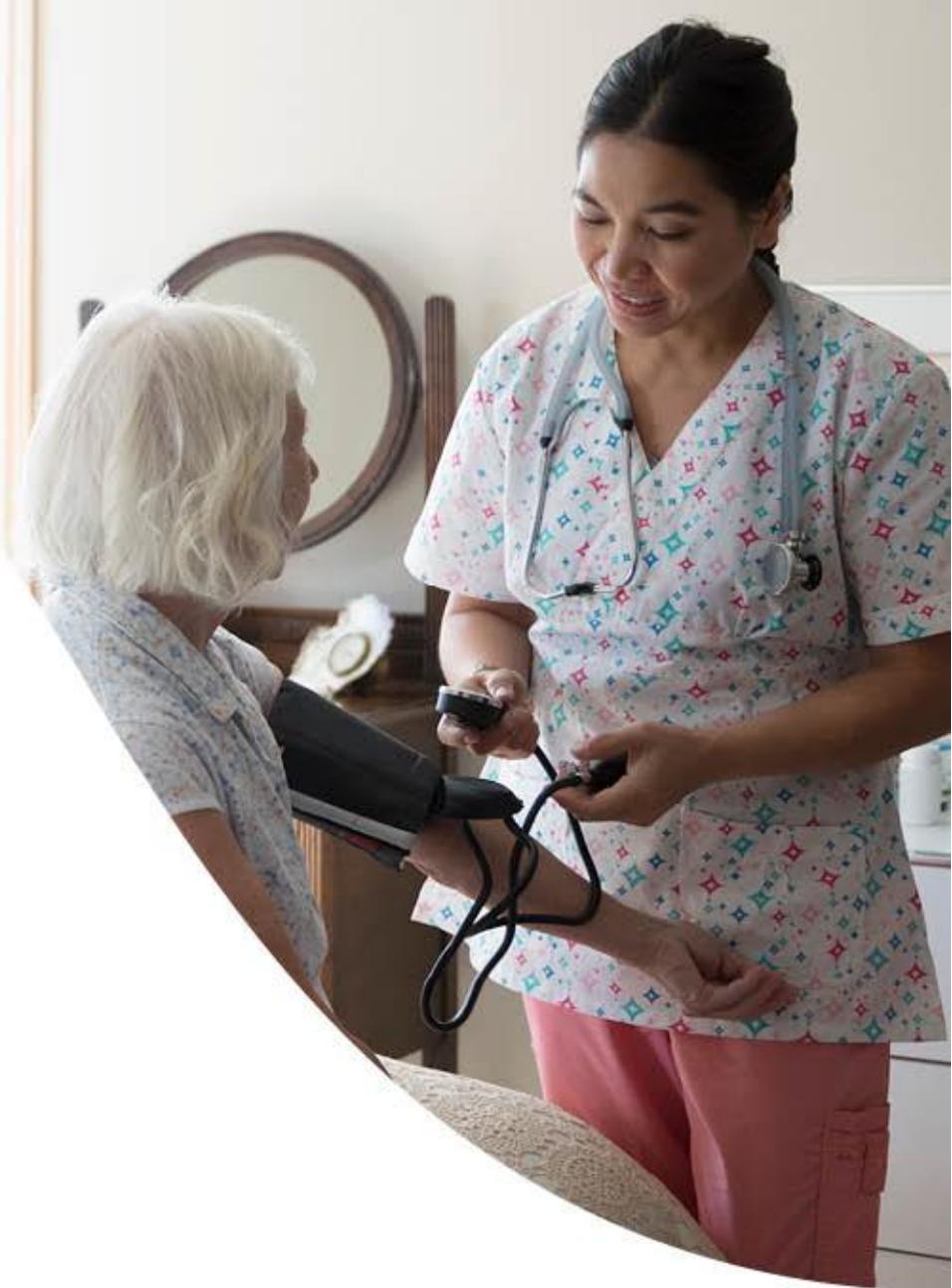
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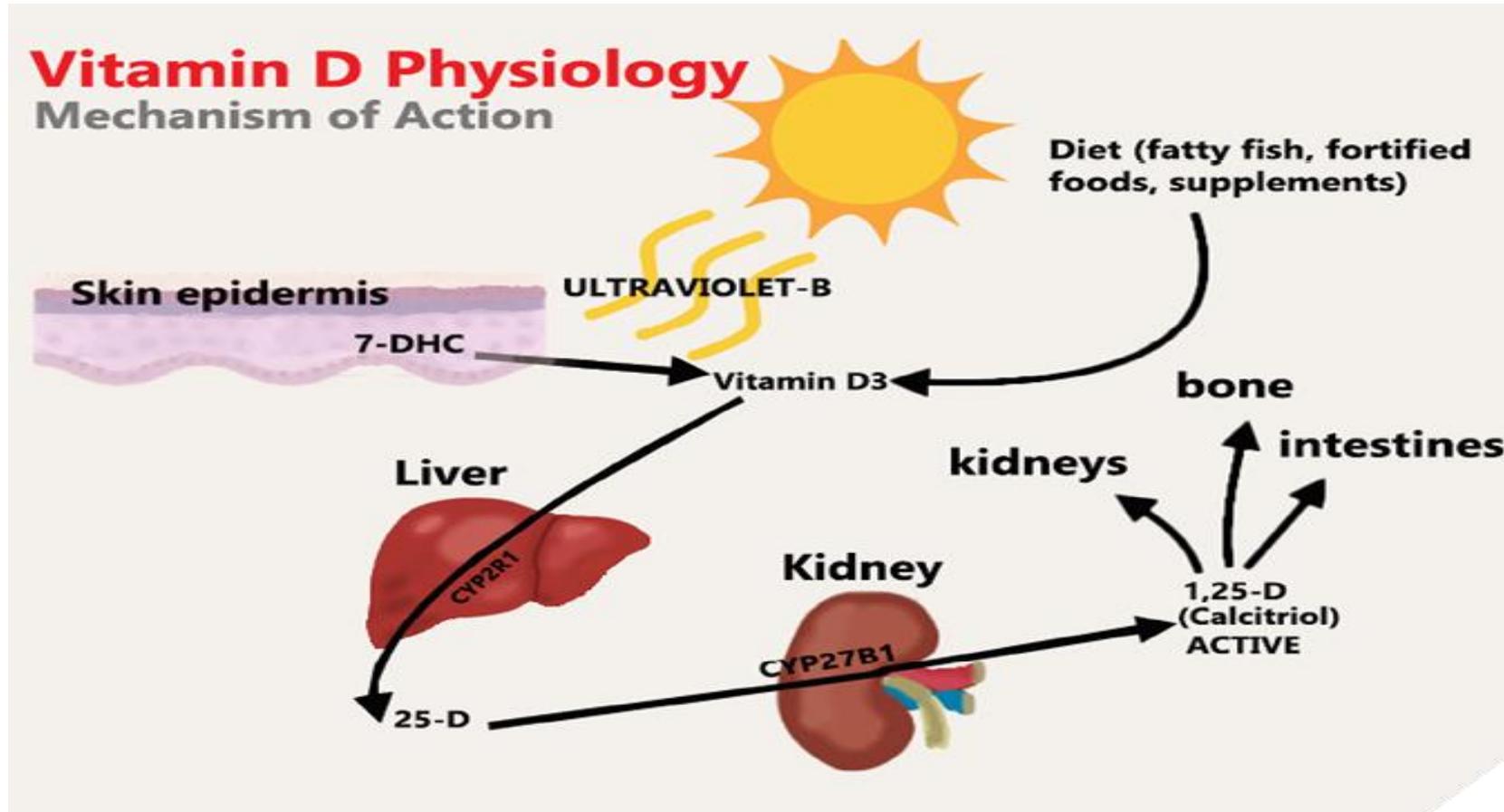


Conflicts of Interest

There are no conflicts of interest from either the presenter or the collaborating authors for this presentation.

Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline

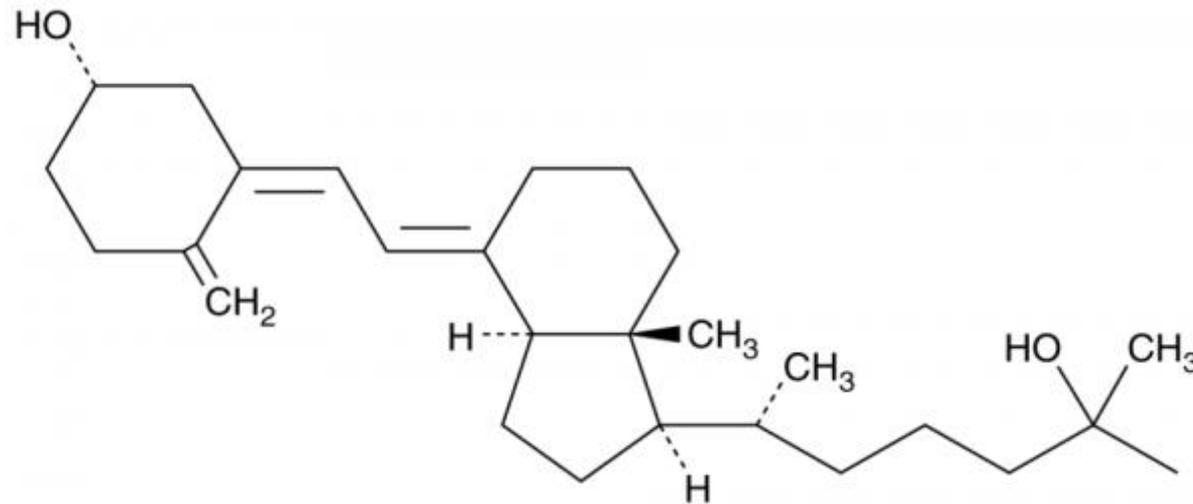
The role of Vitamin D



Oral Health Group. (2025, February 7). *Vitamin D in orthodontics: A literature review* - Oral Health Group. <https://www.oralhealthgroup.com/features/vitamin-d-in-orthodontics-a-literature-review/>

Empiric supplementation defined

- Vitamin D intake that exceeds the dietary reference intake (DRI)
 - 600-800 IU daily
- WITHOUT testing for 25-hydroxyvitamin D aka 25(OH)D



*The following guidelines do not apply to those who have malabsorption syndromes, nephrotic syndromes or any other comorbidity that may significantly alter vitamin D physiology

Empiric vitamin D and the groups recommended

- **Children and adolescents (1-18)**
 - Rickets, respiratory infections
 - 300-2000 IU daily (1200 IU daily average)
- **Adults aged 75 years and older**
 - Slight decrease in all-cause mortality
 - 400-3333 IU daily (900 IU daily average)

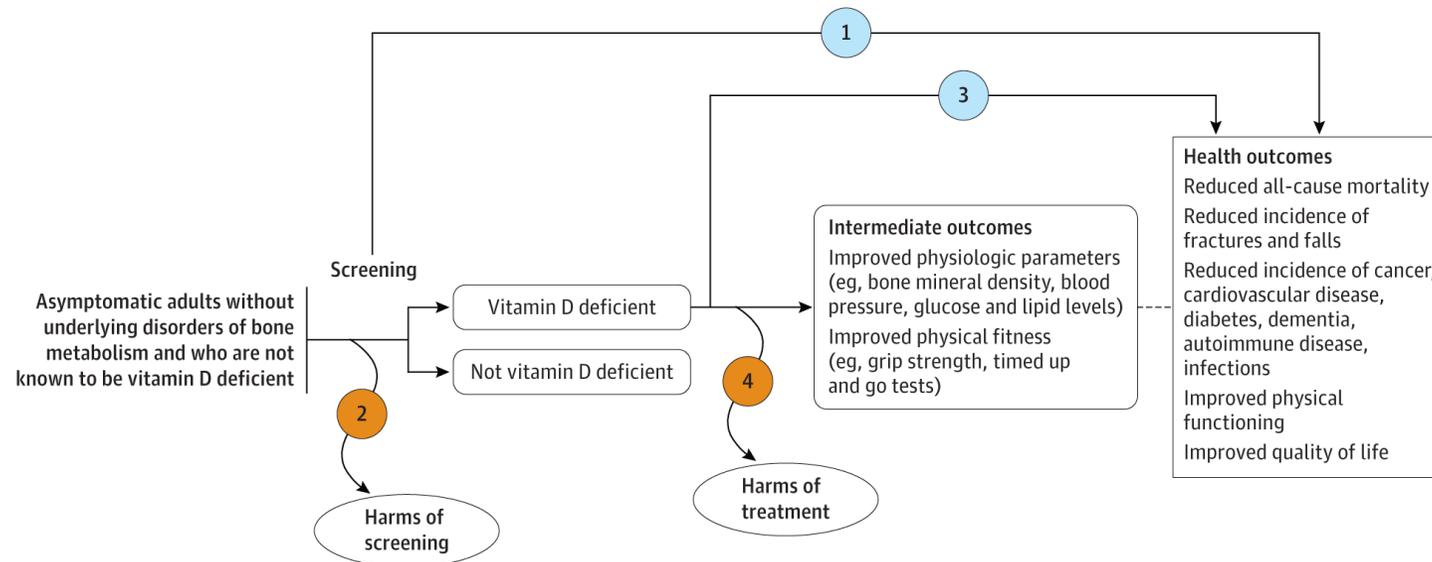
Recommended groups continued

- **Pregnant women of any age**
 - Decrease risk of preeclampsia, intra-uterine mortality, preterm birth, small-for-gestational-age birth and neonatal mortality
 - 600-5000 IU daily (2500 IU daily average)
- **Adults with high-risk prediabetes**
 - Decrease progression to type 2 diabetes
 - 842-7543 IU daily (3500 IU daily average)

