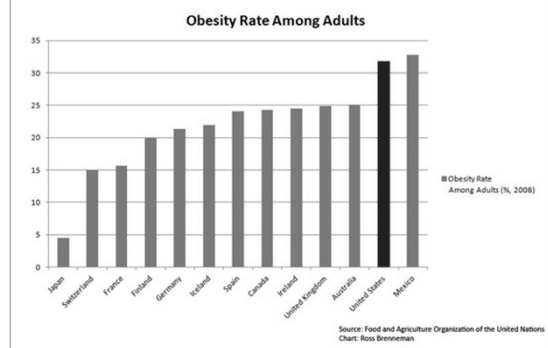
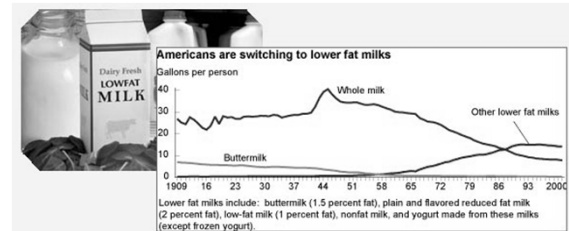


Case of the A Family

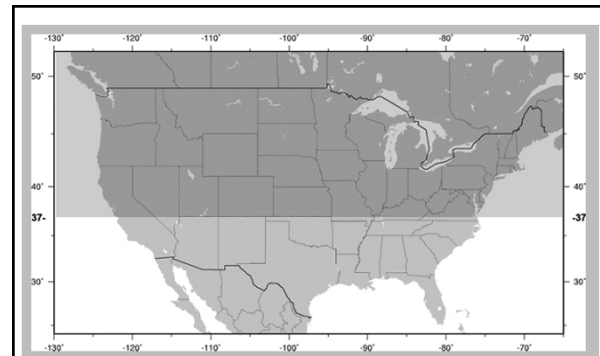
- Osama A. 51 y/o male from Sudan; 4 children

- Oldest son Ahmed, tears ACL Soccer 12 ng/mL
- Youngest Son, Osman, fx Ulna cross St 9 ng/mL
- Second Son, Ayman, Fx Tib/Fib Soccer 15 ng/mL
- Daughter, Amal, Fx wrist PE @ school* Undetect
- Osama (Dad) Fx wrist tripping on curb 12 ng/mL

Theories: Reduced Milk Consumption



- Mexico: 32.8% vs USA: 31.8%
- 2500-3060 calories per day, 30% more than in 1962



Why Is Everyone Vitamin D Deficient?

- **Theories:**
- ↓ Milk Consumption
- Obesity
- Sun Exposure

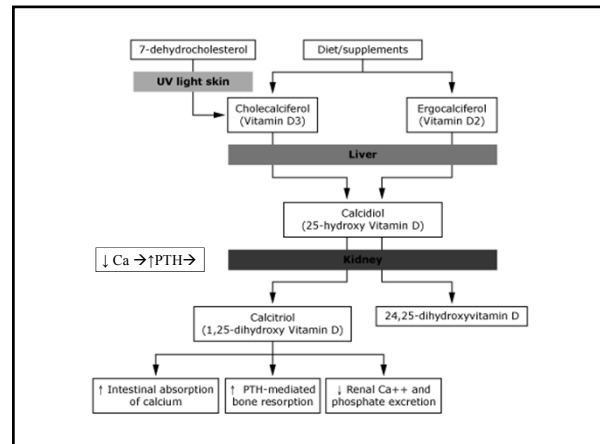
- **PPI Use:**
- PPI → ↑ pH → ↓ Ca Absorption → ↑ PTH

Physiology of Vitamin D

- NOT a Vitamin; but rather a *hormone*
- Fat Soluble
- Vitamin D “job”: to maintain Serum Calcium
- Obtained from Diet or Sun Exposure
- UV B converts 7 dehydrocholesterol to D3
- Dietary Vitamin D3 & D2 thru. Intestine
- Both bound to Vit D3 binding protein.

