



VITAMIN D IN HEALTH & DISEASE

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Summary

- Foods in North America were fortified with vitamin D to reduce the occurrence of rickets. This appeared to resolve the issue of major health problems caused by vitamin D deficiency.
- But vitamin D deficiency is common. The recommended daily allowance of 200 IU is based on *preventing* the disease rickets. This level is too low to maintain optimal health.
- This review considers the role of vitamin D in optimizing skeletal and nonskeletal health.

Summary

- It has become obvious that D levels less than 30 ng/ml are associated with higher rates of falls, fractures (osteoporosis), bone pain (osteomalacia), proximal muscle weakness, and muscle pain and cramps.
- New daily recommendations have doubled to 400 IU for children and 800 IU for adults and are probably still too low.
- Multiple epidemiological studies suggest an increasingly important role of vitamin D in preventing disease.

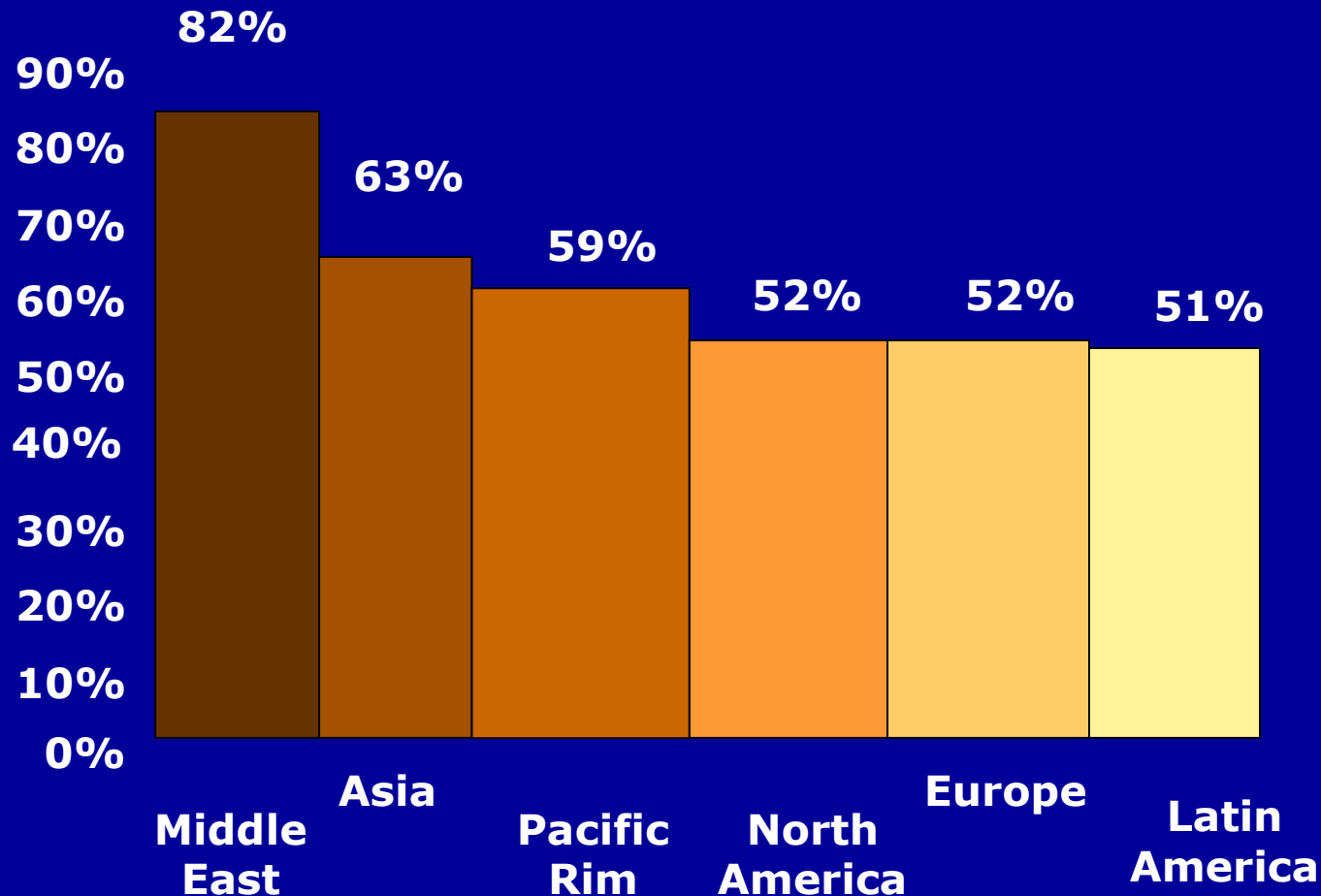
Prevalence of Vitamin D Deficiency

In USA

% with values <20 ng/ml

Patients with hip fracture	>80%
Nursing home residents	75%
In-patients on Medicine service in Boston hospital	66%
Healthy women 60 years and older in Portland, OR (latitude 45°)	60%
Medical students and residents in Boston	32%
10-13 year old girls in Maine	43%

Prevalence of vitamin D inadequacy by region



Hosking D et al. EULAR 2005; June 8-11, 2005;
Vienna, Austria.

Is too little sun exposure leading to vitamin D deficiency? [*Rheumawire*
> *News*; September 14, 2005]

What you need to know for this presentation

1. Vitamin D intake is usually measured in International Units (IU).
2. Vitamin D is most easily measured in the body as 25 OH vitamin D, the active form.
3. Most US studies report 25 OH D in ng/ml units. International measurements are reported as nmol/l. We will be referring to ng/ml.
4. You can figure one ng/ml unit=2.5 nmol/l.

What you need to know for this presentation

5. Parathyroid hormone (pth) controls serum calcium. As D levels decrease, pth levels increase to normalize calcium levels by removing calcium from bone.
6. Epidemiological studies are usually the first step in research and attempt to find relationships between factors and disease (eg: Vitamin D levels and CVD).
7. The studies may be “cohort” where all are well at the start. These can further be “prospective” or “retrospective”. Prospective would take decades to complete.

What you need to know for this presentation

8. Studies may be case-control where all people with the disease are studied and D levels compared to people without CVD.
9. There are obviously many limitations to epidemiological studies. A close relationship between vitamin D levels and CVD does not mean low D is the cause or that giving D will prevent CVD.
10. The gold standard is still the “double blind controlled clinical study”. These have yet to be done for vitamin D.