**Screening for Vitamin D
Deficiency in Adults:
Updated Evidence Report and
Systematic Review for the US
Preventive Services Task Force**

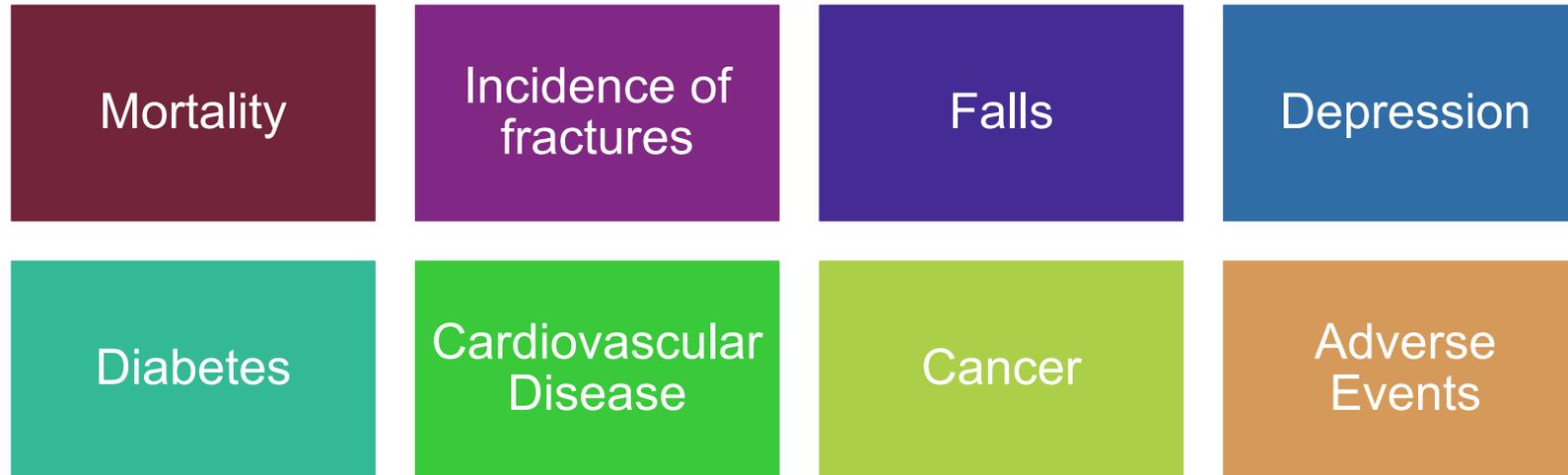
Systematic Review of 77 Articles (46 Total Studies)

- 2020 update of 2014 USPSTF recommendations
- Four key questions:
 1. How does screening improve health?
 2. Are there harms caused by screening?
 3. Does treatment of deficiency improve outcomes?
 4. Are there harms to treatment?



Overall Conclusions

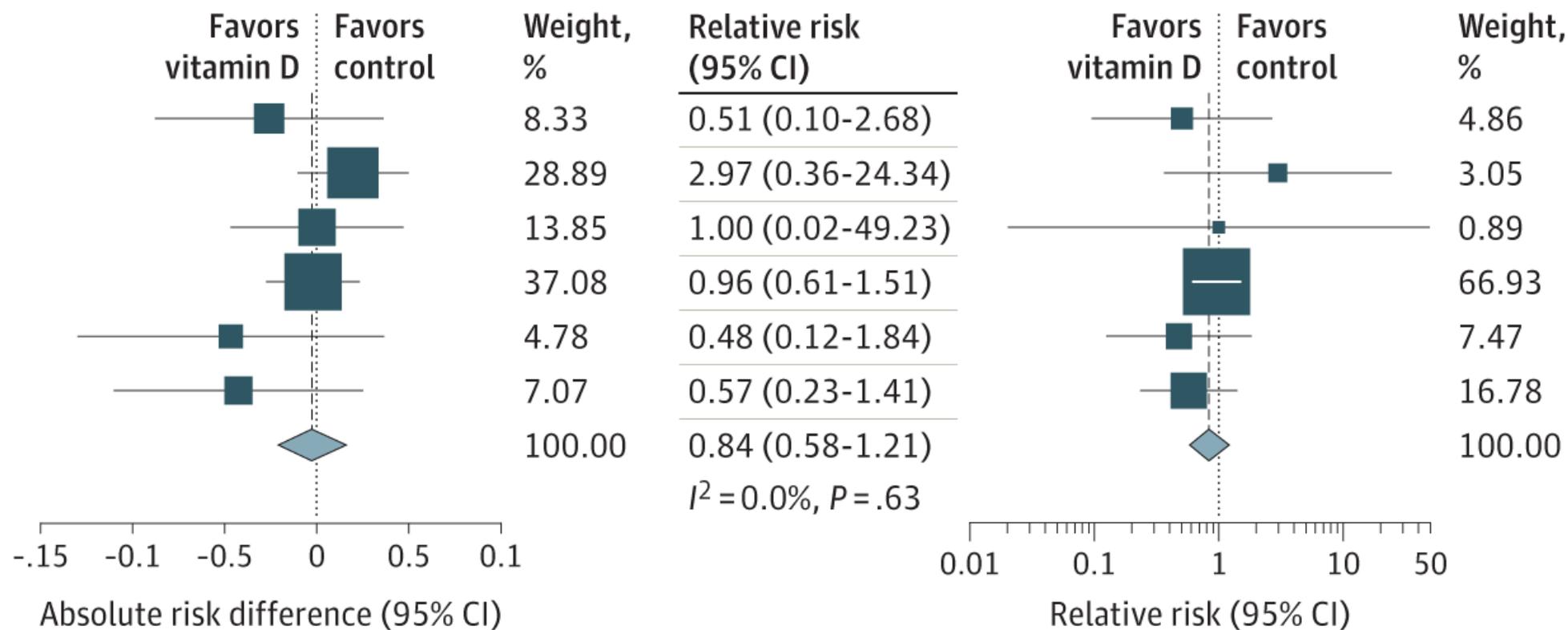
Evidence suggests vitamin D (with or without calcium) has no effect on:



Evidence is inconclusive about effect on:



Effect of Vitamin D Treatment on Incidence of Any Fracture in Community-Dwelling Participants



Limitations of Review

- Several studies involved institutionalized settings rather than community-dwelling populations
- Did not assess specific diagnoses or symptoms
- Did not compare various doses, formulations, durations of treatment
- Various vitamin D assays used, likely not standardized

Table 1. Study Characteristics of RCTs Reporting Benefits and Harms of Treating Low Serum Vitamin D Levels in Adults