Glossary

- **Vitamin D** —Calciferol; group of chemicals related to Vitamin D
- **Cholecalciferol (D3)** In animal foods and supplements
- **Ergocalciferol (D2)** from Plant sources
- **Calcidiol (25 Hydroxy D3)** *** Serum Level
- **Calcitriol (1, 25 Hydroxy D3)** Active Form



Vit D Recommendations

- | | USDA 1999 | IOM 2011 |
|---|---------------|-----------------|
| ■ 19-50 years | 200 IU/Day | 600 IU |
| ■ 51-70 years | 400 IU/Day | 600 IU |
| ■ 71- up | 600 IU/Day | 800 IU |
| ■ Pregnancy | (PNV 400) | 600 IU |
| ■ Infants (Breastfed) | 200 IU/Day | 400 IU** |
| ■ Children (< 16 oz milk) | 200 IU/Day | 600 IU |
| ■ http://dietary-supplements.info.nih.gov/factsheets/vitaminD.asp#h3 | | |
| ■ USPSTF: 65 Years | >= 800 IU/Day | |

2011: Newborns 400 IU/Day

- American Academy of Pediatrics updated their 2003 recommendation
- **“all Breastfed children should be give 400 IU/day *within a few days of birth.*”**
- This is a doubling of their previous recommendation.

www.cdc.gov/breastfeeding/recommendations/vitamin_d.htm

Global Consensus Recommendations on Prevention and Management of Nutritional Rickets

- Universally supplement all infants with vitamin D from birth to 12 months of age, independent of their mode of feeding.
- Beyond 12 months, supplement all groups at risk and pregnant women.
- *J Clin Endocrinol Metab.* 2016 Feb; 101(2): 394–415.

Dietary Sources

Table 1: Selected food sources of vitamin D [10-12]

Food	International Units (IU) per serving	Percent DV*
Cod liver oil, 1 Tablespoon	1,360	340
Salmon, cooked, 3oz ounces	360	90
Mackerel, cooked, 3oz ounces	345	90
Tuna fish, canned in oil, 3 ounces	200	50
Trout, broiled, 3oz ounces	250	70
Milk, nonfat, reduced fat, and whole, vitamin D fortified, 1 cup	98	25
Margarine, fortified, 1 Tablespoon	60	15
Pudding, prepared from mix and made with vitamin D fortified milk, 1/2 cup	50	10
Ready-to-eat cereal: fortified with 10% of the DV for vitamin D, 1/2 cup to 1 cup servings (servings vary according to the brand)	40	10
Egg, 1 whole (vitamin D is found in egg yolk)	20	6
Liver, beef, cooked, 3oz ounces	15	4
Cheese, Swiss, 1 ounce	12	4

*DV = Daily Value. DVs are reference numbers developed by the Food and Drug Administration (FDA) to help consumers determine if a food contains a lot or a little of a specific nutrient. The DV for vitamin D is 400 IU (10 µg) for adults. Most food labels do not list vitamin D content unless a food has been fortified with this nutrient. The percent DV (DV%) listed on the label.

Centrum Silver 500 IU

*Who is at RISK for VitD D

- ?Women at Menopause
- Dark Skinned Individuals
- Veiled
- Seniors/Nursing Home
- Multiple Fractures
- Pregnant/Lactating/PMS
- Malabsorption
- Seizure Meds

USPSTF 2014

Only Test those "At Risk"

Annals of Internal Medicine

REVIEW

Screening for Vitamin D Deficiency: A Systematic Review for the U.S. Preventive Services Task Force

Eric S. LeBlanc, MD, MPH; Bernadette Zakher, MBS; Monica O'Gara, BA; Miranda Pappas, MA; and Roger Chou, MD

Background: Vitamin D deficiency has been associated with adverse health outcomes.

Purpose: To systematically review benefits and harms of vitamin D screening in asymptomatic adults.

Data Sources: Ovid MEDLINE (through the third week of August 2014), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews.

Study Selection: Randomized trials of screening for and treatment of vitamin D deficiency and case-control studies nested within the Women's Health Initiative.

Data Extractions: One investigator abstracted data, a second reviewed data for accuracy, and 2 investigators independently assessed study quality using predefined criteria.