Causes Vitamin D Deficiency

1. Reduced skin synthesis:
 - a) sunscreen
 - b) aging
 - C) sun intensity: season, latitude, hour
2. Decreased bioavailability
 - a) malabsorption: celiac, cystic fibrosis, Crohn's, obesity surgery, statins
 - b) obesity > fat stores Vitamin D
 - c) increased catabolism drugs as anti-convulsants, steroids
3. Breastfeeding > poor levels in breast milk

Causes Vitamin D Deficiency

4. Decreased synthesis: liver failure, renal failure
5. Increased urinary loss > nephrotic syndrome
6. Hereditary disorders > rickets five types
7. Acquired disorders: tumor induced osteomalacia, hyperparathyroidism, hyperthyroidism

Facts

- Vitamin D deficiency is defined as a 25 OH vitamin D level less than 30 ng/ml, but some authors label levels 20-30 as “insufficiency”
- Ohio D levels peak August 6
- Humans typically get 90 % of their D from the sun
- Incidence of D deficiency increases proportionally as distance from the equator increases.
- Edmonton residents (52 deg N) have no D synthesis Oct-April: referred to as “Vitamin D Winter”
- Boston (42 deg N) no D synthesis Nov-Mar

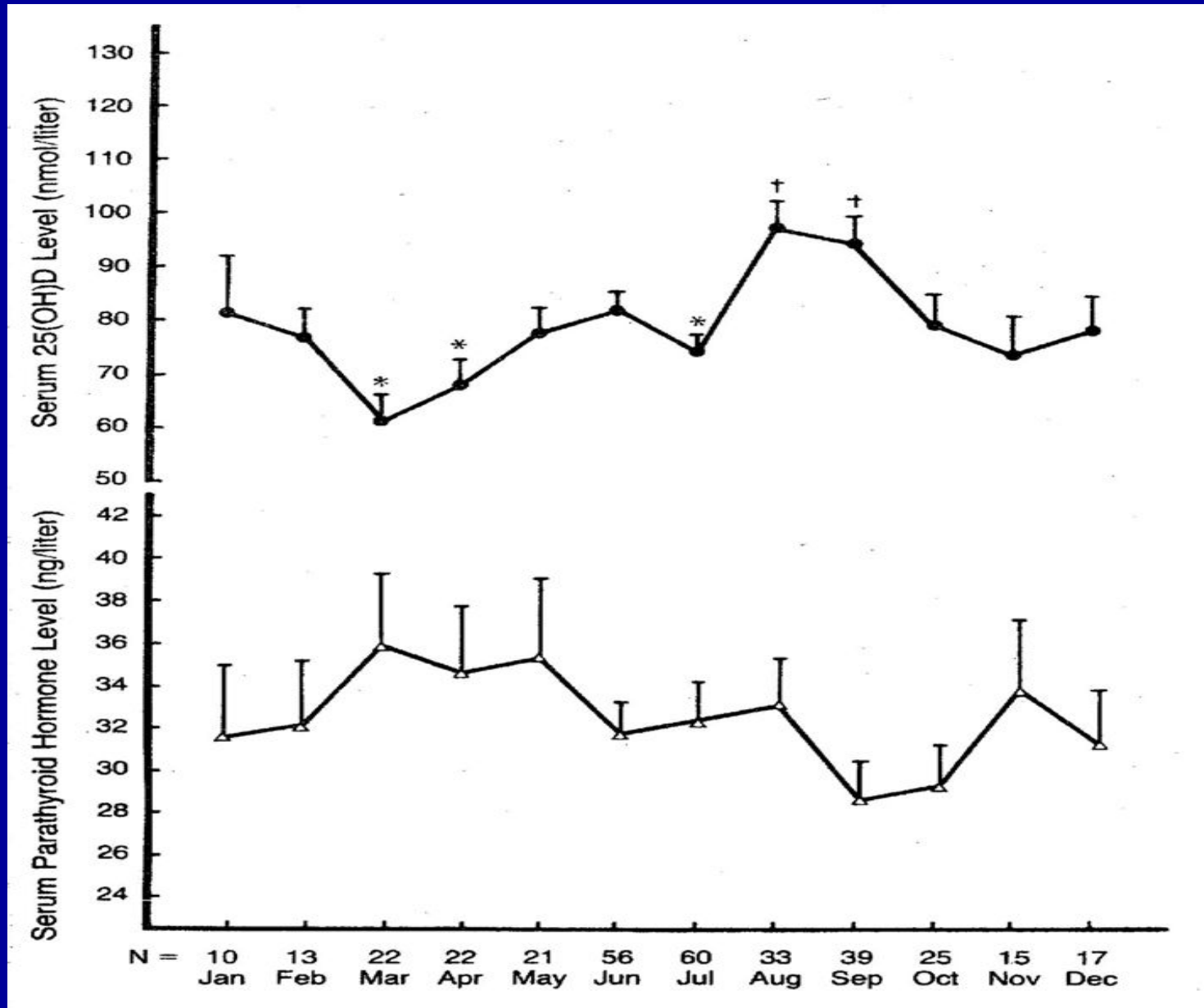
Facts

- Sunscreen SPF 15 blocks 99% D production
- Obesity increases D deficiency because D is a fat soluble vitamin
- Darker skin increases risk of D deficiency
- The UV action spectrum for DNA damage leading to skin cancer and for Vitamin D synthesis are the same so *beneficial/harmful effects are inseparable.*
- The body has a great homeostasis mechanism when humans are exposed to adequate sun: when levels are low the skin produces lots of vitamin D to normalize levels; when levels are high the skin/sun destroys vitamin D to normalize levels

