State of the Science:

How Does Vitamin D Impact the Health of Older Adults?

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Interdisciplinary Faculty, Graduate Program in Nutritional Sciences
University of Washington, Seattle

Learning Objectives

Updating the Science: (20-25 mins)

- To provide an updated review of the physiology, disposition, and genomics of vitamin D, and the assessment of its clinical status.
- To compare the clinical pharmacology between ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3).

Interpreting Vitamin D Status in Practice: (10 mins)

- To discuss the current controversy on the definition of vitamin D deficiency and threshold of initiating vitamin D supplementation in older adults.

Bring to the Bedside and Clinic: (25 mins)

- To evaluate the impact on different vitamin D interventions on the major clinical outcomes in older adults

Looking to the Future: (5 mins)

- To overview the major ongoing clinical trials involving vitamin D interventions in older adults.

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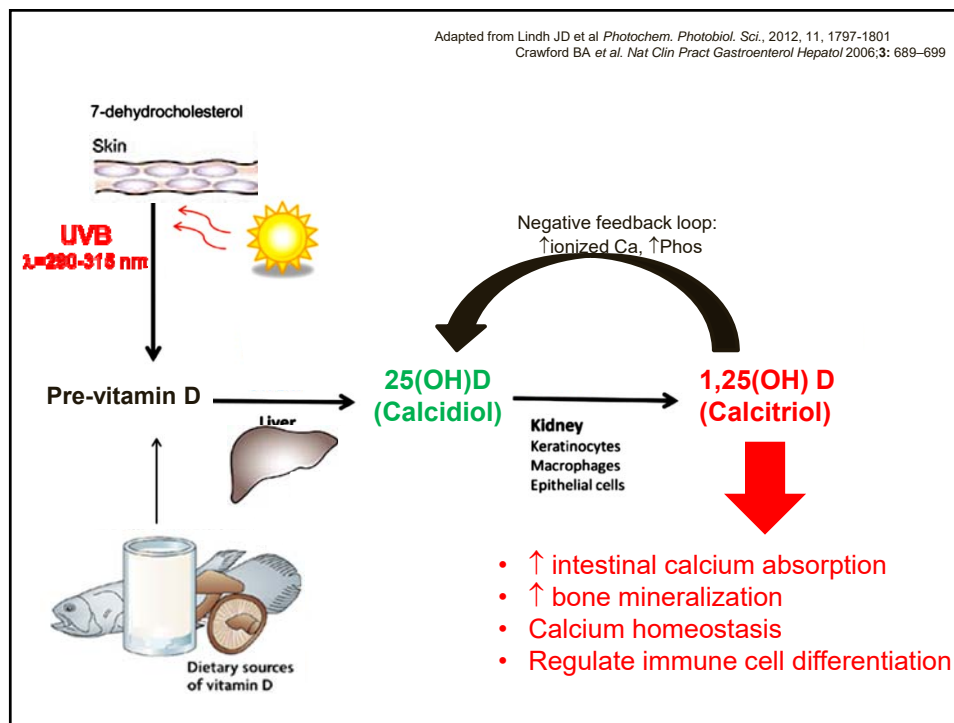**Interpreting Vitamin D Status in Practice: (10 mins)**
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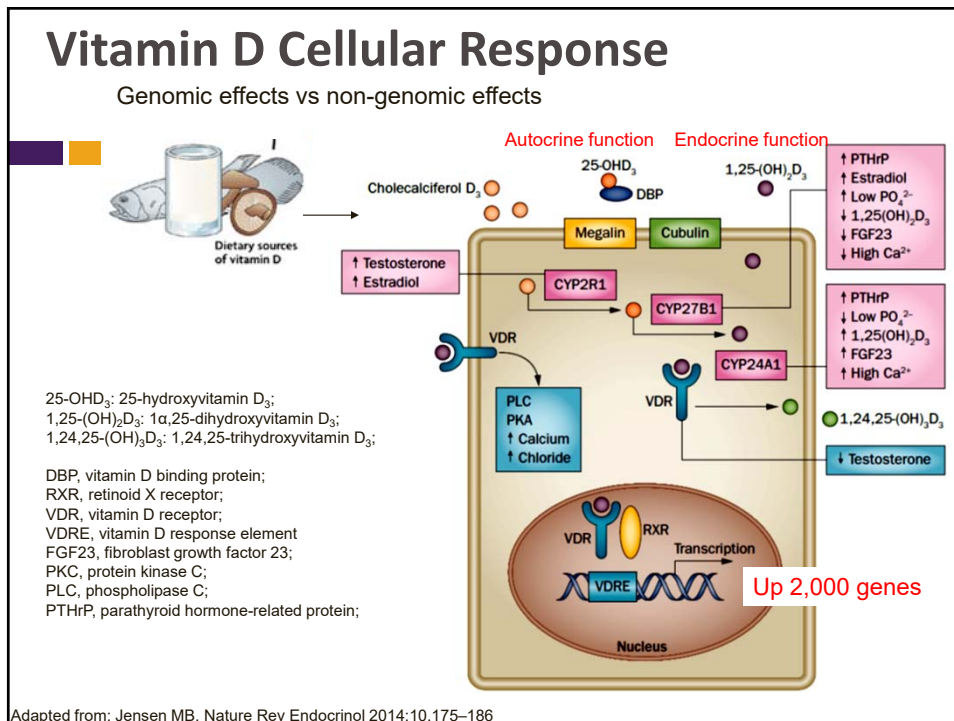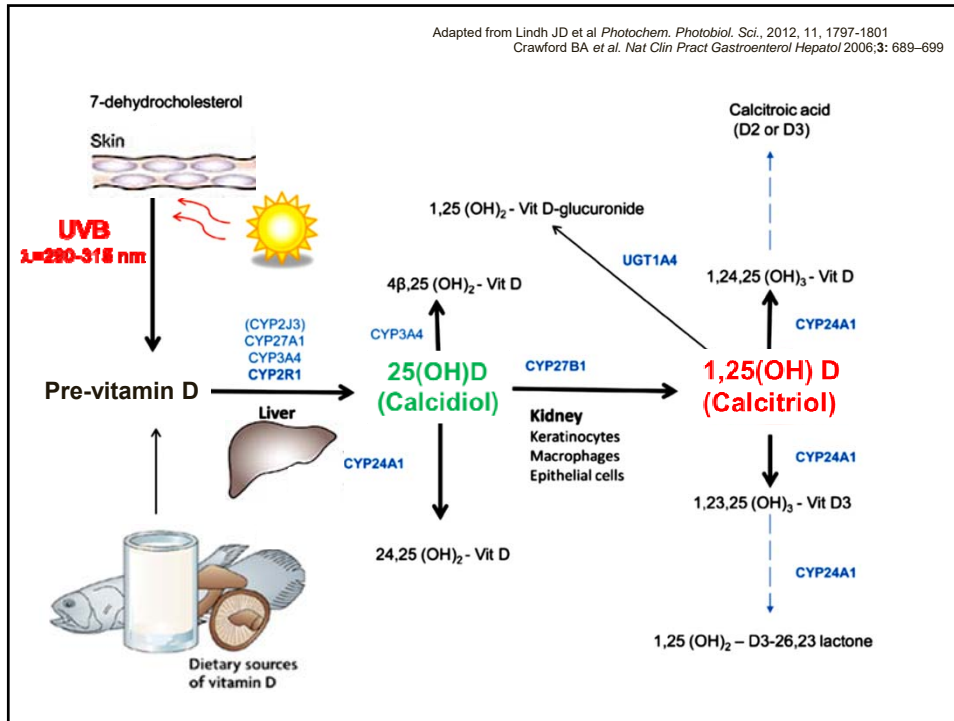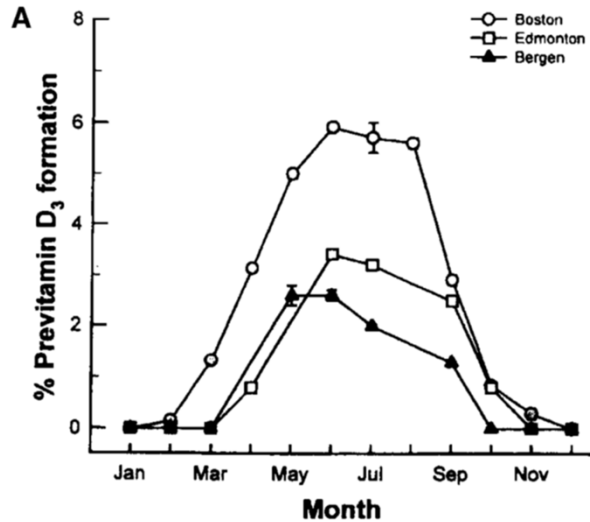
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Adapted from Lindh JD et al *Photochem. Photobiol. Sci.*, 2012, 11, 1797-1801
Crawford BA *et al. Nat Clin Pract Gastroenterol Hepatol* 2006;**3:** 689–699