Data Synthesis: No study examined the effects of vitamin D screening versus no screening on clinical outcomes. Vitamin D treatment was associated with decreased mortality versus placebo or no treatment (11 studies; risk ratio [RR], 0.83 [95% CI, 0.70 to 0.99]), although benefits were no longer seen after trials of institutionalized persons were excluded (8 studies; RR, 0.93

[CI, 0.73 to 1.18]). Vitamin D treatment was associated with possible decreased risk for having at least 1 fall (5 studies; RR, 0.84 [CI, 0.69 to 1.02]) and falls per person (5 studies; incidence rate ratio, 0.66 [CI, 0.50 to 0.88]) but not fractures (5 studies; RR, 0.98 [CI, 0.82 to 1.14]). Vitamin D treatment was not associated with a statistically significant increased risk for serious adverse events (RR, 1.17 [CI, 0.74 to 1.84]).

Limitations: Variability across studies in 25-hydroxyvitamin D assays and baseline levels, treatment doses, use of calcium, and duration of follow-up.

Conclusion: Treatment of vitamin D deficiency in asymptomatic persons might reduce mortality risk in institutionalized elderly persons and risk for falls but not fractures.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. doi:10.7326/M14.1619
For author affiliations, see end of text.
This article was published online first at www.annals.org on 25 November 2014.

www.annals.org

Vitamin D testing: Coding

- | | |
|------------------------|--------|
| ■ Pre Menstrual Synd | 625.4 |
| ■ Arthralgias | 719.49 |
| ■ Fatigue | 780.79 |
| ■ Diabetes (T2) | 250.00 |
| ■ Malabsorption | 579.8 |
| ■ Irritable Bowel Synd | 564.1 |
| ■ Menopausal Disorder | 627.8 |

How to Test

- **25 Hydroxy (OH) Vitamin D level**
 - Most sensitive measure of body stores
- 1,25 Vitamin D active form, but varies
- Interpretation: **IOM (PTH)**
WNL: 20-100 ng/ml
Deficient < 20 ng/ml
- No need for PTH and Calcium except:
 - Serious Cardiac Arrhythmias
 - Renal Insufficiency
 - Malignancy

Case of the A Family

- Osama A. 51 y/o male from Sudan; 4 children
- 25 Vit D: 20-100 WNL, < 20 ng/mL Deficient
25 Vit D
- Oldest son Ahmed, tears ACL Soccer 12 ng/ml
- Youngest Son, Osman, fx Ulna cross St 9 ng/ml
- Second Son, Ayman, Fx Tib/Fib Soccer 15 ng/ml
- Daughter, Amal, Fx wrist PE @ school Undetect
- Osama (Dad) Fx wrist tripping on curb 12 ng/ml



Treatment

- | <u>25 Vitamin D*</u> | <u>Status</u> | <u>Treatment</u> |
|----------------------|---------------|---|
| ■ 20 – 100 ng/mL | Sufficient | 800-4,000 IU D3/Day |
| ■ < 20 ng/mL | Deficient | 50,000 IU D2/week
(Ergocalciferol) x 12 Wk
Then 2,000 D3/Day |
| ■ ???? | Calcium | |
- IOM/ES: Tolerable Upper Intake Level (UL) **4,000 IU/d**

D2 vs D3: Cochrane 2014

- “Vitamin D in the form of vitamin D(3) seems to decrease mortality in predominantly elderly women who are mainly in institutions and dependent care.
- Vitamin D(2), had no statistically significant effect on mortality (small, short RCT’s).
- Vitamin D(3) combined with calcium significantly increased nephrolithiasis

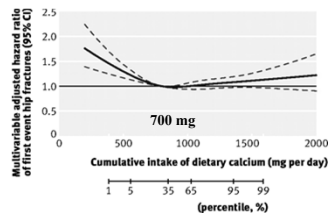
■ Cochrane Database Syst Rev, 2014 Jan 10;1:CD007470