Source	Country; study quality	Interventions (No. randomized)	Calcium use	Treatment duration	Age, mean (SD), y	Women, No. (%)	Setting	Outcomes reported
Aloia et al, ⁶¹ 2005 Talwar et al, ⁶² 2007	US; fair	Placebo once daily (n = 104) Vitamin D ₃ 800 IU once daily, changed to 2000 IU once daily at 2 y (n = 104)	Active and control intervention	3 y	Placebo: 61.2 (6.3) Vitamin D ₃ : 59.9 (6.2)	208 (100)	Community-dwelling	Serious adverse events Kidney stones
PODA Aloia et al, ⁶⁰ 2018	US; fair	Placebo once daily, titrated to match vitamin D group (n = 130) Vitamin D ₃ titrated to a serum level of 30 ng/mL; dosage adjusted every 3 mo; doses provided as a single daily dose (n = 130)	Active and control intervention	3 y	Median, 68.2 (IQR, 65.4-72.5)	258 (100)	Community-dwelling	Total adverse events Serious adverse events
Arvold et al, ¹⁵ 2009	US; fair	Placebo weekly (n = 50) Vitamin D ₃ 50 000 IU weekly (n = 50)	None	8 wk	Placebo: 57.8 (15.8) Vitamin D ₃ : 59.7 (14.0)	Placebo: 15 (36) Vitamin D ₃ : 21 (44)	Community-dwelling	Physical functioning Total adverse events
Bischoff et al, ¹⁶ 2003	Switzerland; fair	Placebo twice daily (n = 60) Vitamin D ₃ 400 IU twice daily (total daily dose, 800 IU) (n = 62)	Active and control intervention	12 wk	Placebo: 85.4 (5.9) Vitamin D ₃ : 84.9 (7.7)	122 (100)	Institutionalized	Falls Total adverse events Other harms
Bislev et al, ¹⁷ 2018	Denmark; good	Placebo once daily (n = 41) Vitamin D ₃ 2800 IU once daily (n = 40)	None	12 wk	NR, all women participating were aged between 60 and 79 y	81 (100)	Community-dwelling	Fractures Total adverse events Serious adverse events
Borgi et al, ⁶³ 2016 McMullan et al, ⁶⁴ 2017	US; good	Placebo weekly (n = 47) Vitamin D ₂ 50 000 IU tablets weekly (n = 46)	None	8 wk	37 (12.3)	Placebo: 31 (66 ^a) Vitamin D ₂ : 31 (67 ^a)	Community-dwelling	Total adverse events Serious adverse events
Brazier et al, ¹⁸ 2005	France; fair	Placebo twice daily (n = 97) 500 mg calcium carbonate + vitamin D ₃ 400 IU twice daily (1000 mg/800 IU total daily dose) (n = 95)	Active treatment intervention	52 wk	74.6 (6.9)	192 (100)	Community-dwelling	Mortality Total adverse events Serious adverse events Discontinuation
Decalys II Chapuy et al, ¹⁹ 2002	France; fair	Placebo once daily (N NR) Vitamin D ₃ 800 IU and 1200 mg tricalcium phosphate as fixed combination (N NR) Vitamin D ₃ 800 IU and 1200 mg tricalcium phosphate as separate combination (N NR)	Active treatment intervention	2 y	Placebo: 85.7 (7.6) Vitamin D ₃ + calcium (fixed): 84.9 (6.6) Vitamin D ₃ + calcium	583 (100)	Institutionalized	Mortality Falls Fractures Other harms Kidney stones

Consensus Statement on Vitamin D Status Assessment and Supplementation: *Whys, Whens, and Hows*

Clinically Significant Low Vitamin D

- Vitamin D < 25 nmol/L (10 ng/mL)
- Potential side effects for deficiency
 - MSK: 2^o hyperparathyroidism
 - Respiratory
 - Autoimmune Disease
- Potential outcomes when appropriately supplemented
 - Cancer
 - Diabetes

Recommendations on Assessment

Screening patients at risk for vitamin D deficiency with 25(OH)D (vitamin D3)

Screening with 25(OH)D (vitamin D3) is recommended

Other Vitamin D labs are *not* for screening

Older people

- Housebound people, Disabled people
- Institutionalized people

- People working long hours indoors, Office workers
- Factory or warehouse workers
- Taxi drivers
- Night-shift workers

People with dark skin

Low levels of physical activity

- People with a debilitating/chronic disease, Diabetes
- Chronic kidney disease
- Gastrointestinal malabsorptive syndromes
- Parathyroid disorders
- Liver diseases

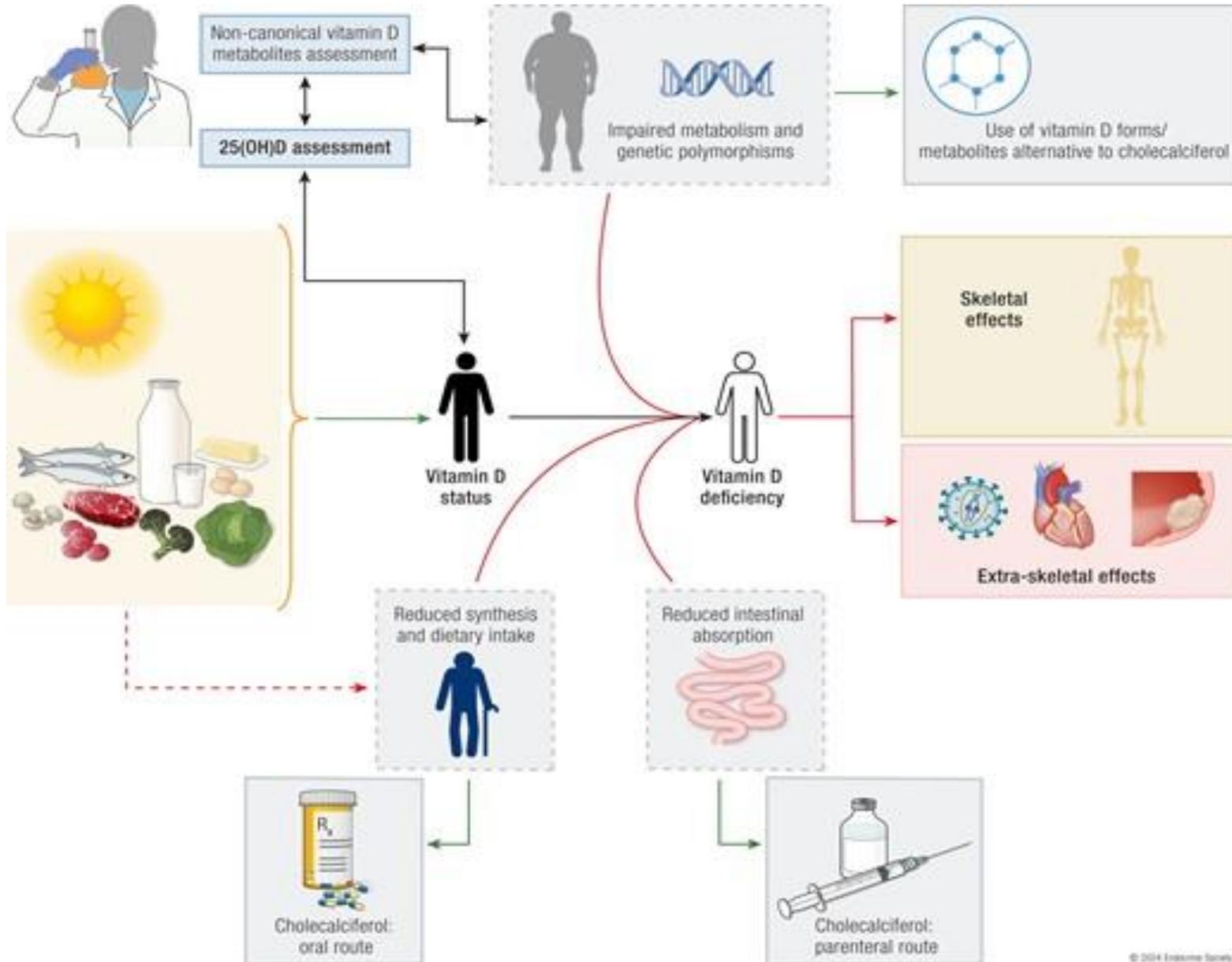
Obesity—in particular those with highest levels of waist circumference