7-dehydrocholesterol
Skin

UVB
λ=280-315 nm

Pre-vitamin D

Liver

Dietary sources of vitamin D

25(OH)D (Calcidiol)

Kidney
Keratinocytes
Macrophages
Epithelial cells

Negative feedback loop:
↑ionized Ca, ↑Phos

1,25(OH) D (Calcitriol)

- ↑ intestinal calcium absorption
- ↑ bone mineralization
- Calcium homeostasis
- Regulate immune cell differentiation

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Adapted from Lindh JD et al *Photochem. Photobiol. Sci.*, 2012, 11, 1797-1801
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Vitamin D Cellular Response

Genomic effects vs non-genomic effects

Autocrine function   Endocrine function

25-OHD$_3$: 25-hydroxyvitamin D$_3$;
1,25-(OH)$_2$D$_3$: 1α,25-dihydroxyvitamin D$_3$;
1,24,25-(OH)$_3$D$_3$: 1,24,25-trihydroxyvitamin D$_3$;

DBP, vitamin D binding protein;
RXR, retinoid X receptor;
VDR, vitamin D receptor;
VDRE, vitamin D response element
FGF23, fibroblast growth factor 23;
PKC, protein kinase C;
PLC, phospholipase C;
PTHrP, parathyroid hormone-related protein;

Up 2,000 genes

Adapted from: Jensen MB. Nature Rev Endocrinol 2014;10,175–186

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Epigenetics of Vitamin D Disposition

- Genetic polymorphisms affecting a person's response to vitamin D have been identified

- Genes regulating vitamin D metabolism:
  - *DHCR7* (7-dehydrocholesterol reductase)
  - *CYP2R1* (25-hydroxylase) – synthetic pathway
  - *CYP24A1* (24-hydroxylase) – catabolic pathway

- Other polymorphisms
  - *GC* (Vitamin D binding protein)
  - *VDR* (Vitamin D receptor)
  - *CASR* (Calcium-sensing receptor)

Vitamin D – Cutaneous Synthesis

- Takes place between 10 AM and 3PM
- Driven by exposure to UV-B radiation, which is affected by the zenith angle of the sun

- Factors affecting cutaneous vitamin D3 production:
  - skin pigmentation,
  - sunscreen use,
  - time of day,
  - season,
  - latitude & altitude,
  - adiposity
  - air pollution (especially ozone)

- Solar photoproducts inactive to calcium metabolism (tachysterol and lumisterol) are produced with prolonged exposure to solar UV-B radiation

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Influence of Latitude on the Synthesis of Previtamin D3

Holick MF. J Cell Biochem 2003;88: 296–307

Comparison of Cutaneous Vit. D Synthesis After UV-B Exposure between Normal Weight and Obese Individuals

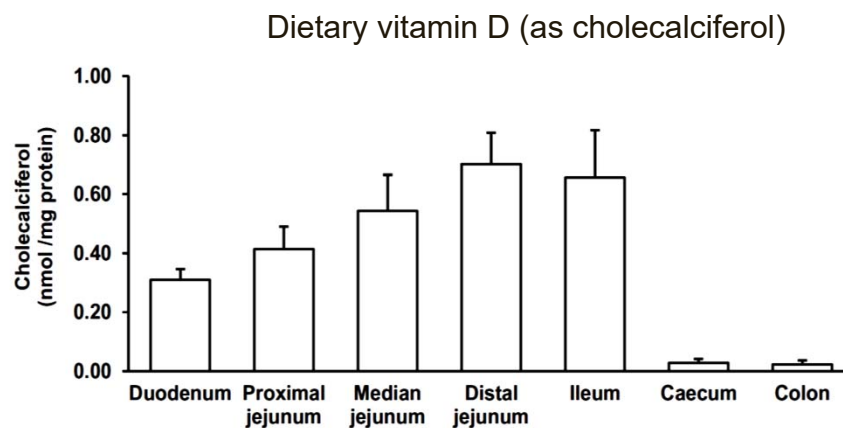Wortsman J, et al, *Am J Clin Nutr* 2000;72:690–3.
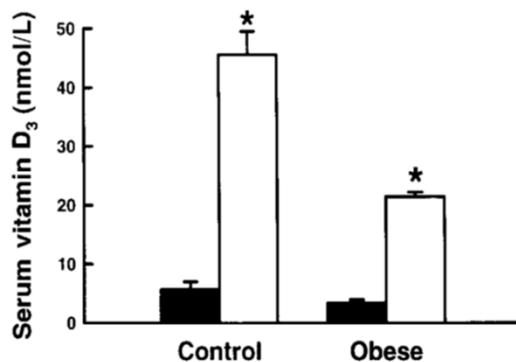
- 13 control subjects and 13 obese subjects; all Caucasians

- Subject received 27 mJ/cm^2 of UV-B radiation after refrain from sun exposure for 24 hrs