Caution with Vitamin D Supplementation

- Sarcoid
- Tuberculosis
- Lymphoma
- Vitamin D + Ca++ → Renal Calculi

Why not just take extra Calcium? Ca Does NOT ↓ Osteoporotic Fractures

- Cohort Study of 61,000 women x 19 years
- Influence of Ca intake and Fracture
- Ca Intake beyond 700 mg did NOT reduce Fx Risk
BMJ 2011; 342: d1473



2010 Calcium Without Vitamin D Increases Risk of MI

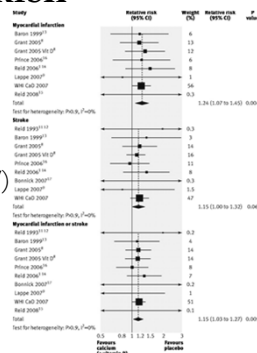
- Meta Analysis of 15 trials, ~20,000 patients
- Age > 40 yr; > 1 year, Men & Women
- Median F/U > 3.5 years
- Ca alone ↑ MI (RR = 1.27; 95CI 1.02-1.67)
- NNH ~125

BMJ 2010; 341: c3691

2011 Ca + Vit D in Women ↑ CHD RISK

- Reanalysis of WHI data
- Meta Analysis of subset of data (28,000)
Ca + Vit D Supp →
RR MI/CVA 1.15(1.03-1.27)
- HOLD the Ca+

BMJ 2011; 342: d2040



Instead:

Dietary Sources of Calcium

- Dairy (Milk, Yogurt) (300mg)
- Green leafy vegetables: broccoli, collards, kale, mustard greens, turnip greens, and bok choy
- Salmon & sardines canned (w/bones)
- Nuts & Beans: Almonds, Brazil nuts, sunflower seeds, tahini, and beans

What Outcomes are influenced by Vitamin D?

2012: USPSTF *Exercise or PT & Vitamin D (800 IU/D) for Adults* *≥/ = 65 years*

Annals of Internal Medicine

CLINICAL GUIDELINE

Prevention of Falls in Community-Dwelling Older Adults: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moye, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 1996 U.S. Preventive Services Task Force (USPSTF) recommendation statement on counseling to prevent household and recreational injuries, including falls.

Methods: The USPSTF reviewed new evidence on the effectiveness and harms of primary care-relevant interventions to prevent falls in community-dwelling older adults. The interventions were grouped into 5 main categories: multifactorial clinical assessment (with or without direct intervention), clinical management (with or without screening), clinical education or behavioral counseling, home hazard modification, and exercise or physical therapy.

The USPSTF does not recommend automatically performing an in-depth multifactorial risk assessment in conjunction with comprehensive management of identified risks to prevent falls in community-dwelling adults aged 65 years or older because the likelihood of benefit is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of the circumstances of prior falls, comorbid medical conditions, and patient values. (Grade C recommendation)

Ann Intern Med May 29, 2012; 157

Ann Intern Med 2012;157

For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the Appendix (available at www.annals.org).

This article was published at www.annals.org on 29 May 2012.

2012 Vitamin D (>800 IU/Day) Reduces Hip and Non-Vertebral Fractures in Community Dwelling Adults aged ≥/ = 65 Years

- Meta-analyses on **800 IU Vitamin D** & fracture
- 11 RCT; 31,000 patients aged > 65 years of age
- **30% reduction risk of hip fracture** (HR: 0.70; 95% CI, 0.58 to 0.86) and
- **4% reduction in risk of any nonvertebral fracture** (HR: 0.86; 95% CI, 0.76 to 0.96).

N Engl J Med 2012;367:40-9.

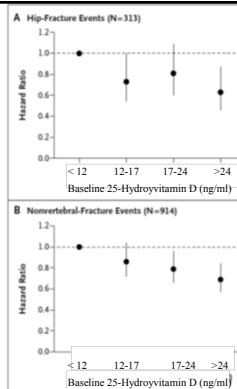


Figure 1. Threshold Assessment for the Risk of Fracture, According to Quartile of Baseline 25-Hydroxyvitamin D Level.