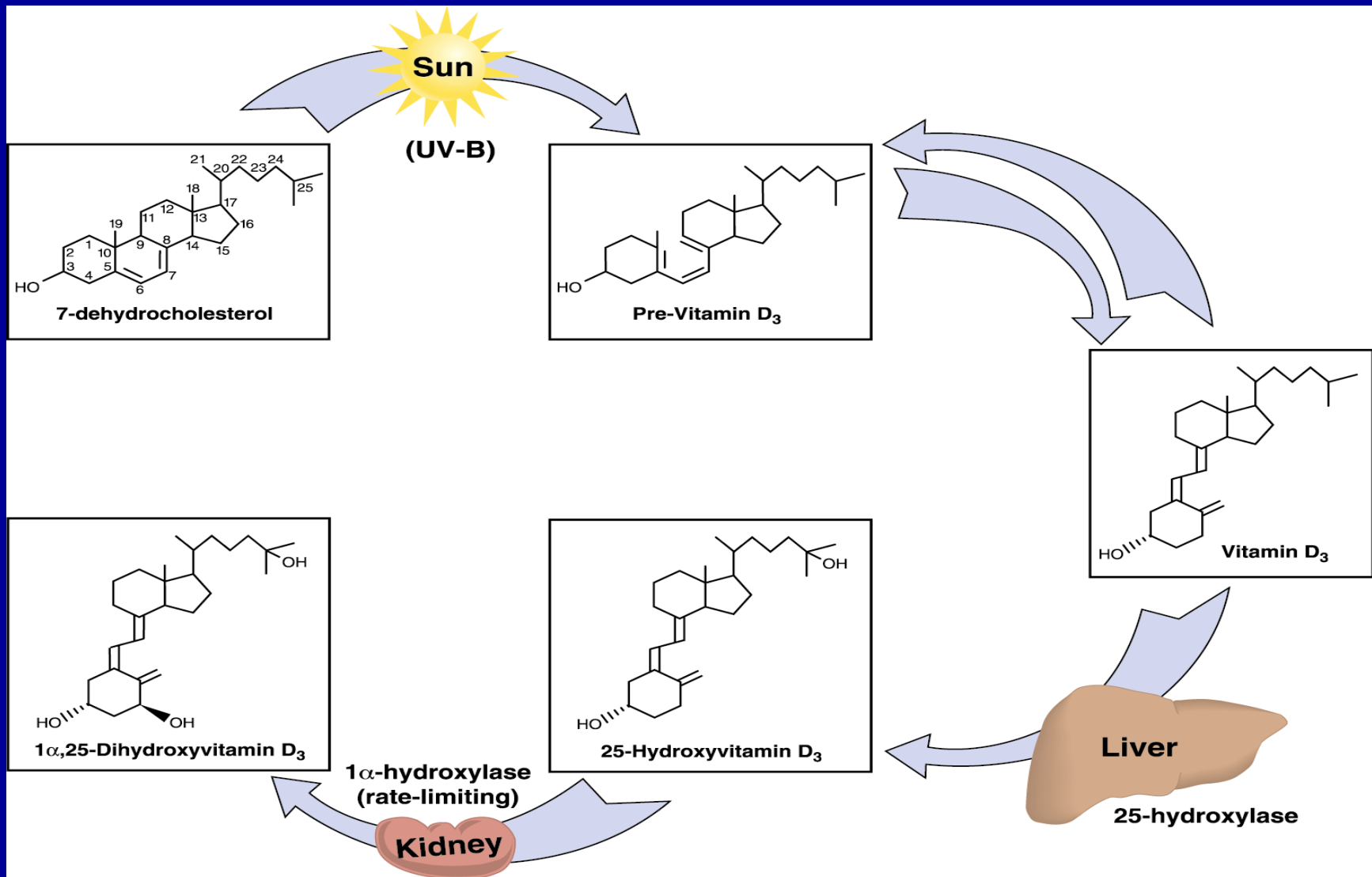
Facts

- D2 (ergocalciferol) comes from plants, is less potent, and is about 30 % as effective as D3
- D3 (cholecalciferol) comes from oily foods and skin synthesis from the sun
- There are Vitamin D receptors in osteoblasts, brain, breast, heart, muscle, pancreas, prostate, immune cells, vascular endothelium
- Vitamin D controls 200 different genes so it really acts like a hormone in the human body

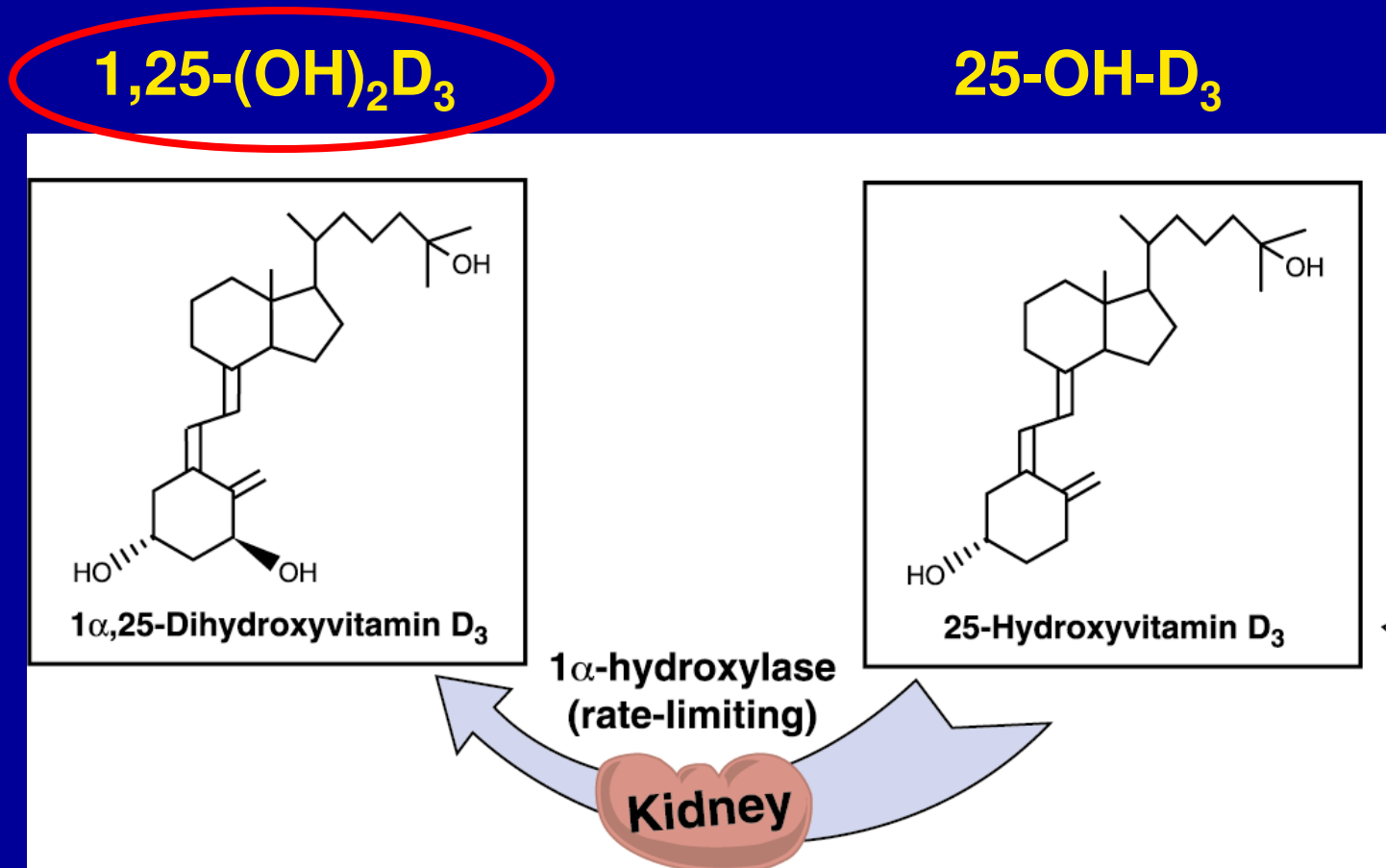
Serum PTH, Serum 25 OH Vitamin D and Month of Year