- BMI: Control - 22.2 ± 0.04 kg/m^2
        Obese - 38 ± 1.7 kg/m^2

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Vitamin D – Kinetics

- Transporter-mediated intestinal absorption
  - *CD36 (Cluster determinant 36)*
  - *NPC1L1 (Niemann–Pick C1-Like 1)*
  - *SR-BI (Scavenger receptor class B type I)*
  - *Unidentified apical efflux transporter*
- Passive diffusion
- Facilitate by micelle formation and bile salt

- Bioavailability varies : 55 – 98%
- Max absorption between 4 – 10 hrs

Regional enterocytic content of vitamin D after oral administration in mice

Goncalves A, et al, Food Chemistry 2015;172:155–160

Dietary vitamin D (as cholecalciferol)

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25(OH)D - Physiological Characteristics

- 25(OH)D is physiologically active [1/200th of 1,25(OH)D]

- 25(OH)D is VERY HIGHLY protein bound
  - Vitamin D binding protein (VDBP): 80-88%
  - Albumin: 10-15%
  - Free fraction in plasma : 0.03-0.04%

- Free + Albumin bound 25(OH)D is considered the mobile, bioavailable pool for physiological functions

- Highly distributed to adipose tissues

- Likely acute phase response

Distribution of Plasma Vitamin D concentration in Obese Patients Based on Body Mass Index (BMI)

Chan L-N et al. Obes Surg. 2015;25:2321-7

Baseline 25(OH)D Concentration by BMI Groups

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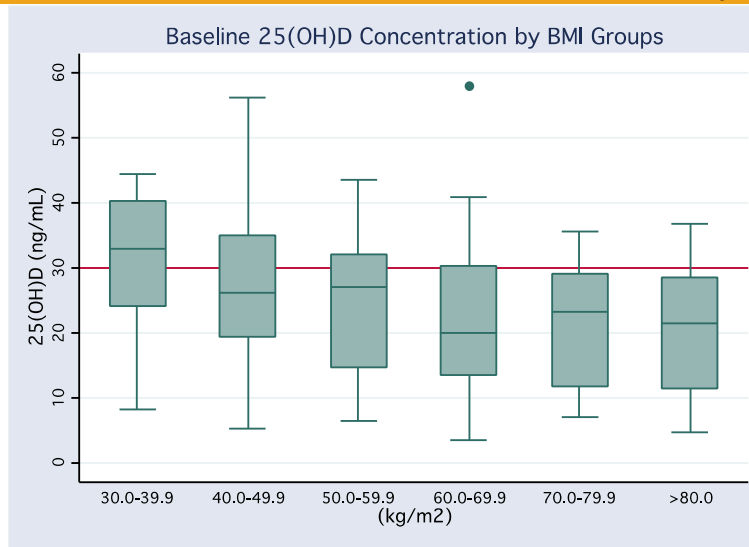
Assessing Clinical Status of Vitamin D

Approaches

- Daily intake

- Plasma vitamin D concentrations
  - Total 25(OH) vit. D (D2 + D3)
  - 25(OH) vitamin D3
  - 1,25(OH) vitamin D

- Other potentially helpful tests

Vitamin D

Dietary sources of vitamin D
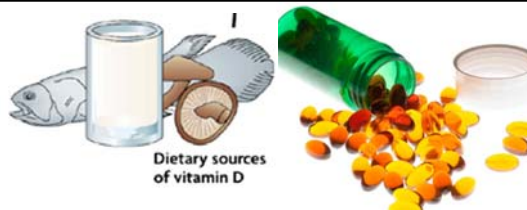
Precursor compounds	**Cholecalciferol (D3)** **Ergocalciferol (D2)**	• Endogenous compounds & diets • Half-life ~ 24 hrs
Prohormone	**25(OH) vitamin D (Calcidiol)**	• Regarded as "body pool" & storage; weak physiological activities • Half-life ~ 15 days
Active hormone	**1,25(OH) vitamin D (Calcitriol)**	• Most active form as a hormone • Half-life 4 to 6 hours

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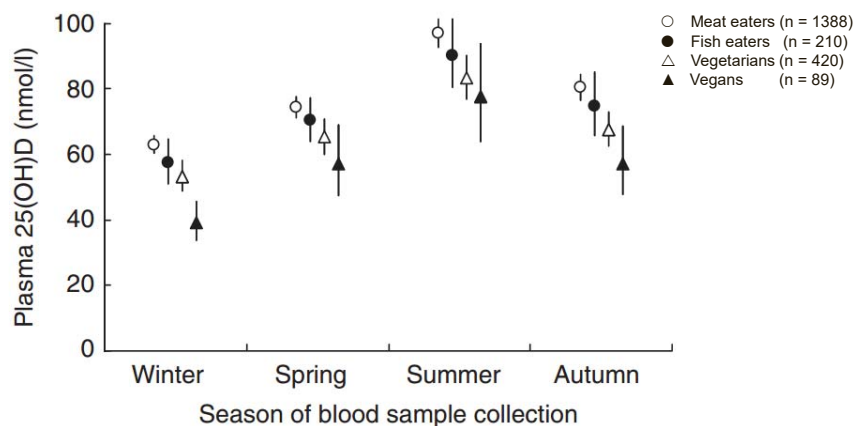# Assessing Clinical Status of Vitamin D
Considerations

- Clinical risk factors

- Timing of sampling
  - Dose
  - Replacement regimen
  - Acute illness or stress response?

- Seasonal variation
  - 1.5 to 4 times more Europeans have below threshold 25(OH)D concentration in winter than summer months
  - Seasonal variation for 25(OH)D in the region:
    Seattle area: 7 ng/mL (or 30%) in Seattle area
    Southwestern Alaska: Up to 11.1 ng/mL (43%)

Cashman KD, et al. Am J Clin Nutr 2016;103:1033–44.
Fohner AE et al. J Nutr. 2016;146:318-25.

Chan L-N et al. Obes Surg. 2015;25:2321-7

Comparison of 25(OH)D concentrations in British cohorts with different dietary habits
[Results from the EPIC-Oxford Study]

Legend:
- ○ Meat eaters (n = 1388)
- ● Fish eaters (n = 210)
- △ Vegetarians (n = 420)
- ▲ Vegans (n = 89)

Y-axis: Plasma 25(OH)D (nmol/l)
X-axis: Season of blood sample collection (Winter, Spring, Summer, Autumn)

Conversion from nmol/L to ng/mL: divided by 2.5
European Prospective Investigation into Cancer and Nutrition (EPIC)

Crowe FL et al, Public Health Nutr. 2011;14(2):340-6.