Prenatal Vit D & Outcomes

- China: low serum VD ↑ Autism risk J Psychosom Res. 2016 Oct;89:98-101.
- Low Vit D in early pregnancy doubles MS risk; JAMA Neurol. 2016 May 1;73(5):515-9
- Vit D status does NOT Correlate with T1DM risk; Diabetologia. 2012 May;55(5):1291-4

Vit D Def in Pregnancy : ↑ Gest DM, Pre-Eclampsia & SGA, BV, LBW

- Systematic Review & Meta Analysis of 31 Observational Studies
- **Vitamin D Insufficiency (< 30 ng/ml):**
 - ↑ Gestational diabetes OR = 1.49
 - ↑ Pre-eclampsia OR = 1.79 ,
 - ↑ Small for gestational age infants OR = 1.85.
 - ↑ Bacterial vaginosis & Lower birth weight infants

BMJ 2013;346:f1169

Vit D Supp Reduces Adverse Asthma Outcomes

- 7 trials involving children & adults in the primary setting.
- Vitamin D reduced the rate of exacerbations requiring systemic corticosteroids (rate ratio 0.63, 95% CI 0.45 to 0.88)
- Decreased risk of having at least one exacerbation requiring an emergency department visit or hospitalization or both (odds ratio (OR) 0.39, 95% CI 0.19 to 0.78)
- Vitamin D had NO impact on FEV1 or the risk of serious adverse events (OR 1.01, 95% CI 0.54 to 1.89)
- Dosage Variable

■ [Cochrane Database Syst Rev](#). 2016 Sep 5;9:CD011511

Obesity

- 2 Year Vit D Weight Loss Trial, 300+ Patients
- Baseline; Higher BMI → Lower 25 OH Vit D
- After 2 Years & Adjusting for age, sex, baseline BMI, total fat intake, and diet group assignment
- **Highest D intake lost additional 5.6 Kg x 2 yrs**
- ? Fecal Fat Excretion
- Higher Intake Vit D → Greater Wt Loss

[Am J Clin Nutr](#). 2010 Nov;92(5):1017-22

Obesity & Depression

- Cross Sectional, then **RCT** of Vit D on Depression in Obese Patients
- 440+, BMI: 28-47, √ 25 VD & Beck Dep Inventory
- Subjects with Low Vit D → Higher Beck scores
- RCT: D3--40K, 20K/week vs Placebo x 1 Yr
- 1Yr: ↓ Beck in 40K & 20K D3, ↓ PTH; No Δ Placebo
- **Treat patients with Depression with Vitamin D**
- [Jorde: J Intern Med](#) 2008; Dec;264(6):599-609

Multiple Sclerosis & VDD

- **Strong Epidemiologic data that Poor Vitamin D status increases risk for MS**
- Observational data → VDD may predict poor clinical course in those with MS
- MS patients higher risk of falls & Osteoporosis
- **Initial Clinical trial data of MS patients + high dose Vitamin D pending**
- **Suggested serum goal of 30-60 ng/mL**

[Expert Rev Neurother](#). 2012 Sep;12(9):1101-12

Vitamin D Deficiency Increases Risk of Dementia & Alzheimer disease

- 1,658 elderly adults W/O dementia, CV disease, and stroke
- 25 (OH)D vs. all-cause dementia & Alzheimer disease x 5 yr
- | | <u>All-cause Dementia</u> | <u>Alzheimers</u> |
|-------------------------------------|---------------------------|-------------------|
| ■ <u>Severe VDD</u>
(<10 ng/ml) | 2.25 (1.23-4.13) | 2.22 (1.02-4.83) |
| ■ <u>Deficient</u>
(10-20 ng/ml) | 1.53 (1.06-2.21) | 1.69 (1.06-2.69) |
- **Conclusion:** Vitamin D deficiency is associated with an ↑ risk of all-cause dementia and Alzheimer disease.

[Neurology](#)® 2014;83:920-928

Pre Menstrual Syndrome

- PMS is related to cyclic decrease in Calcium and increase in PTH
- Nurses' Health Study II Case/Control 1000+
- Highest Vit D (~700 IU/D) RR of PMS of 0.59
- Similar trend with Calcium Intake

Vit D and Calcium MAY reduce PMS

■ [Journal of the American College of Nutrition](#). 19(2):220-7, 2000 Apr
 ■ [Arch Intern Med](#). 2005 Jun 13;165(11):1246-52 .