Patients after bariatric surgery

- People taking medications increasing vitamin D catabolism : Phenobarbitone
- Carbamazepine
- Dexamethasone
- Rifampicin
- Nifedipine
- Spironolactone
- Ritonavir
- Cyproterone acetate

Babies of vitamin D-deficient mothers

Recommendations on Administration



**50-75 nmol/L
(20-30 ng/mL)**
with consideration
of time of year

- 400 to 800 IU per day
- up to 4000 IU per day

Current Myths Regarding Vitamin D: Complete screening prior to supplementation

Myth 1: Complete screening prior to supplementation

Per the USPSTF:

- Insufficient evidence to recommend routine screening of asymptomatic adults
- No consensus on a threshold value to offer Vitamin D supplementation

Conclusion:

- Routine screening is not recommended
- DRI (600 IU for ages 1-70 years; 800 IU for ages 70-74 years)

JAMA Clinical Guidelines Synopsis

Vitamin D for Prevention of Disease

Eva S. Liu, MD; Andrew M. Davis, MD, MPH; Sherri-Ann M. Burnett-Bowie, MD, MPH

GUIDELINE TITLE Vitamin D for the Prevention of Disease

RELEASE DATE June 3, 2024 (revised February 13, 2025)

PRIOR VERSION 2011

FUNDING SOURCE The Endocrine Society

TARGET POPULATION Healthy children and adults

SELECTED RECOMMENDATIONS

- In addition to the recommended dietary reference intake (DRI), additional empirical vitamin D from fortified foods, multivitamins, or oral supplements should be started without testing for 25-hydroxyvitamin D (25(OH)D) levels (conditional recommendation [CR]; low certainty of evidence [COE]) for
 - Children aged 1 to 18 years, to prevent nutritional rickets and potentially lower risk of respiratory tract infections (RTIs). The average daily dose of supplemental vitamin D used in clinical trials was 1200 IU, although participants could continue vitamin D supplements up to the maximum DRI of 600 IU (CR; very low COE).

- Adults aged 75 years or older, to potentially lower risk of mortality. The average daily dose of supplemental vitamin D used in clinical trials was 900 IU, although participants could continue vitamin D supplements up to the maximum DRI (800 IU) (CR; moderate COE).
- Pregnant women, to potentially lower risk of preeclampsia, intrauterine mortality, preterm birth, small-for-gestational-age birth, and neonatal mortality. The average daily dose of supplemental vitamin D used in clinical trials was 2500 IU (CR; moderate COE).
- Adults with prediabetes, to potentially decrease risk of progression to diabetes. The average daily dose of supplemental vitamin D used in clinical trials was 3500 IU, although participants could continue vitamin D supplements up to 1000 IU (CR; moderate COE).
- Routine screening of serum 25(OH)D levels in healthy children and adults is not recommended (CR; very low COE). Healthy people should consume the DRI (600 IU for ages 1-70 years; 800 IU for ages 70-74 years).

Summary of the Clinical Problem

Vitamin D regulates bone homeostasis,¹ and epidemiologic studies suggest that lower vitamin D levels may be associated with increased risk of RTIs, cardiovascular disease, malignancy, and metabolic disorders.^{2,3} Increased awareness of possible health benefits associated with higher

25(OH)D levels has resulted in widespread vitamin D testing and supplementation in the general US population. Nonetheless, there is no consensus on a threshold value below which people should be offered vitamin D

and the recommendations do not apply to people with underlying conditions that affect vitamin D homeostasis, such as advanced kidney disease, malabsorption, dietary risks (eg, vegetarian diet, lactose intolerance, or breastfed infants), or those with clinical indications for 25(OH)D screening, such as those with hypocalcemia, fragility fractures, or osteoporosis.⁵

Evidence Base

Meta-analyses of 12 randomized clinical trials (RCTs; n = 12 951) among children aged 1 to 18 years suggest that vitamin D supplementation (average dose, 1200 IU/d) may be associated with reduced risk of RTI vs no supplementation (risk difference [RD], -4.3%; 95% CI, -9.3%