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25(OH) Vitamin D Assays

- Competitive protein binding assay
- Chemiluminescence
- Immunoassays
  - EIA
  - RIA
- Direct UV detection–based HPLC assays
- GC-MS
- Liquid chromatography–tandem mass spectrometry (LC-MS/MS)

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The Numbers Game: D2 vs D3

- Vitamin D3: Cholecalciferol
  - Endogenous vitamin D
  - Meat-based sources, including fish
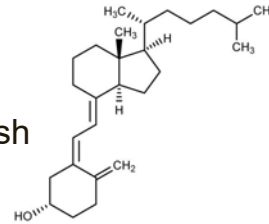
- Vitamin D2: Ergocalciferol
  - Plant-based sources
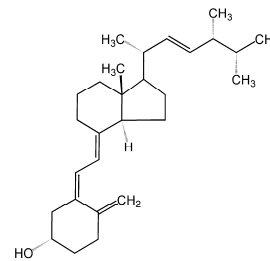
D2 vs D3: Are they Clinical Equivalent?

- D2 has shorter serum half-life
- D3 has higher affinity to CYP27B1 than D2
- D3 has higher binding affinity to VDBP
- CYP24A1 metabolite of D3 [$1,24,25(OH)_3D3$] has higher has affinity to VDR

- Different binding affinity towards VDBP (D2 vs D3) results in different free plasma 25(OH)Dx, which may contribute to different clinical effects
- HOWEVER, because of the regulation (DSHEA), it is almost impossible to determine the difference clinically

Houghton LA, et al. Am J Clin Nutr 2006;84:694-7
Chun RF, et al. Endocrinology 2016;157:3420-30
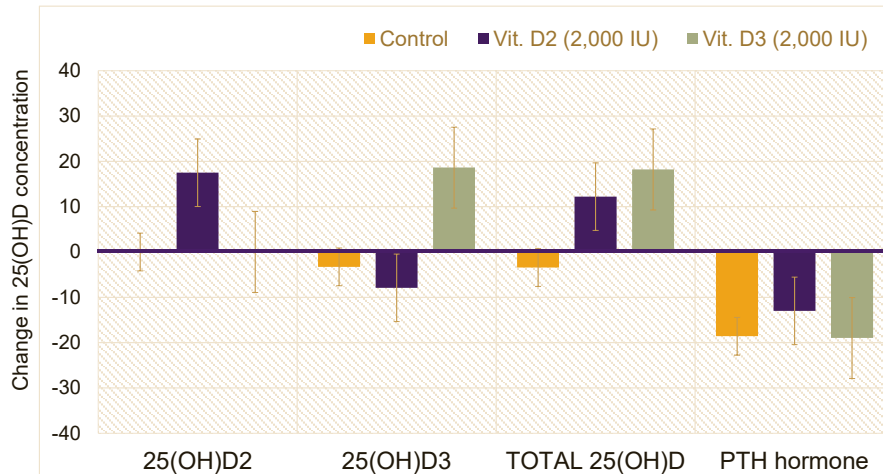
Tripkovic L. Nutr Bul 2013;38:243-8.

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Baseline vitamin D2, vitamin D3 and metabolite ratio in a cohort

Biancuzzo RM et al, J Clin Endocrinol Metab 2013;98: 973–979

	Placebo (n = 8)	Vit. D2 (n = 17)	Vit. D3 (n = 9)
25(OH) D2 (ng/mL)	0.9 ± 2.1	3.8 ± 4.9	0.9 ± 2.7
25(OH) D3 (ng/mL)	17.6 ± 7.8	15.5 ± 6.9	21.3 ± 12.9
1,25(OH) D2 (pg/mL)	0.0 ± 0.0	2.8 ± 6.7	0.0 ± 0.0
1,25(OH) D3 (pg/mL)	30.3 ± 8.1	30.5 ± 9.0	35.4 ± 13.0

Changes in vitamin D profile after supple-mentation with placebo, vit D2, or vit D3.

Lehmann U, et al. J Clin Endocrinol Metab 2013;98: 4339–45

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Summary

- Vitamin D is a hormone with broad endocrine, paracrine, autocrine, and intracrine functions.

- The disposition and physiological actions of vitamin D appear to be altered by many factors, including genetic polymorphism.

- There is also an inter-ethnic variance on the disposition of 25(OH)D.

- It is unclear how aging may alter the endogenous synthesis, intestinal transport and absorption, and metabolism of vitamin D.

- It is also unclear how the action of vitamin D, especially its interaction with VDR, is affected by aging.

- A standardized vitamin D assay is needed.

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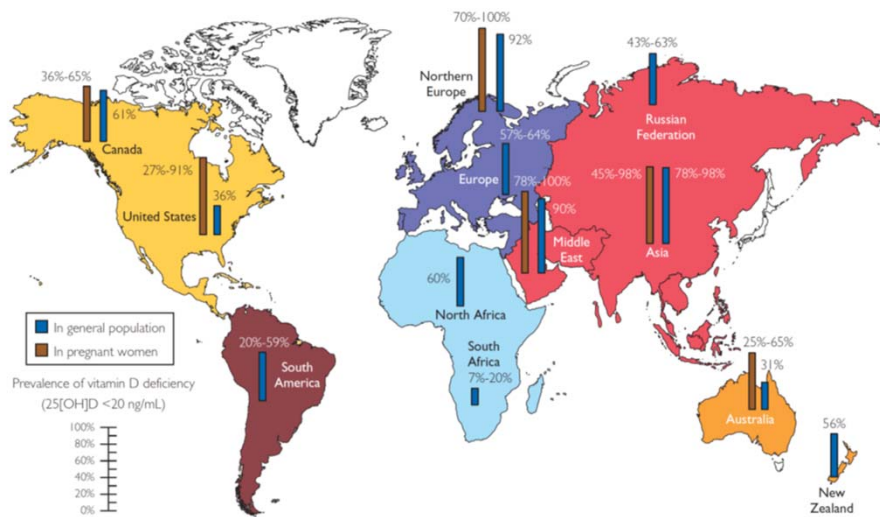
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What is the prevalence of Vitamin D Deficiency in the U.S.?

A. 8.1%
B. 21.0%
C. 41.6%
D. 82.1%

Reported incidence of vitamin D deficiency defined as 25(OH)D level below 20 ng/mL

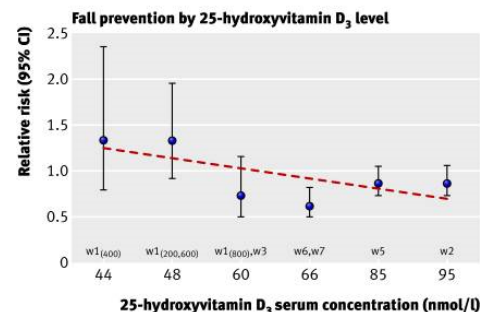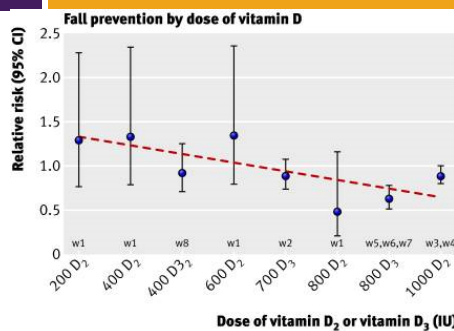Hossein-nezhad A & Holick MF. Mayo Clin Proc. 2013;88(7):720-755