Vitamin D & Cancer

2006 Sys. Review of 63 *Observation* Studies

Adequate Vit D Levels -> ↓ Risk

- 30 Colon Cancer (20/30)
- 13 Breast Cancer (9/13)
- 26 Prostate Cancer (13/26)
- Low VD Level → ↑ Ovarian Cancer (7)

Am J Public Health. 2006 Feb;96(2):252-61

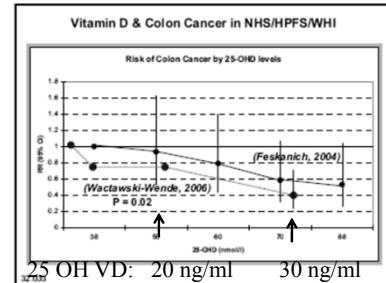


2007 Colon Cancer Reduced

- Meta-analysis of 5 studies
- highest quintile (> 33 ng/ml)

- 50% reduction in colo-rectal cancer risk.

Am J Prev Med. 2007; 32(3):210-6



2014 AHRQ Umbrella Review Vitamin D and Cancer –

- Colorectal cancer – low serum 25 OHVD concentrations increased risk of colorectal cancer. No data on supplementation and risk change.
- Breast cancer – some relationship between low 25 OH vitamin D levels and a risk for breast cancer.
- Pancreatic cancer – high vitamin D concentration (≥ 40 ng/ml) in an increased risk of pancreatic cancer.
- Prostate cancer – no new data association between 25 OHVD concentration and risk for prostate cancer.

BMJ 2014;348:g2035

Low Vit D -> Increased Risk of MI

- Case Control study of 18,000+ Men
- If Deficient (≤ 15 ng/mL) → RR=2.09
- If Insufficient (≤ 30 ng/mL) → RR=1.6

after adjusting for:

FHx CAD, BMI, EtOH, Activity level, Diabetes mellitus, HTN, Ethnicity, LDL

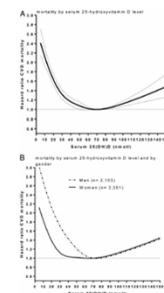
Vitamin D Def increases risk of MI

Giovanucci, et al. Arch Intern Med 2008; 168(11): 1174-80

J Shaped Association Between VD and CV Mortality

- Observational cohort study of approximately 250,000 subjects.
- Compared 25(OH)VD level and mortality from cardiovascular disease, stroke, acute MI, among 161,000 women and 86,000 men.
- Results: Over 7 years, 5,454 adults died from cardiovascular disease. 25(OH) vitamin D levels with the lowest risk for cardiovascular mortality with 70nmol/l (28ng/ml).
- Hazard ratios were highest for extremely lower level (6ng/ml)
- Extremely high levels (> 60 ng/ml) had hazard ratio of 1.3.
- Conclusion: Maintaining serum 25(OH)VD level between 20 and 36 correlates with lowest cardiovascular mortality risk (show graphs).

J Clin Endocrinol Metab. 2015; 100(6):2339-46



2008 Vitamin D Deficiency & ↑ Risk of All Cause Mortality

- Melamed: Cohort 13,000 NHANES
- **Lowest quartile of 25 OH Vitamin D →
↑ Risk of All Cause Mortality**
- **Mortality RR=1.26 (95% CI 1.08 - 1.46)**
Arch Intern Med. 2008;168:1629-1637.

2014: Meta Analysis Vit DD ↑ Risk of Cardiovascular, Cancer, and Other Causes of Death

- Systematic review & meta analysis ~ 900,000
- Top vs. Bottom Third of serum 25 OH VD:
LOW →:
 - CV Mortality RR=1.35 (CI=1.13-1.16),
 - Cancer Mortality 1.14 (1.01-1.29),
 - Non-vasc/non-cancer death 1.30 (1.07-1.59)
- All Cause Mortality 1.35 (1.22-1.49)**

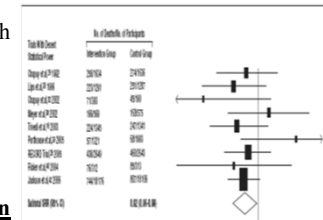
BMJ 2014; 348:g1903.