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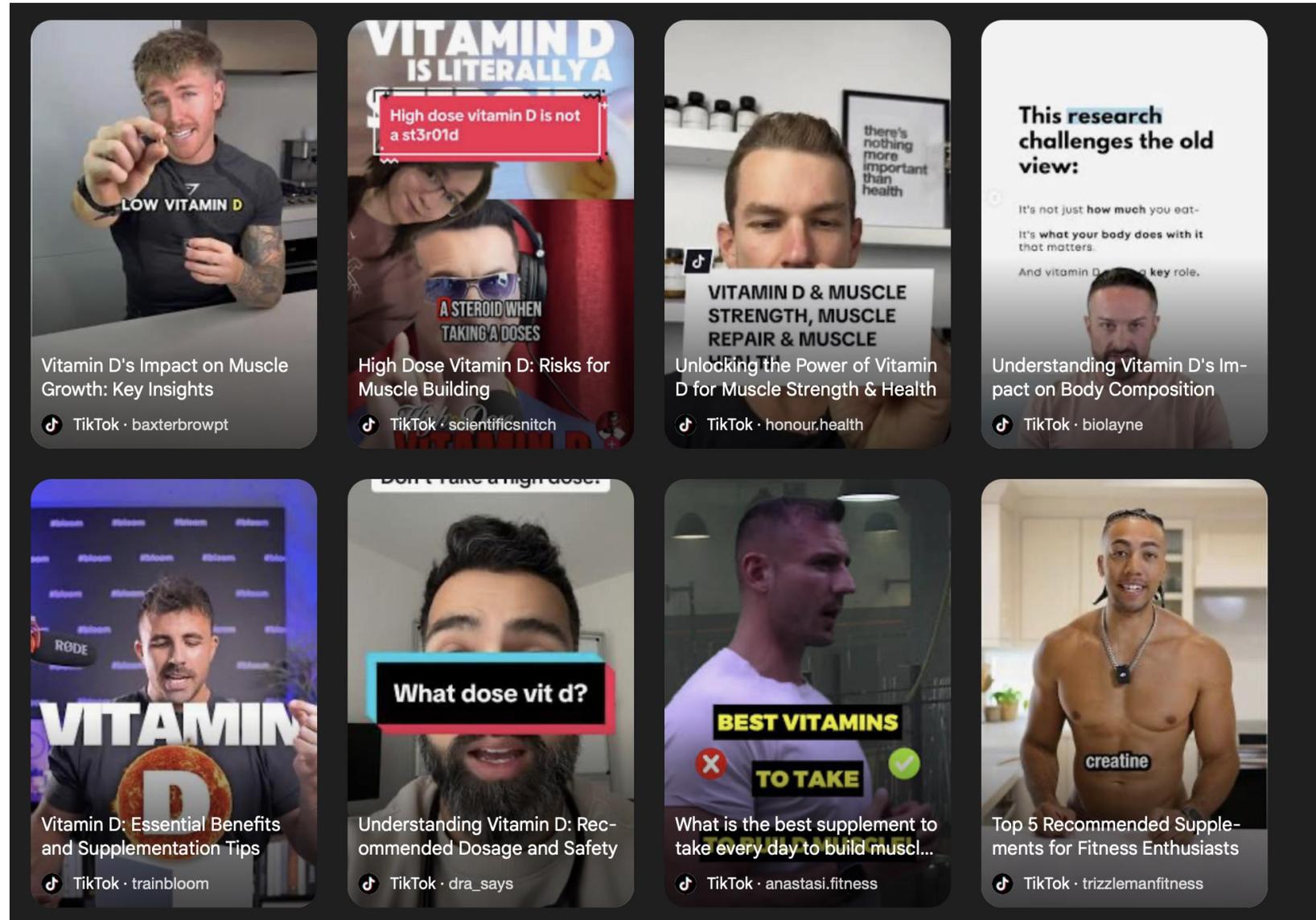
 Multimedia

 CME at jamacmelookup.com

Myth 2: Vitamin D for muscle mass?

Why the controversy?

- Muscle mass/strength declines with age
- Skeletal muscle expression of receptors for 1,25 dihydroxy vitamin D decrease with age
- Vitamin D deficiency associated with loss of type II muscle fibers in older adults



Low vitamin D status is associated with reduced muscle mass and impaired physical performance in frail elderly people

M Tieland ¹, E M Brouwer-Brolsma, C Nienaber-Rousseau

Affiliations + expand

PMID: 23942175 DOI: [10.1038/ejcn.2013.144](https://doi.org/10.1038/ejcn.2013.144)

Abstract

Background/objectives: Serum 25-hydroxyvitamin D muscle mass, strength and physical performance in frail elderly people this association has not been studied. The association between vitamin D intake and serum 25(OH)D physical performance in a pre-frail and frail elderly population.

Subjects/methods: This cross-sectional study included 100 elderly people from the Netherlands. Whole body and appendicular lean mass, leg strength (one repetition maximum), handgrip strength and physical performance battery were measured, and blood samples for serum 25(OH)D status (liquid chromatography-tandem mass spectrometry), dietary intake (3-day food records) and physical activity were collected.

Results: In total, 53% of the participants had a serum 25(OH)D status below 20 nmol/L. After adjustment for confounding factors, 25(OH)D status was associated with physical performance ($\beta=0.020$, $P<0.05$). Vitamin D status was not associated with muscle mass or ALM ($P>0.05$).

Conclusion: In this frail elderly population, 25(OH)D status was associated with reduced ALM and impaired physical performance. These findings need to be confirmed in well-designed intervention trials to assess the impact of vitamin D supplementation on muscle mass and physical performance in pre-frail elderly people.

Effects of Vitamin D3 Supplementation on Muscle Strength, Mass, and Physical Performance in Women with Vitamin D Insufficiency: A Randomized Placebo-Controlled Trial

Lise Sofie Bislev ^{1 2}, Lene Langagergaard Rødbro ³, Lars Rolighed ^{4 5}, Tanja Sikjaer ³, Lars Rejnmark ^{3 6}

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PMID: 29931459 DOI: [10.1007/s00223-018-0443-z](https://doi.org/10.1007/s00223-018-0443-z)

Abstract

Vitamin D insufficiency and hyperparathyroidism have been associated with reduced muscle strength, physical performance, postural stability, well-being, and quality of life. In a double-blind, randomized placebo-controlled trial, we aimed to investigate effects of vitamin D3 supplementation on above-mentioned outcomes in healthy community-dwelling postmenopausal women with plasma levels of 25-hydroxyvitamin D (25(OH)D) below < 50 nmol/l and high parathyroid hormone (PTH) levels. Participants ($N = 81$) were 1:1 treated with vitamin D3, 70 μg (2800 IU)/day or identical placebo for three months during wintertime (56°N). Vitamin D3 supplementation increased levels of 25(OH)D and 1,25(OH)₂D by 230% (95% CI 189 to 272)%, $p < 0.001$ and 58% (190 to 271%), $p < 0.001$, respectively, and reduced PTH by 17% (- 23 to - 11%), $p < 0.001$. Compared with placebo, vitamin D3 significantly reduced maximal handgrip strength by 9% (- 15 to - 3%; $p < 0.01$) and knee flexion strength by 13% (- 24 to - 2%; $p = 0.02$) and increased the time spent on performing the Timed Up and Go test by 4.4%; (0.1-8.6%; $p < 0.05$). Levels of physical activity, total lean body mass, appendicular lean mass index, postural stability, well-being, and quality of life did not change in response to treatment. Compared with placebo, a daily supplement with a relatively high dose of vitamin D3 had no beneficial effects on any outcomes. In some measures of muscle strength and physical performance, we even saw a small unfavorable effect. Our data call for caution on use of relatively high daily doses of vitamin D3 in the treatment of vitamin D insufficiency.

A randomized study on the effect of vitamin D₃ supplementation on skeletal muscle morphology and concentration in older women

Auricio da Silva Morais, Donato A Rivas, Susan S Harris, Jess Dawson-Hughes

DOI: [10.1210/jc.2013-2820](https://doi.org/10.1210/jc.2013-2820)

Whether vitamin D₃ supplementation increases muscle mass or muscle concentration in older women are lacking.

The aim of the present study was to determine whether vitamin D₃ 4000 IU/d alters muscle fiber cross-sectional area (CSA) and intramyonuclear vitamin D receptor (VDR) concentration over 4 months.

The study was a randomized, double-blind, placebo-controlled study in a single center.