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Clinical Debate: Interpretation of Vitamin D Concentration

25-(OH)D Level Cutoff	Opinions of Expert and Professional Bodies About Cutoff Levels	Summary of Previous Research on the Associations Between 25-(OH)D Levels and Risk for Health Outcomes
< 20 ng/mL	Widely used by researchers and available guidelines as indicative of deficiency	Levels ≥50 nmol/L (≥20 ng/mL) have been associated with decreased risk for fractures, CVD, CRC, diabetes, depressed mood, cognitive decline, and death
20 – 30 ng/mL	Debate about whether these levels represent deficiency	Levels >60 nmol/L (>24 ng/mL) associated with decreased risk for CVD. Levels >75 nmol/L (>30 ng/mL) associated with decreased risk for death and CRC. Data conflict about whether levels >75 nmol/L (>30 ng/mL) are associated with decreased risk for fractures
30 – 50 ng/mL	General agreement that these levels do not represent deficiency; however, some recommend targeting 25-(OH)D levels to this range because results of 25-(OH)D testing vary	Levels between 87 and 100 nmol/L (35 to 40 ng/mL) may be associated with decreased for death and CRC
50 – 200 ng/mL	Debate about whether these levels are associated with adverse health outcomes	Possible U-shaped association between vitamin D levels and risk for death and pancreatic cancer

# Summation of fall prevention by dose and achieved 25(OH)D concentrations

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Calcium absorption fraction plotted as a function of serum 25(OH)D concentration

The total fraction of calcium absorption from the intestine appears to reach plateau when serum 25(OH)D approaches 80 nmol/L (~ 30 ng/mL)
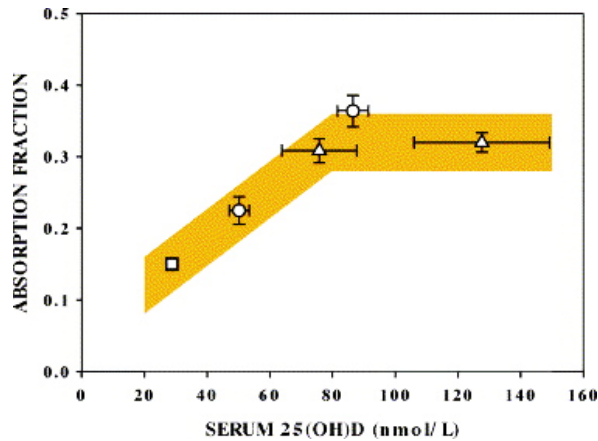
Data interpreted based on 3 studies:
- Heaney RP et al, J Am Coll Nutr.,(2003)
- Barger-Lux & Heaney J Clin Endocrinol Metab (2002)
- Bischoff HA et al, J Bone Miner Res (2003)

Distribution of serum 25-hydroxyvitamin D levels by racial/ethnic group in the US population aged 13 years and older, and in dark-skinned, traditionally living peoples in equatorial Africa
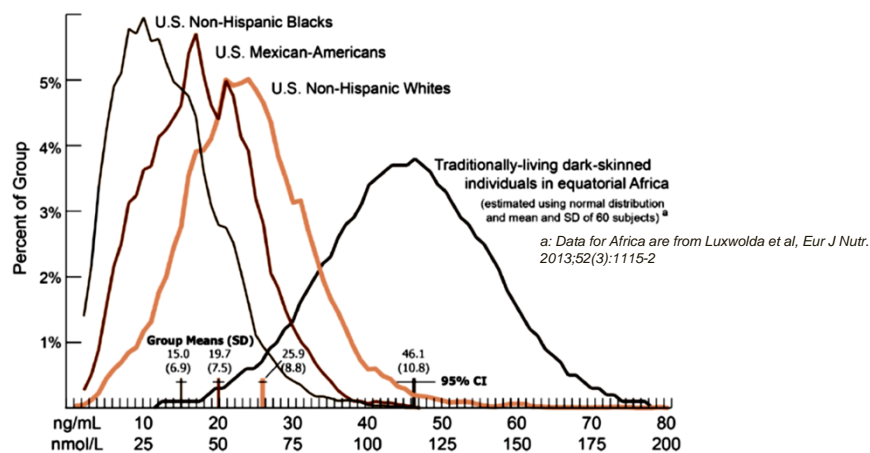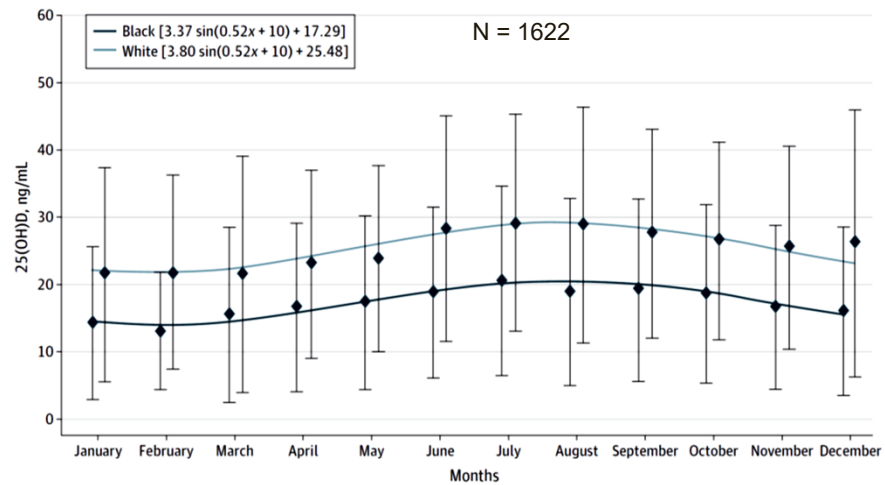
Distributions are smoothed by averaging each set of three adjacent data points. The area under each curve represents 100% of that group. Means, standard deviations (SD), and confidence intervals (CI) are shown near the X axis.

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Inter-ethnic Variation of Plasma 25(OH)D Concentration Throughout a Calendar Year

Legend:
- Black [$3.37 \sin(0.52x + 10) + 17.29$]
- White [$3.80 \sin(0.52x + 10) + 25.48$]

N = 1622

Y-axis: 25(OH)D, ng/mL

X-axis (Months): January, February, March, April, May, June, July, August, September, October, November, December

Subjects were from Forsyth County, North Carolina, and Jackson, Mississippi

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Summary

- The prevalence of vitamin D deficiency varies depending on the cut off for 25(OH)D. The cutoff value indicating clinical deficiency may also be specific to race or ethnicity.

- The benefits of routine surveillance 25(OH)D monitoring in lower risk older adults require further investigation.

- The threshold plasma 25(OH)D concentration that warrants routine vitamin D supplementation in older adults has not been determined.

- Despite having lower average 25(OH)D concentration in African Americans, it is unclear whether it consistently translates to increased risks for metabolic bone disease.