What Decreases Risk of All Cause Mortality?

- Seatbelts
- Clean Water
- Vaccines
- Exercise

2007 Vit. D Supplementation Decreases of All Cause Mortality

- Meta Analysis: 18 studies
of 57,000+ Adults
- Examined Risk of Death
Any Cause in RCT
Vitamin D
Supplementation
- Average dose
- > 500 IU/D



- **Vit D Supplementation
Decrease in All Cause
Mortality (RR = 0.93)**
- Autier: Arch Int Med 2007;167(16): 1730

2011 Systematic Review on VD Supplementation

- Cochrane Systematic Review: 50 trials, 90,000+
- Vitamin D Supp →
 - **DECREASE ALL CAUSE MORTALITY**
 - Vitamin D decreased mortality → RR 0.97
 - Subgroup Analysis: **Older women best outcomes**

Cochrane Database of Systematic Reviews 2011,
Issue 7. Art. No.: CD007470

What Didn't Improve in RCT of Vitamin D Supplementation

- Chronic Myalgias/Fibromyalgia
- Upper Respiratory Tract Infections
- "Cure" Psoriasis
- Seasonal Affective Disorder
- Treat Osteoarthritis pain (again JAMA)
- COPD exacerbations
- Academic Achievement in Adolescents
- Diabetes Prevention

Is this Real?

- **MOST data is *observational* research, rather than RCT's**
- Reference Range of 25 OH Vitamin D based loosely on suppressing PTH
- VDD Association with poor health status
- OTC Drug-- little initiative to study
- Analogous to Treating ↑ Homocysteine or Vitamin E and CHD

RCT In Progress 2017

Table. Ongoing Large-Scale Randomized Trials (N ≥ 10 000 Participants) of Vitamin D Supplementation Worldwide^a

Trial, Location	Sample Size ^b	Age Range, y	Treatment Duration, y	Vitamin D Intervention	Primary End Points	Trial Registry No.
Vitamin D and Omega-3 Trial (VITAL), United States	25 874	≥50 for men; ≥55 for women	5	2000 IU/d (oral)	Cancer, CVD	NCT01169259
D-Health, Australia	20 000	60-84	5	60 000 IU/mo (oral)	Total mortality, cancer	ACTRN12613000743763
Finnish Vitamin D trial (FIND), Finland	18 000	≥60 for men; ≥65 for women	5	1600 IU/d or 3200 IU/d (oral)	Cancer, CVD	NCT01463813
Vitamin D and Longevity (VIDAL), United Kingdom ^c	20 000	65-84	5	100 000 IU/mo (oral)	Total mortality, cancer	ISRCTN46328341

Abbreviations: CVD, cardiovascular disease.

^a Several moderate-sized randomized trials (2000-10 000 participants) also are in progress in the United States and worldwide.

^b VITAL has completed recruitment; enrollment for other trials is in progress.

^c In pilot phase.

- *JAMA*. Published online February 19, 2015. doi:10.1001/jama.2015.1353.

Data Summary

SR Data:

- **Lower Risk of Falls/Fx**
- Lower Risk of Some **Cancers**
- **↓ All Cause Mortality**

Intermediate Data:

- PMS, Pregnancy
- CHD Risk, Dementia

Benefit:

Osteoporosis, Depression, Obesity

2,000-4,000 IU/Day

Summary: Tomorrow

- **Screen ONLY at risk:** Seniors, Menopause, Dark Skinned, Veiled, Home Bound & NH, DM, Multiple Fx , Pregnant, Malabsorption, CHD, Depression
 - **Test:** 25 OH Vitamin D
 - Treat according to status
- **Prevention** for all: 2-4,000 IU/Day + NO Ca
 - Weight Bearing Exercise