Sunlight catalyzes vitamin D₃ biosynthesis

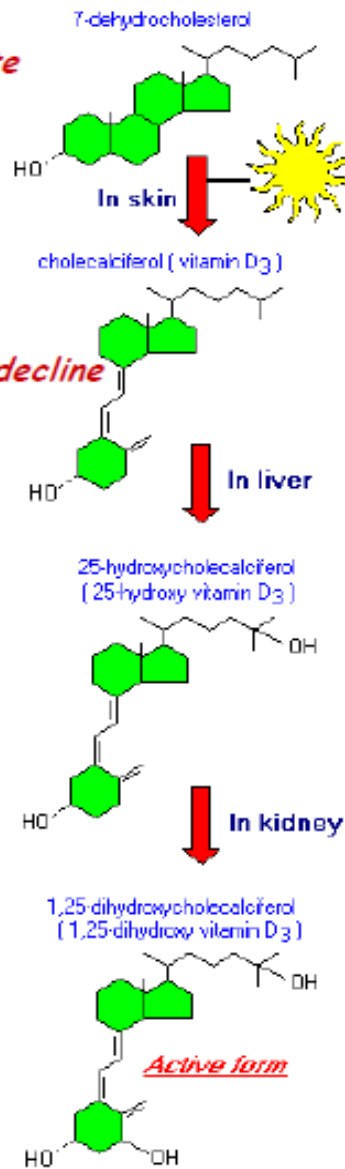


The *Cyp27b1* gene encodes the enzyme that produces 1,25-(OH)₂D₃



*Exposure for 5min with bathing suite
In the summer without sunscreen,
between 10 am and 3pm
can produce 10.000 units of D3*

*Vitamin D stores may be depleted
When Vit. D binding protein levels decline
substantially:
-severe liver failure
-nephrotic syndrome
-severe malnutrition*



4 variables:

- Quantity of UVB (intensity)
- Quality (UVB 270-290nm wavelength)
- Concentration of 7dehydrocholesterol in epidermis
- Concentration of melanin (absorbs UVB 270-320nm in competition with 7dehydrocholesterol)

D3 and dietary Vitamin D are transferred to the liver bound to vitamin D binding protein.

Vitamin D and Sun Exposure

1 minimal erythema dose of sun (about 20 minutes in summer) is equivalent of 10,000-25,000 IU of vitamin D

Decreased cutaneous production of vitamin D with
aging
pigmented skin
sunscreen

Number 8 sunblock reduces vitamin D synthesis by 95%

Dietary Sources of Vitamin D

<u>FOOD SOURCE</u>	<u>IU per Serving</u>
• Cod Liver Oil, 1 Tbs	1,360
• Salmon, cooked, 3 1/2 oz	360
• Mackerel, cooked, 3 1/2 oz	345
• Sardines, canned in oil, drained, 3 1/2 oz	270
• Milk, vitamin D fortified, 1 cup	98
• Margarine, fortified, 1 Tbs	60
• Liver, beef, cooked, 3 1/2 oz	30
• Egg, 1 whole (vitamin D is present in the yolk)	25

Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D₂ and D₃

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D ₃
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D ₃ or D ₂
Canned (3.5 oz)	About 300–600 IU of vitamin D ₃
Sardines, canned (3.5 oz)	About 300 IU of vitamin D ₃
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D ₃
Tuna, canned (3.6 oz)	About 230 IU of vitamin D ₃
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D ₃
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D ₂
Sun-dried (3.5 oz)	About 1600 IU of vitamin D ₂
Egg yolk	About 20 IU of vitamin D ₃ or D ₂
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose) †	About 3000 IU of vitamin D ₃

Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D₂ and D₃

Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D ₃
Fortified orange juice	About 100 IU/8 oz vitamin D ₃
Infant formulas	About 100 IU/8 oz vitamin D ₃
Fortified yogurts	About 100 IU/8 oz, usually vitamin D ₃
Fortified butter	About 50 IU/3.5 oz, usually vitamin D ₃
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D ₃
Fortified cheeses	About 100 IU/3 oz, usually vitamin D ₃
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D ₃
Supplements	
Prescription	
Vitamin D ₂ (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D ₂) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D ₂ , or D ₃ ‡
Vitamin D ₃	400, 800, 1000, and 2000 IU

Vitamin D Supplements

- RDA for vitamin D is 400-600 IU daily ¹
- The 400 IU dose based on dose found to prevent rickets in children
- 1000 IU daily increases serum 25-OH vitamin D by about 10 ng/ml ²
- Vitamin D₂ is about 1/3 as effective as vitamin D₃ ²

¹ Food and Nutrition Board, Institute of Medicine. Vitamin D. National Academies Press; 1999:250-287.

² Armas LA, Hollis BW, Heaney RP. J Clin Endocrinol Metab. 2004;89:5387-91.

From [Nature Clinical Practice Rheumatology](#)