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Disease States of Focused Discussion

- Bone health
  - Fracture
  - Fall prevention
  - Functional impairment

- Cardiovascular
  - Stroke/ CVA
  - CVD, CHD

- Others
  - Cancer
  - Mortality

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Does Vitamin D **Prevent Fractures** in post-menopausal women and older men?

Avenell A, et al, Cochrane Database Syst Rev. 2014;(4):CD000227

- Cochrane Review on RCTs or quasi-RCTs
- Interventions:
  - Vitamin D ± calcium *vs* placebo
  - Community, nursing home, and hospital settings

- Data captured:
  - 53 trials (total n = 91,791)
  - Vitamin D doses – 400 IU/day to 500,000 IU x1

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Avenell A, et al, Cochrane Database Syst Rev. 2014;(4):CD000227

Treatment	Outcomes	Risk Ratio (vs placebo)	95% CI
Vitamin D alone	Hip and new fractures	1.12	0.98 to 1.29
Vitamin D + calcium	Hip fracture	0.84	0.74 to 0.96
Vitamin D + calcium	Non-vertebral fractures	0.95	0.90 to 0.99

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Exercise and Vitamin D in Fall Prevention Among Older Women – 2-year RCT

- To determine the effectiveness of exercise training and vitamin D supplementation in reducing falls

- Settings: Finland, 409 home-dwelling women
  - 70 – 80 years old

- Interventions:
  - Placebo
  - Placebo with exercise
  - Vitamin D 800 IU/day without exercise
  - Vitamin D 800 IU/day + exercise

- Vitamin D assay – fasting samples; EIA

## Hazard Ratios (95%CIs) for Fallers, Injured Fallers, and Multiple Fallers

Category	Placebo No exercise	Vitamin D No exercise	Placebo + Exercise	Vitamin D + Exercise
All fallers	HR = 1.00	HR = 0.77 (0.54 - 1.11)	HR = 0.93 (0.66 - 1.31)	HR = 0.91 (0.64 - 1.28)
Injured fallers	1.00	0.89 (0.47 - 1.69)	0.47 (0.23 - 0.99)	0.38 (0.17 - 0.83)
Multiple fallers	1.00	1.07 (0.71 - 1.62)	1.14 (0.76 - 1.71)	1.14 (0.77 - 1.71)

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Other Findings

- Mean baseline calcium intake: 1040 – 1125 mg/day

- Femoral neck BMD ↓ in all groups, but greatest in the placebo without exercise group
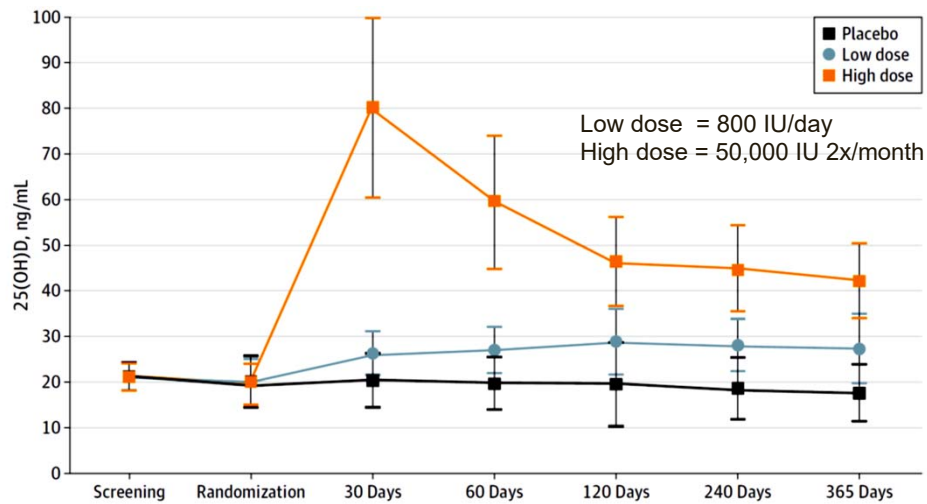- Lumbar spine BMD did not change significantly in any group

Vitamin D Status
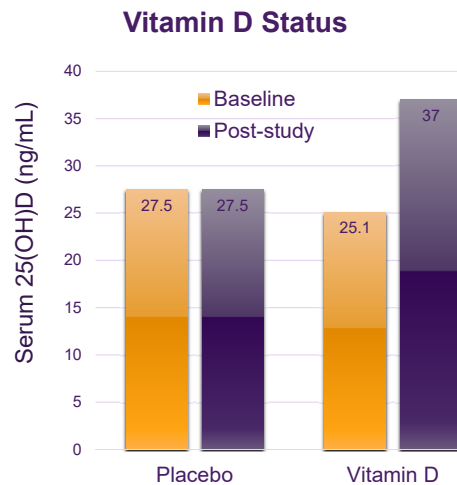
Does Treating Vitamin D Insufficiency Improves Calcium Absorption and Bone Density?

- Goal:
  - Determine if maintaining 25(OH)D levels > 30 ng/mL for 1 year would increase total fractional calcium absorption (TFCA) and BMD more than low-dose vitamin D3 or placebo

- Interventions:
  - Enrollment criteria- 25(OH)D between 14 and 27 ng/mL
  - Loading dose 50,000 IU D3 daily x15 days; then
    - 800 IU/day OR
    - 50,000 IU q 15 days (~ 3,333 IU/day)

- Assessments:
  - BMD, Muscle mass
  - Dual stable calcium isotope methods for TFCA

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Longitudinal Changes in Serum 25(OH)D Concentrations by Treatment Assignment

Low dose = 800 IU/day
High dose = 50,000 IU 2x/month

Vitamin D Supplementation and Outcomes

	Placebo	800 IU/day	50,000 IU 2x/month
TFCA Changes	↓ 1.3%	↓ 2%	↑ 1%

- No differences between treatment arms:
  - The absolute or annualized percentage change in lumbar spine, mean total hip, or total-body BMD;
  - Trabecular bone score
  - Muscle mass,
  - Number of falls, or number of fallers
  - C-telopeptide or bone-specific alkaline phosphatase
  - 1-year change in Health Assessment
  - Questionnaire score or Physical Activity for the Elderly score

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Annualized Percent Change in Bone Mineral Density by Treatment Assignment

Hansen KE, et al, JAMA Intern Med. 2015;175:1612-1621.