Twenty mobility-limited women (aged ≥ 65 years) with serum 25(OH)D < 60 nmol/L.

At baseline, muscle fiber CSA and intramyonuclear VDR were measured. Muscle fiber type I/IIa/IIx and VDR using immunohistochemistry were probed for muscle fiber type (I/IIa/IIx) and VDR using immunohistochemistry. Mean age was 78 ± 5 years; body mass index was 27 ± 5 kg/m², 25(OH)D was 50 ± 10 nmol/L and physical performance battery score was 7.95 ± 1.57 out of 12. At baseline, serum 25(OH)D was 50.0 ± 11.5 nmol/L (vitamin D [VD]; $P < .01$), which was associated with percent change in intramyonuclear VDR concentration of $18.7 \pm 18.2\%$ (placebo) vs $29.7 \pm 11.7\%$ (VD; $P = .03$) in type II vs I fibers. Percent change in total (type I/II) VDR concentration was $18.7 \pm 20.0\%$ (VD; $P = .048$).

Conclusion: Vitamin D₃ supplementation increased intramyonuclear VDR concentration by 30% and increased muscle fiber size by 10% in older, mobility-limited, vitamin D-insufficient women.

Myth 2: Vitamin D for muscle mass?

Evidence saying otherwise:

- The VITAL trial studied prevention of cancer and cardiovascular diseases with Vitamin D
- Of 25871 US adults, 1054 of which were included in in an ancillary study
- Study assessed muscle mass post vitamin D supplementation

Conclusion:

- Neither Vitamin D nor omega-3 fatty acids for 2 years improved physical performance in a generally healthy adult population

Effects of Supplemental Vitamin D₃, Omega-3 Fatty Acids on Physical Performance Measures in the VITamin D and OmegA-3 Trial

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Abstract

Context: Declining muscle strength and performance in older adults are associated with falls, fractures, and premature death.

Objective: This work aimed to determine whether supplementation with vitamin D₃ or omega-3 fatty acids vs placebo for 2 years improves physical performance measures.

Methods: VITamin D and OmegA-3 Trial (VITAL) was a double-blinded, placebo-controlled randomized trial of supplemental vitamin D₃ and/or omega-3 fatty acids vs placebo in the prevention of cancer and cardiovascular disease in 25 871 US adults. This ancillary study was completed in a New England subcohort that had in-person evaluations at baseline and 2-year follow-up. This study was conducted with 1054 participants (age: men ≥50 and women ≥55 years) at the Center for Clinical Investigations in Boston. Interventions included a 2 × 2 factorial design of supplemental vitamin D₃ (cholecalciferol, 2000 IU/day) and/or marine omega-3 fatty acids (1 g/day). Main outcome measures included 2-year changes in physical performance measures of grip strength, walking speed, standing balance, repeated chair stands, and Timed-up and Go (TUG).

Results: At 2 years, all randomized groups showed worsening walking speeds and TUG. There were no differences in changes in grip strength, walking speeds, Short Physical Performance Battery (composite of walking speed, balance, and chair stands), and TUG between the vitamin D₃-treated and the placebo-treated groups and between the omega-3-treated and the placebo-treated groups. Effects overall did not vary by sex, age, body mass index, or baseline measures of total or free 25-hydroxyvitamin D (25(OH)D) or plasma omega-3 index; TUG slightly worsened with vitamin D supplementation, compared to placebo, in participants with baseline total 25(OH)D levels above the median ($P = .01$; P for interaction = .04).

Conclusion: Neither supplemental vitamin D₃ nor marine omega-3 fatty acids for 2 years improved physical performance in this generally healthy adult population.

Key Words: vitamin D, omega-3 fatty acids, physical performance

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ALA, alpha-linolenic acid; ALM, appendicular lean mass; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CTSC, Clinical and Translational Science Center; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EWGSOP2, European Working Group on Sarcopenia in Older People 2; RCT, randomized controlled trial; SPPB, Short Physical Performance Battery; TUG, Timed-Up and Go; VDR, 1,25-dihydroxyvitamin D receptor; VITAL, VITamin D and OmegA-3 Trial.

Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults

Vitamin D Supplementation and Incidental Fractures

- VITAL Trial
- Ancillary study assessing vitamin D supplementation and fractures in generally healthy adults
 - Participants not recruited based on vitamin D level, bone health or fracture history
 - 2000 IU vitamin D3 daily for 5.3 years
 - Primary endpoint: confirmed incidental fractures

Vitamin D Supplementation and Incidental Fractures

- Data from the VITAL trial:
 - 25,871 participants
 - 1991 incidental fractures in 1551 participants
 - 769 in placebo group
 - 781 in vitamin D group
 - 95% CI 0.89-1.08
- Ultimately, no lower risk of fracture in vitamin D group vs placebo
- No benefit in small number of participants (401) with vitamin D level <12

Vitamin D Supplementation and Incidental Fractures

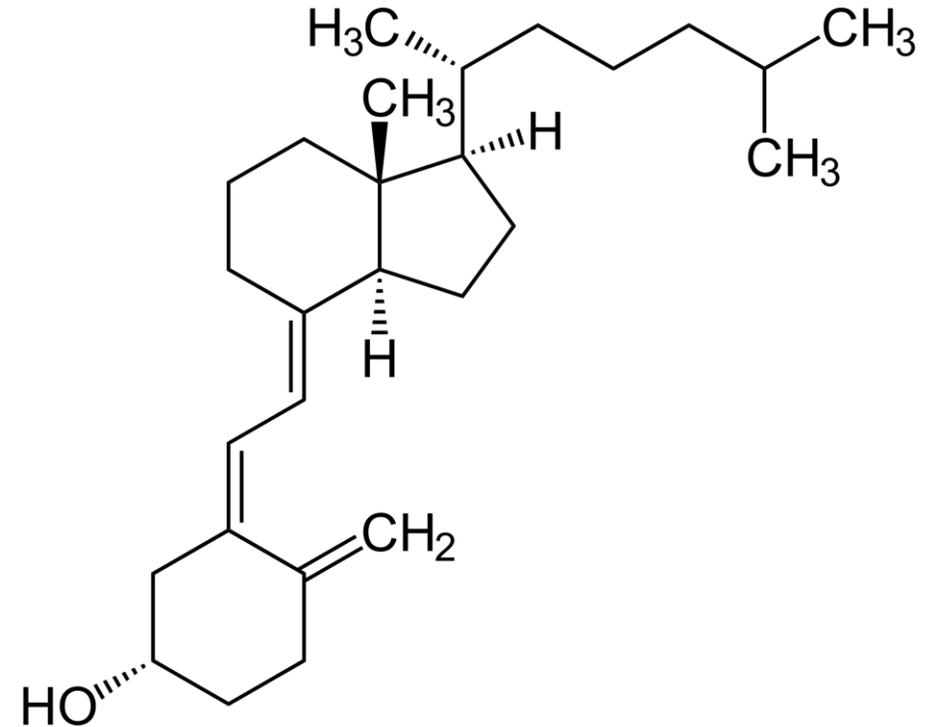
Study Limitations:

- Only one specific dose of vitamin D
- Not designed to test effects of supplementing vitamin D in vitamin D deficient patients
 - Unethical to perform placebo vs treatment in vitamin D deficient individuals

Vitamin D: 100 years of discoveries, yet controversy continues

Overview of last 100 years

- Historically known as the 4th vitamin
 - Available as Vitamin D3 since 1936
 - Available as Vitamin D2 since 1931
- Half life of Vitamin D:
 - 25 (OH) vitamin D3 = 2 weeks
 - 1,25 (OH)2D3 = 4-6 hour
- Upper limit generally set at 4,000 IU daily
 - Based on toxicity case reports with evidence of hypercalcemia, hypercalciuria, nephrocalcinosis, renal stones and arterial calcification beginning at doses of 10,000 IU daily
 - However, some studies suggest even lower doses (400-800 IU daily) resulted in adverse effect, particularly in older individuals



Molecular structure of cholecalciferol, vitamin D3

The Controversy

IOM committee

- Recommendation of Vitamin D 800 IU with 1200 mg calcium
- Normal Vitamin D serum concentration 50 nmol/L (20 ng/mL)

Endocrine Society

- Recommendation of Vitamin D 1500-2000 IU up to 6000 IU daily
- Normal Vitamin D serum concentration: 75 nmol/L (30 ng/mL)

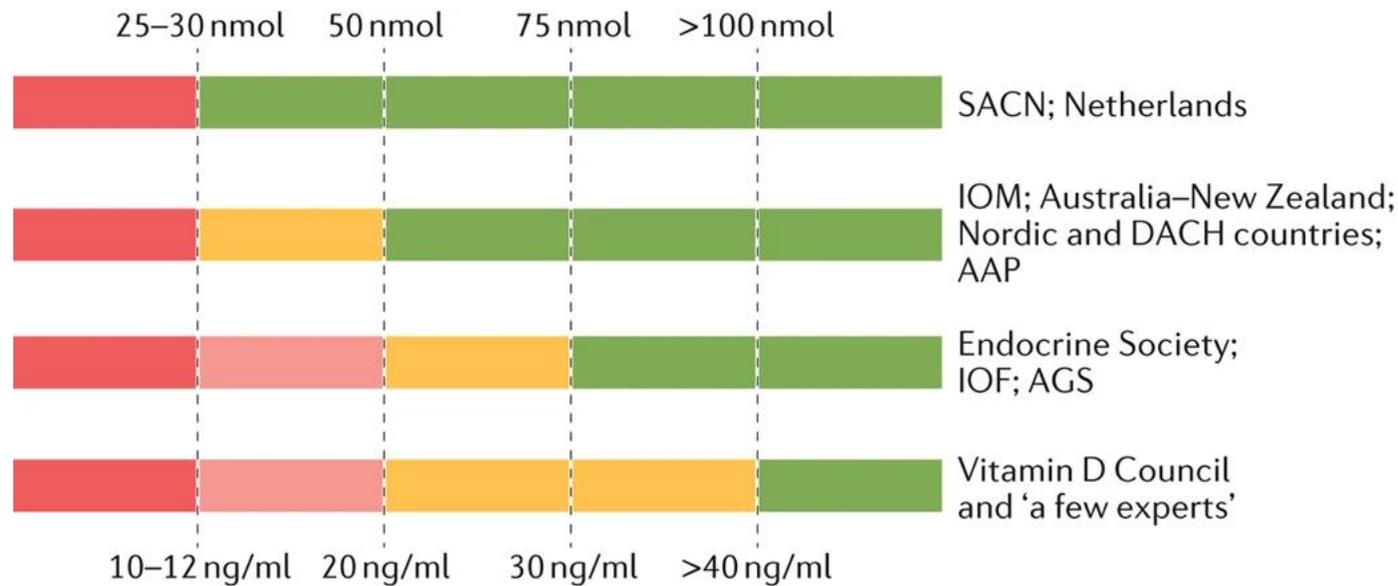


Image from : Bouillon, R. Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol* **13**, 466–479 (2017). <https://doi-org.offcampus.lib.washington.edu/10.1038/nrendo.2017.31>

Results of Several RCTs on the effects of Vitamin D



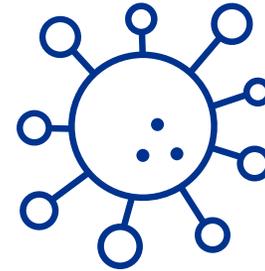
Fracture:

Dose dependent effects on incidence of fractures



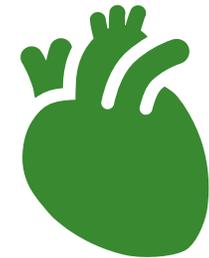
Falls:

No difference of incidence



Cancer:

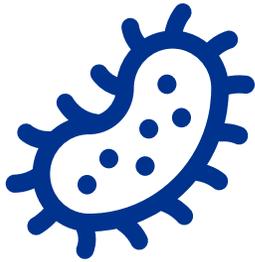
No difference of incidence



Cardiovascular Disease:

No effect on prevention of disease

Results of Several RCTs on the effects of Vitamin D



Respiratory Infections:

No difference of incidence



Tuberculosis:

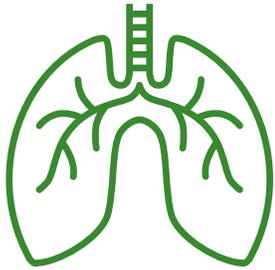
No difference in incidence



COVID-19:

No preventative effects

Results of Several RCTs on the effects of Vitamin D



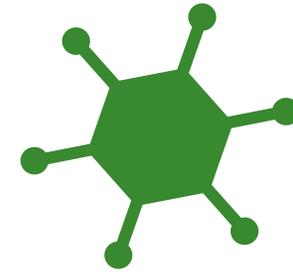
Asthma:

No significant difference in incidence or exacerbations in children or adults



Type II Diabetes Mellitus:

No significant reduction in incidence



Autoimmune Disease:

Reduction of overall incidence of disease in the vitamin D only group (2000 IU daily)

Final Takeaways: Pearls for the Busy Physician

- Routine screening not recommended
- Empiric supplementation for ages 1-18, 75 and up, pregnant women, prediabetics
- Serum goal 50-75 nmol/L (20-30 ng/mL)
- Oral supplementation sufficient in most cases
- Dose recommendation varies, but 800 IU to 2000 IU daily likely appropriate
- Monitoring not necessary in most cases
- Thus far, no solid data to suggest vitamin D supplementation significantly impacts health outcomes BUT studies vary considerably in specific intervention, dosing, assays, and reportable outcomes likely skewing data somewhat

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Thank You!

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