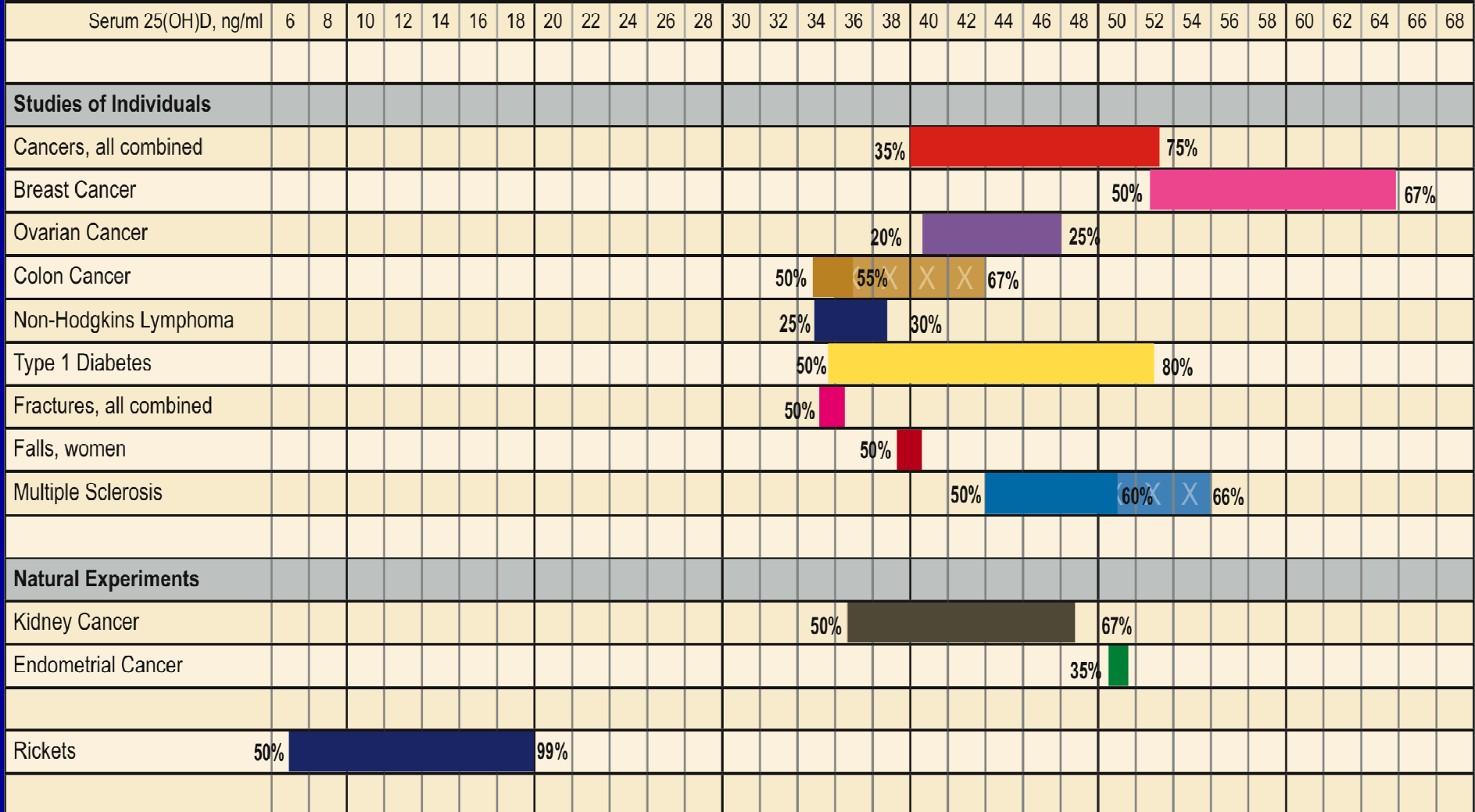
Vitamin D and Musculoskeletal Health

10/16/2008 Anne E. Wolff, MD; Andrea N. Jones, MA;
Karen E. Hansen, MD

- In a meta-analysis of 12 random controlled studies it was found that a daily intake of >800 IU D3 daily resulted in a 26 % reduction in osteoporotic fractures.
- Three recent meta-analyses concluded that vitamin D must be administered in combination with calcium in order to substantially reduce the risk of nonvertebral fracture in adults over the age of 50 years.
- Fracture protection is optimal when patient adherence to medication exceeds 80% and vitamin D doses exceed 700 IU/day. As long as vitamin D status is adequate, 800 mg of calcium daily is all that is necessary to prevent osteoporosis (400 IU twice daily).

What are non-classical vitamin D functions?

Disease Incidence Prevention by Serum 25(OH)D Level



Odds of CVD risk factors, lowest vs highest vitamin-D quartile

Risk factor	Odds ratio (95% CI)*
Hypertension	2.36 (1.33–4.19)
Hyperglycemia	2.54 (1.01–6.40)
Metabolic syndrome	3.99 (1.21–13.20)

***Adjusted for age, sex, race/ethnicity, body-mass index,
socioeconomic status, and physical activity**

Reis JP et al. AHA 49th Annual Conference on Cardiovascular Disease
Epidemiology and Prevention; March 11, 2009; Palm Harbor, FL.

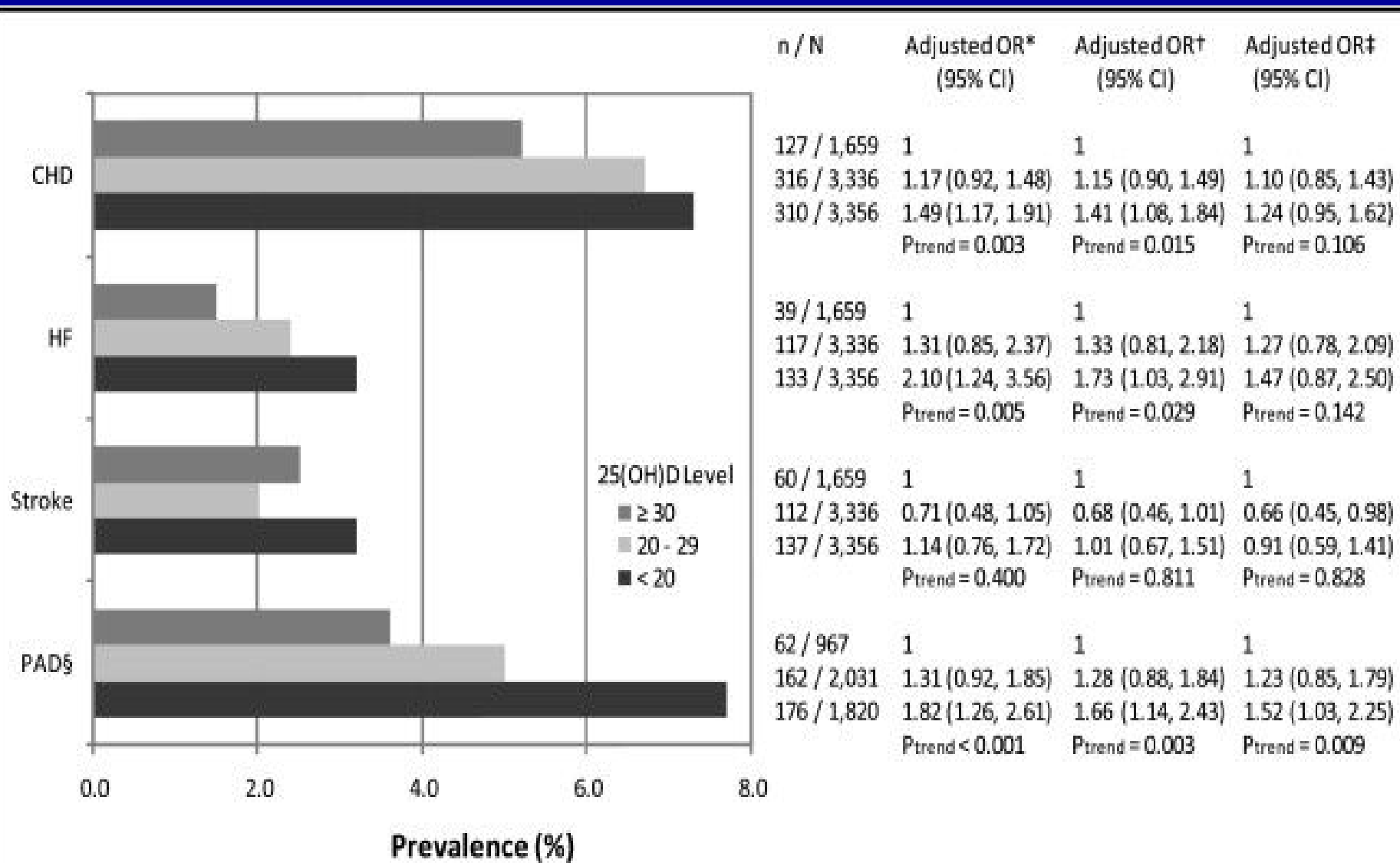
Prevalence of Hypovitaminosis D in Cardiovascular Diseases (from the National Health and Nutrition Examination Survey 2001 to 2004)