Change in Total-Body Bone Mineral Density — Overall P = .93, Adjusted P = .93. (Placebo −0.5, Low dose −0.5, High dose −0.4)

Change In Total-Hip Bone Mineral Density — Overall P = .06, Adjusted P = .12. Low dose = 800 IU/day; High dose = 50,000 IU 2x/month. (Placebo −0.9, Low dose −0.5, High dose −0.2)
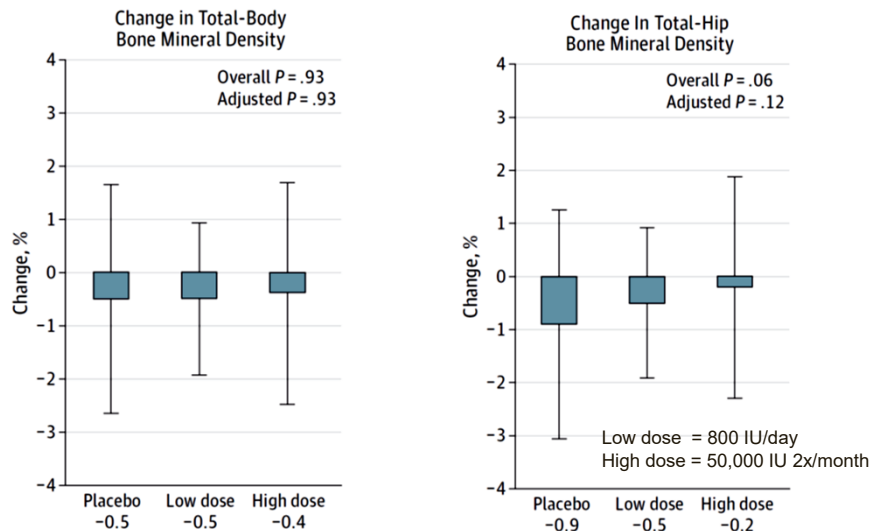

Can High Dose Vitamin D Prevent Functional Decline in Older Adults?

Bischoff-Ferrari HA, et al, JAMA Intern Med. 2016;176:175-183

- Goal:
  - To determine if high dose monthly vitamin D prevents functional decline in home-dwelling adults > 70 years old

- Interventions:
  - 24,000 IU vitamin D3 monthly (~800 IU/day)
  - 60,000 IU vitamin D3 monthly (~2,000 IU/day)
  - 24,000 IU vitamin D3 + 300 µg 25(OH)D

- Assessments:
  - Short Physical Performance Battery (SPPB score)
  - Physical examination
  - Appendicular muscle mass (per DEXA)

Longitudinal Changes in 25(OH)D Concentration by Treatment Arms

Bischoff-Ferrari HA, et al, JAMA Intern Med. 2016;176:175-183
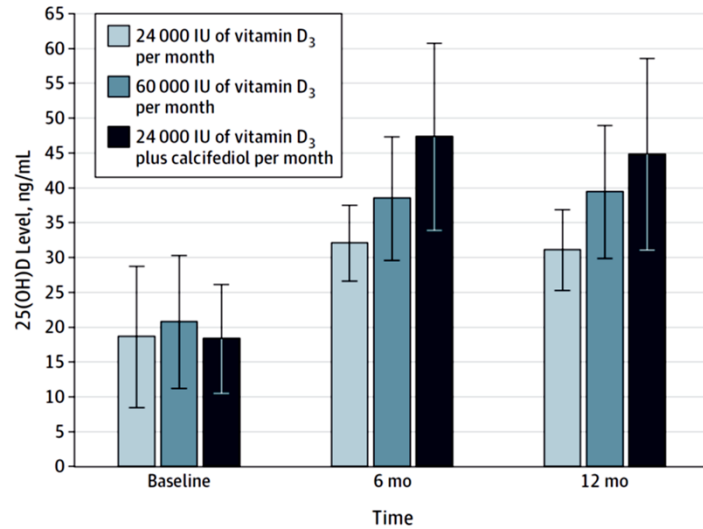
Clinical Outcomes

Bischoff-Ferrari HA, et al, JAMA Intern Med. 2016;176:175-183

- SPPB score did not differ significantly among the treatment groups (P = .26)
- Functional and muscle mass end points were qualitatively similar.

Falls Assessment	24,000 IU	60,000 IU	24,000 IU + 25(OH)D	P value
Incidence of falls	47.9%	66.9%	66.1%	0.048
Adjust mean # of falls	0.94	1.47	1.24	0.09

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Vitamin D Supplementation Among Patients With Symptomatic Knee Osteoarthritis (OA)

- Background:
  - Association between Vitamin D supplementation and benefits for knee OA is based on observational trials

- Goal:
  - An RCT to evaluate the effects of 2 years of vitamin D supplementation on knee pain and tibial cartilage volume

- Enrollment:
  - Based line 25(OH)D between < 60 nmol/L (24 ng/mL)
  - Treatment arm: 50,000 IU vitamin D_3 monthly x 24 months
  - Vitamin D assay: chemiluminescent immunoassays

Baseline Characteristics

	Vitamin D (n = 209)	Placebo (n = 204)
Study site		
Hobart, No. (%)	129 (61)	132 (64)
Melbourne, No. (%)	80 (38)	72 (35)
Age, mean (SD), y	63.5 (6.9)	62.9 (7.2)
Women, No. (%)	106 (50)	102 (50)
Body mass index, mean (SD)[a]	29.6 (5.4)	29.6 (4.6)
Serum 25-hydroxyvitamin D, mean (SD), nmol/L	43.7 (11.8)	43.8 (12.7)
Radiographic osteoarthritis, No. (%)	163 (96)	157 (96)
Total WOMAC score (0-2400), mean (SD)[b]	687.3 (426.3)	664.7 (390.8)
Pain (0-500)	137.9 (88.8)	134.7 (83.4)
Stiffness (0-200)	61.5 (41.5)	61.7 (40.1)
Function (0-1700)	487.9 (318.1)	467.6 (292.8)

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Bone Health and Fracture:
Vitamin D 50,000 IU monthly in OA

Jin X et al, JAMA. 2016;315(10):1005-1013

Western Ontario and McMaster University Index of osteoarthritis (WOMAC) score
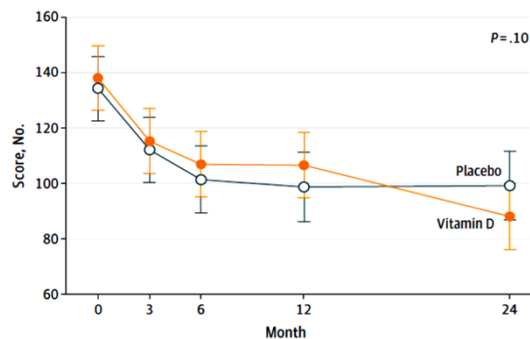
- Assess during walking, using stairs, in bed, sitting or lying, and standing

- Mean changes at 24 months:
  - -49.9 for placebo,
  - -35.1 for vitamin D (p = 0.10)

No. of participants				
Vitamin D	208	196	199	195	183
Placebo	202	193	183	163	168

Vitamin D and Cardiovascular Outcomes

- Hypertension (60.1 ± 11.3 year old)
  - 2,800 IU vitamin D3 QD x 8 weeks had no effect on SBP, DBP, Renin, BNP, but mild increase in serum triglycerides

- Heart failure (65.9 ± 10.4 years old)
  - NYHA Class II-IV
  - Vitamin D3 50,000 IU weekly for 6 months was not associated with improved peak VO_2, 6MW, and muscle strength
  - Serum 25OHD increased by 42.3 ± 16.4 ng/mL

- CVD, CHD, stroke risks (34.7% > 65 years old)
  - Observational trial showed that 25(OH)D < 20 ng/mL is associated with higher risk

Pilz S, et al. Hypertension. 2015;65:1195-1201.
Perna L, et al. J Clin Endocrinol Metab 2013;98:4908-15.