Dae Hyun Kim, MD, MPH_a, Siamak Sabour, MD, PhD_{ac}, Utpal N. Sagar, MD_a, Suzanne Adams, RN, MPH_a,

American Journal of Cardiology, December, 2008

This cross-sectional study examined the burden of cardiovascular diseases (CVDs) using serum 25-hydroxyvitamin D (25[OH]D) and prevalence of hypovitaminosis D in adults with CVDs using data from NHANES 2001 to 2004. Serum 25(OH)D levels were divided into 3 categories (>30, 20 to 29, and <20 ng/ml), and hypovitaminosis D was defined as vitamin D <30 ng/ml. Of 8,351 adults who had 25(OH)D measured, mean 25(OH)D was 24.3 ng/ml, and the prevalence of hypovitaminosis D was 74%. The burden of CVDs increased with lower 25(OH)D categories, with 5.3%, 6.7%, and 7.3% coronary heart disease; 1.5%, 2.4%, and 3.2% heart failure; 2.5%, 2.0%, and 3.2% stroke; and 3.6%, 5.0%, and 7.7% peripheral arterial disease. Compared with persons at low risk for CVDs (68%), it was more prevalent in those at high risk (75%; odds ratio [OR] 1.32, 95% confidence interval [CI] 1.05 to 1.67), with coronary heart disease (77%; OR 1.48, 95% CI 1.14 to 1.91), and both coronary heart disease and heart failure (89%; OR 3.52, 95% CI 1.58 to 7.84) after controlling for age, race, and gender. ***In conclusion, hypovitaminosis D was highly prevalent in US adults with CVDs, particularly those with both coronary heart disease and heart failure.***

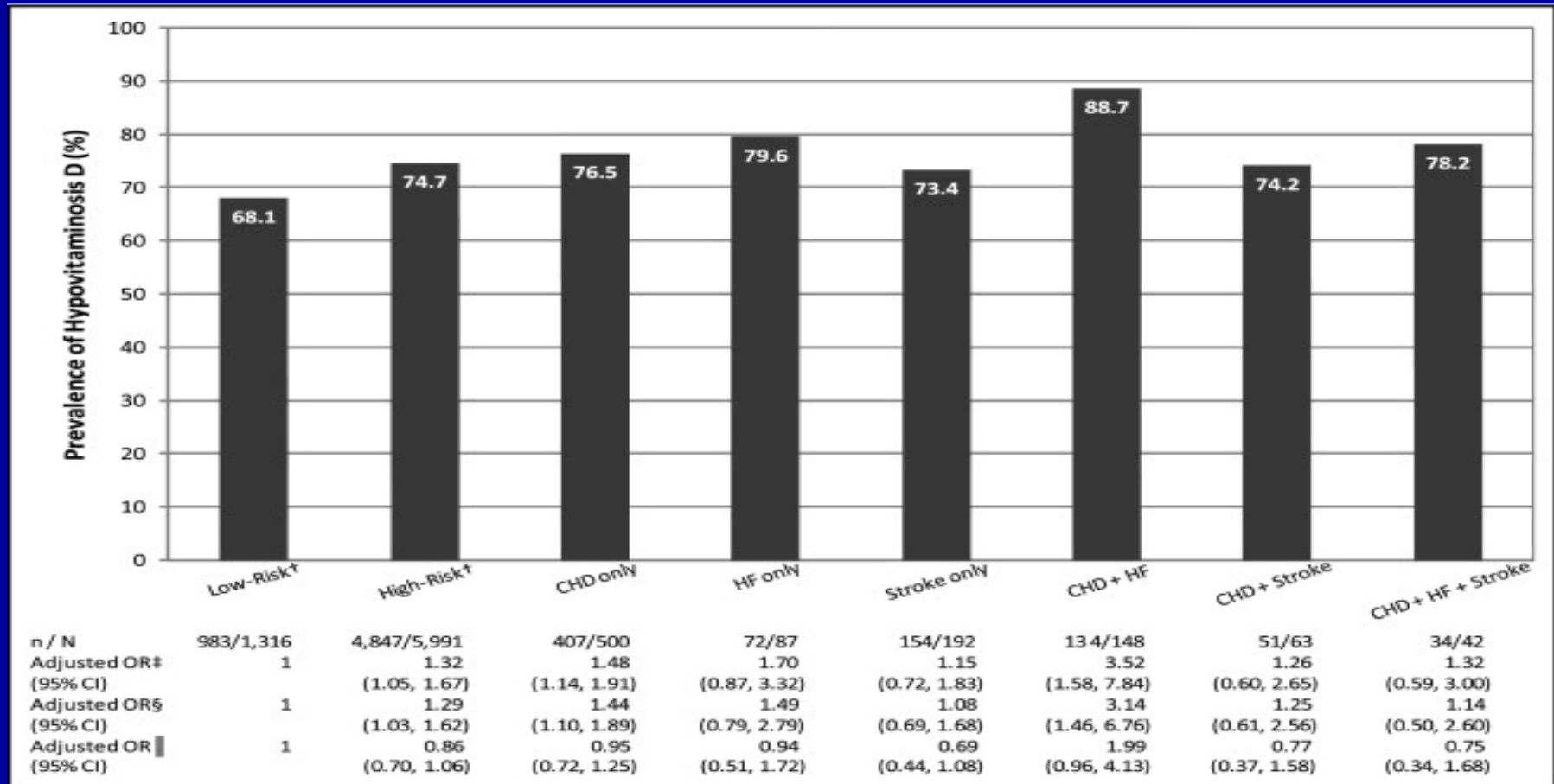
Prevalence of Various CVD and Vitamin D Levels (NHANES)



NHANES 2001-2004 Prevalence of Hypovitaminosis D in Various Cardiovascular Diseases (adjusted)

§ Controlled for age, race, gender, current smoking, leisure-time physical activity, vitamin D supplement use, and regular milk drink.

// Controlled for body mass index category, chronic kidney disease, hypertension, and diabetes mellitus in addition to the mentioned demographic and lifestyle characteristics



Primary source: Journal of Clinical Endocrinology & Metabolism
Ward KA, et al "Vitamin D status and muscle function in post-menarchal
adolescent girls" *J Clin Endocrinol Metab* 2009; 94: 559 - 563.

- Vitamin D may play a key role in muscle function in adolescent girls, researchers here said.
- Serum levels of 25-hydroxyvitamin D (25(OH)D) and parathyroid hormone (PTH) were significantly associated with muscle force and power in girls ages 12 to 14, Kate Ward, Ph.D., of the University of Manchester, and colleagues reported in the February issue of the *Journal*
- "We know vitamin D deficiency can weaken the muscular and skeletal systems, but until now, little was known about the relationship of vitamin D with muscle power and force," Dr. Ward said.
- The median serum 25(OH)D concentration of the study population was 21.3 nmol/L.
- Many of the girls had low levels of 25(OH)D even though they did not present with symptoms, the researchers said.
- ***Girls without vitamin D deficiency performed significantly better across the jumping tests. There was a positive linear relationship between 25(OH)D levels and jump velocity, jump height, force, and power (P=0.002, P=0.006, P=0.04, and P=0.004, respectively) up to 40 ng/l***

Several high-profile studies have suggested that high levels of vitamin D lower the risk of developing multiple sclerosis (MS), but more research is needed to assess these findings. When a person has multiple sclerosis, the immune system attacks the coating that protects the nerve cells. Initial research suggests that a connection between vitamin D and MS could be tied to the positive effects vitamin D has on the immune system. The possible link between vitamin D and MS is strengthened by the association between sunlight and the risk of MS. The farther away from the equator a person lives, the higher the risk of MS — suggesting that exposure to sunlight may offer protection from MS. Whether this is related to ultraviolet radiation or because active vitamin D levels increase with sun exposure remains unclear. Until researchers clarify the possible relationship between vitamin D and MS, there isn't enough evidence to recommend vitamin D as a way to treat or prevent MS. Still, vitamin D remains an important nutrient for overall good health.

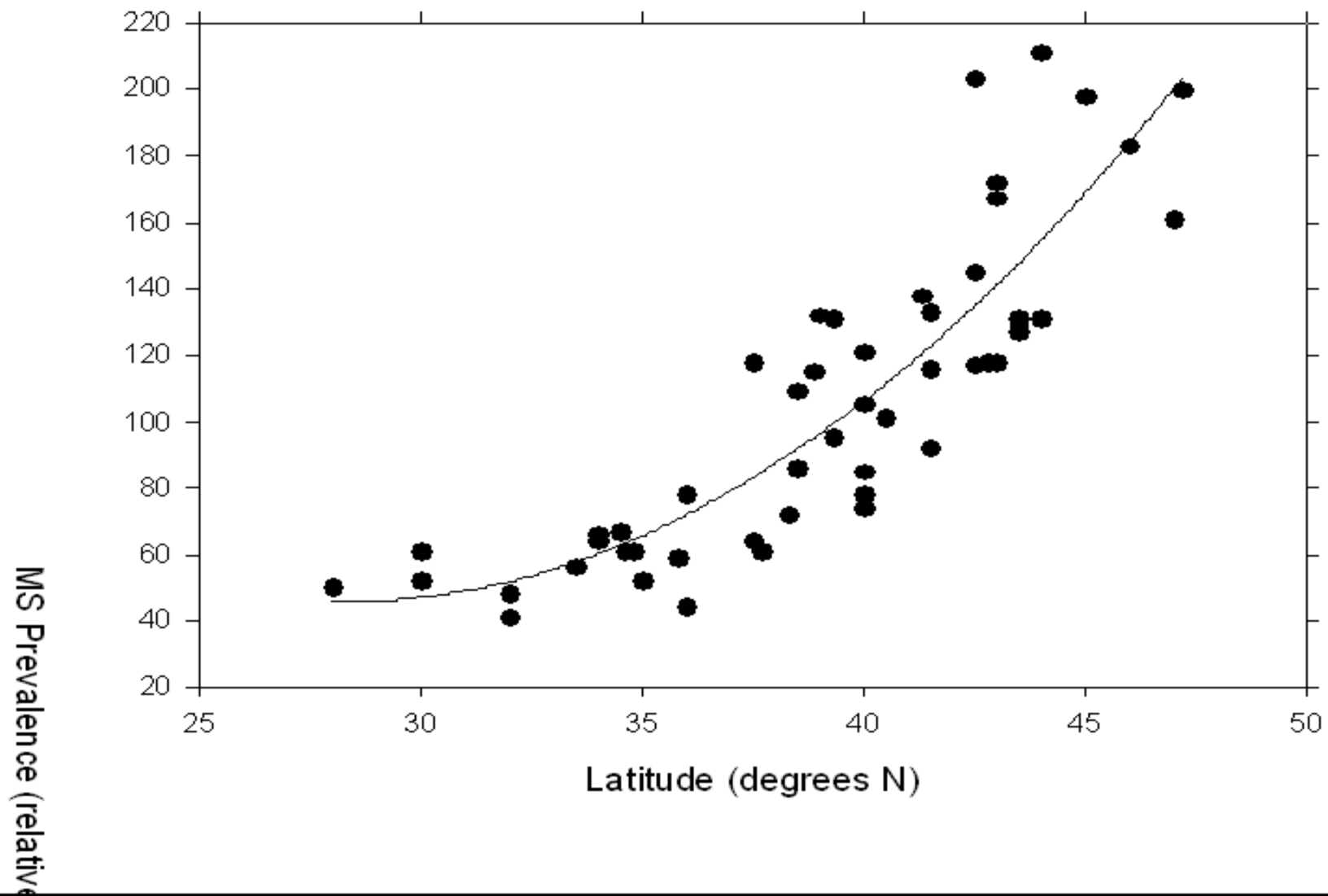
Safety Trial of High Dose Oral Vitamin D3 With Calcium in Multiple Sclerosis (VitD4MS)

Sponsors and Collaborators:	University of Toronto Direct MS-Proactive Charity Multiple Sclerosis Society of Canada
Information provided by:	University of Toronto
ClinicalTrials.gov Identifier:	NCT00644904