Boxer RS, et alJACC Heart Fail. 2013; 1(1): 84–90,

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Vitamin D and Stroke

- Acute ischemic stroke (66.2 ± 12.9 year old)
  - 25(OH)D > 30 ng/mL is associated with better functional outcomes (modified Rankin scale (mRS) score of ≥ 3,) at 3 months

- Subclinical CVD per longitudinal MRI
  - 55-72 year-old with no previous clinical stroke
  - Baseline serum 25(OH)D was not associated with white matter hyperintensities on MRI or prevalent subclinical infarcts as seen on serial cerebral MRIs obtained approximately 10 years apart.

Micho ED, et al. JAMA Neurol. 2014;71(7):863-871.
Park K-Y, et al. Cerebrovasc Dis 2015;40:73–80.

Woman Health Initiative – Extension

Cauley JA, et al. J Women Health 2013;22:915-29

- Incidence similar between vit.D supplemented group (1,000 IU/day) vs placebo based on WHI data (at 5 year after end of intervention) for:
  - Colorectal cancer
  - Invasive breast cancer
  - CVD
  - All-cause mortality

- In *post hoc* analyses, the incidence of vertebral fractures, HR= 0.87 (95% CI: 0.76, 0.98) and in situ breast cancers, HR = 0.82 (95% CI: 0.68, 0.99) were lower among women randomized to supplementation.

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Summary

- Evidence supporting the clinical benefits of maintaining plasma 25(OH)D concentration > 30 ng/mL in geriatric population is weak.

- The health benefits of routine vitamin D supplementation (> 800 IU/day) in older adults remains unclear.

- Benefits in bone health was observed with concurrent vitamin D and calcium supplementation, but not vitamin D alone.

- Exercise appears to offer stronger impact on bone health and fall prevention than vitamin D.

- Oral dose of > 50,000 IU may be associated with increase fall risk in older adults.

Learning Objectives

Updating the Science: (20-25 mins)
- To provide an updated review of the physiology, disposition, and genomics of vitamin D, and the assessment of its clinical status.
- To compare the clinical pharmacology between ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3).

Interpreting Vitamin D Status in Practice: (10 mins)
- To discuss the current controversy on the definition of vitamin D deficiency and threshold of initiating vitamin D supplementation in older adults.

Bring to the Bedside and Clinic: (25 mins)
- To evaluate the impact on different vitamin D interventions on the major clinical outcomes in older adults

Looking to the Future: (5 mins)
- To overview the major ongoing clinical trials involving vitamin D interventions in older adults.

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Major Ongoing Clinical Trials -1

- **BEST-D** (Biochemical Efficacy and Safety Trial of Vitamin D) University of Oxford
  - Study aim: To determine the daily dose of vitamin D needed in older people to maintain blood levels of vitamin D similar to those seen in healthy younger people at the end of the summer months.

- **VDOP** (Vitamin D supplementation in older people) University of Cambridge.
  - Study aim: To examine the relationship between vitamin D supplementation at a range of doses (12,000 IU/month, 24,000 IU/month or 48,000 IU/month, equivalent to 400 IU/day, 800 IU/day and 1,600 IU/day, respectively) and the change in bone mineral density (BMD) in older people living in private households in the North East of England

- **VITAL** (Vitamin D and Omega-3 Trial) Harvard Medical School.
  - Study aim: To determine whether taking daily dietary supplements of vitamin D3 (2000 IU) or omega-3 fatty acids (Omacor® fish oil, 1 gram) reduces the risk for developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses.

Major Ongoing Clinical Trials - 2

- **D-Health**: A trial of vitamin D for prevention of mortality and cancer in older Australian adults –The University of Queensland, Australia
  - Study aim: To determine whether increasing the mean 25(OH)D concentration in the general population through widespread supplementation would result in improved health outcomes.

- **FIND** (Finnish Vitamin D Trial) The University of Eastern Finland.
  - Study aim: To determine the benefits and risks of vitamin D3 (1600 IU/day, 3200 IU/day, or placebo) in the primary prevention of cardiovascular (CVD) and cancer among 18000 men 60 years or older and women 65 years or older.

- **VIDAL**- Vitamin D and Longevity Trial; The London School of Hygiene & Tropical Medicine.
  - Study aim: To determine if taking vitamin D (100,000 IU/month or placebo) can reduce mortality and morbidity among older adults the general population between the ages of 64-85.

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MOVING FORWARD...

- More studies that enroll adults > 80 years of age are needed

- The value of targeted plasma 25(OH)D concentration vs standard oral intake at 800 IU/day should be compared

- Studies should be designed to compare the outcomes based on different targeted 25(OH)D concentration

- The impact of genetic polymorphism of vitamin D disposition on the dosing regimen and clinical outcomes should be investigated

- The reasons behind the increased fall risks with "mega-doses" of vitamin D should be explored.

APPENDIX 1:
Recommendation of vitamin D intake

Institute of Medicine (IOM) 2010 Report

Age group	EAR (IU/day)	RDA (IU/day)	Upper limit
1-year-old to 70	400	600	2,500 for 1-3 yo 3,000 for 4-8 yo 4,000 others
> 70-year-old	400	800	4,000
Pregnant/ lactating women	400	600	4,000

www.iom.edu/vitamind

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APPENDIX 2a:
Vitamin D replacement "Simple Rule"

Cannell JJ et al. Expert Opin. Pharmacother. (2008) 9(1):107-118

- Every 1,000 IU/day of D2 or D3 given orally would raise serum 25(OH)D by 10 ng/mL over a period of 3 to 4 months.

- An "unofficial summary" of the dose-response curve based on many small trials.

- A simplified approach and covariances such as sun exposure, dietary effect, GI symptoms, drug/nutrient interactions are not taken into consideration.

APPENDIX 2b:
Vitamin D replacement "The Dutch Sliding Scale"

van Groningen et al. Eur J Endocrinol 2010;162:805-11

- Aweight-base equation based on the plasma 25(OH)D concentration:

  Total Vit. D dose (in IU) = 40 x (75 - current 25(OH)D level) x wt(kg).

- Note that the 25(OH)D level is measured in SI unit (nmol/L). So you need to convert our common unit from ng/mL to nmol/L by multiplying by 2.5.
- You can also rewrite the question to:

Total vitamin D Dose = 40 x (75 - (current 25(OH)D (ng/mL) x 2.5)) x wt (kg).

- Replace this amount with a weekly dose no more than 25,000 IU.
- The equation assumes that the dose-response relationship is linear, which is not true with increased fat mass. So, this method loses sensitivity in obese patients.

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