Purpose

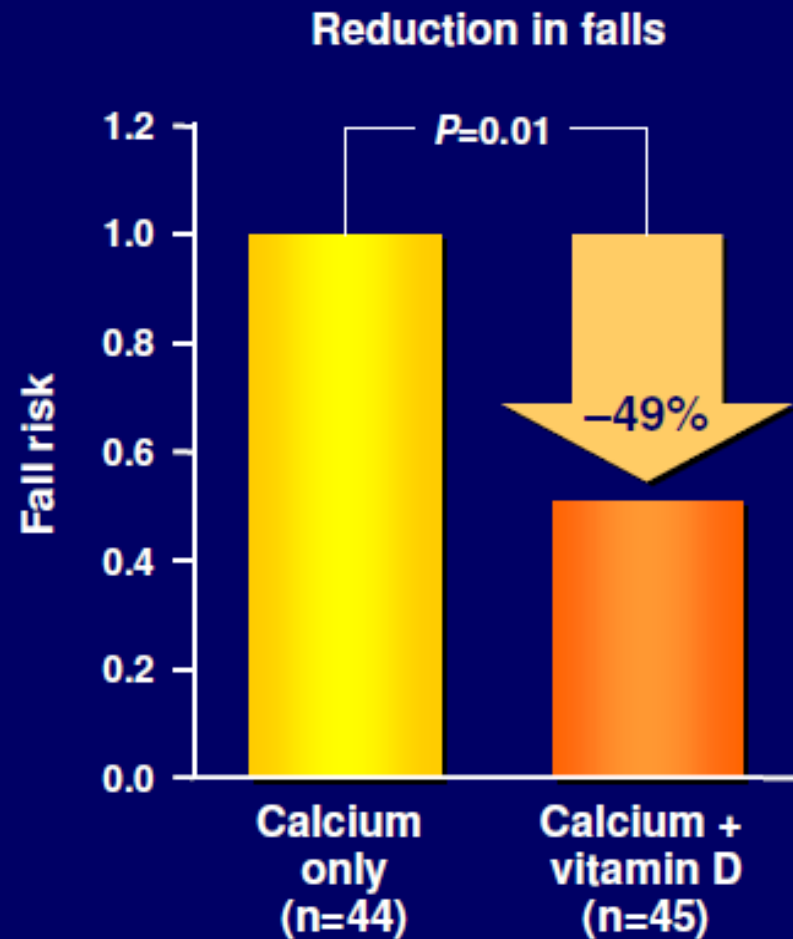
- Vitamin D likely plays a role in the geography of **Multiple Sclerosis** (MS), and patients at risk and with MS have relatively low vitamin D levels compared to their normal counterparts.
- This trial examines the safety of high dose oral Vitamin D3 titrated up to a maximum of 40,000 IU per day over a 12 month period.

Multiple Sclerosis Prevalence for U.S. WWII, KC Veterans at Time of Entry into the Armed Forces vs. Latitude



Lower Levels of Vitamin D May Be Associated with the Risk for Falling

- N =122
- Ages: 63–99
- Randomized, double-blind, controlled trial
 - Calcium 1200 mg/d
 - Calcium 1200 mg/d + vitamin D 800 IU/d
- 12-week duration
- Mean serum 25(OH)D 12 ng/mL at baseline
- Women living in long-term care units



Some Other Studies

- NHANES study following 13,000 people for 8 years showed a 26 % increase in all cause mortality for the lowest quintile of serum Vitamin D (<15 ng/ml).
- Another study showed that even 800 D3 daily prevented hip fractures (NNT 45 for 2 years, vs. 200 for bisphosphonate). Recommended 25 OH vitamin D level > 40 ng/ml with toxicity defined as >150.
- Study of male physicians showed a 2 X risk of MI in Vitamin D deficient vs. sufficient.
- Nurses Health Study Harvard: for every 20 ng/ml increase in Vitamin D levels, there was a 41% decrease in MS. Protective effect was highest for levels > 40.

And More

- A meta-analysis on DM and metabolic syndrome showed even a change from <400 to 800 IU daily decreased DM by 33%.
- Another found a single dose of 100,000 units D2 in hypertensive patients lowered BP by 15 points.
- Mayo Clinic: severe D deficiency + increased pth reported in 88% of women presenting with muscle pains and weakness. Found normalizing D levels resolved statin related myalgia.
- J. Mol. Biol. 2007 found women with levels >50 ng/ml had 50% less chance of breast cancer than women with levels <13.
- Holick: women who are vitamin D deficient have a 253% increased risk of developing colon cancer and ingestion of 1500 mg calcium/day + 1100 IU vitamin D for 4 years reduced risk by 60 %.

Fiscella Kevin, Franks Peter.
“Vitamin D, Race, and Cardiovascular Mortality: Findings
From a National US Sample”
Ann. Fam. Med. 2010; 8 (1) Feb 2010

- Used NHANES III and cause-specific mortality from National Death Index and 25 OH D levels by quartiles (<18, 18-24.9, 25>31.9, >31.9)
- Results: “*The higher age and sex-adjusted cardiovascular mortality observed in blacks vs. whites (incidence rate ratios, IRR=1.38) was attenuated (IRR=1.14) by adjusting for 25 OH D levels and fully eliminated with further adjustment for income (IRR=1.01)*”

ABC's of Vitamin D

Begin supplements

- Up to age 65: 1000 IU D₃ daily
or 100,000 IU D₂ once monthly
- 65 and older: 2000 IU D₃ daily
or 50,000 IU D₂ once weekly
- *Total daily calcium intake 800-1000 mg daily*

<i>dairy-free diet</i>	<i>300 mg</i>
<i>dairy servings</i>	<i>300 mg each</i>
<i>supplements</i>	<u><i>xxx</i></u>
TOTAL	

Conclusions

1. Vitamin D is a critical human need.
2. Previously recommended intake was based on preventing rickets and is too low.
3. Low vitamin D levels are associated with an increase in many diseases including autoimmune, infectious, bone, muscle, cardiovascular and cancer.
4. We should aim for enough vitamin D intake to keep serum 25 OH vitamin D levels above 30 ng/ml. Higher levels may be better pending research. This requires about 50,000 IU D3 monthly or 150,000 IU D2
5. There is a need for longitudinal case-controlled studies to further elucidate the role of vitamin D in optimizing health.

THE END

I leave you with the words of the poet Emily Dickinson:

*If I can stop one heart from breaking
I shall not live in vain;
If I can ease one life the aching,
Or cool one pain,
Or help one fainting robin
Unto his nest again,
I shall not live in vain.*