

VITAMIN D REQUIREMENTS DURING PREGNANCY, LACTATION & EARLY CHILDHOOD: A MOVING TARGET?

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Charleston, South Carolina

Funded in part by the following: Thrasher Research Fund; NIH R01 HD047511 & 5R01HD043921; MUSC Clinical & Translational Research Center; Division of Neonatology and Children's Hospital Fund

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Disclosure Slide



I have no conflict of interest to disclose with regard to this presentation.

Disclaimer

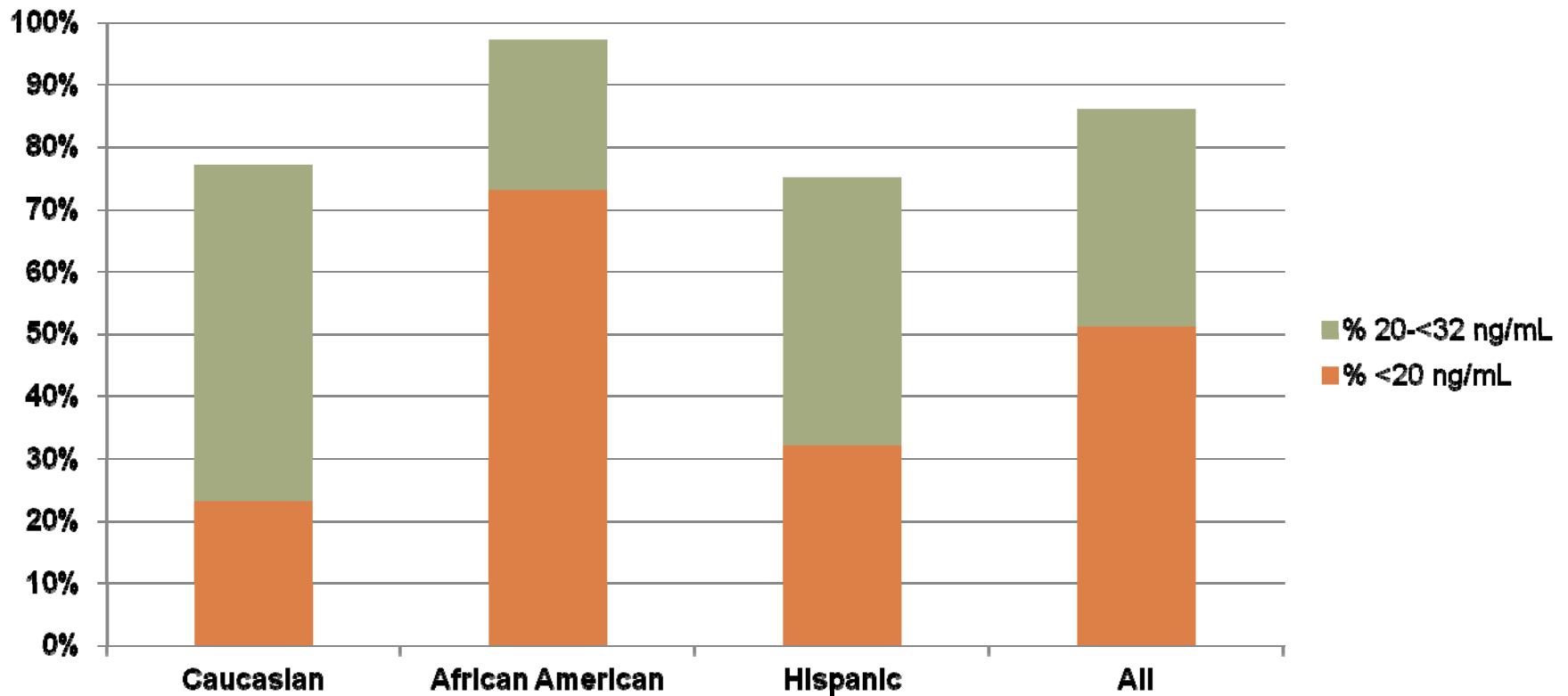
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What we will cover today...

- Why are we deficient in vitamin D?
- What is optimal and what is not?
- Link between vitamin D and other long latency diseases—role of the innate immune system
- Issues specific to pregnancy, lactation & early infancy

Evidence of the Epidemic

Baseline Circulating 25(OH)D Levels





Why is vitamin D deficiency
so prevalent?



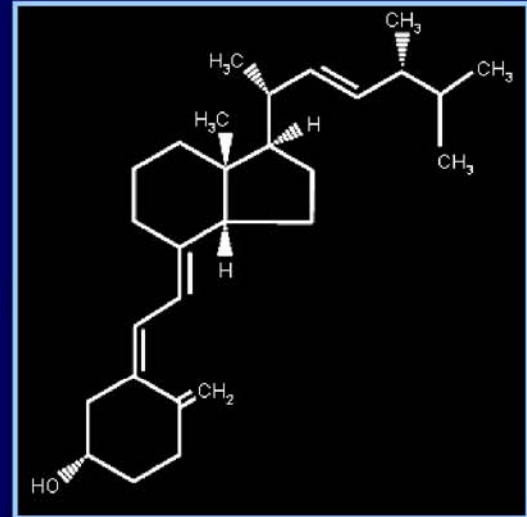
First, let's look at what
vitamin D is...

Types of Vitamin D

Vitamin D₂

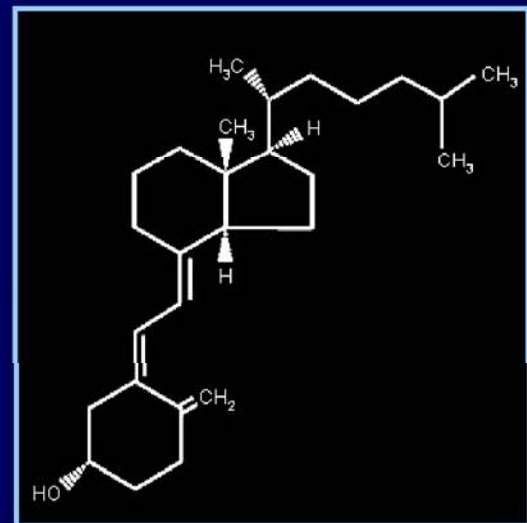
- Formed by irradiation of ergocalciferol, found in plants
- Provided by some dietary sources and multivitamins
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form
- D₂ is less potent than D₃

under certain circumstances



Vitamin D₃

- Naturally occurring form in humans
- Formed by action of ultraviolet light on vitamin D precursors in skin
- Present in certain nutrients
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form



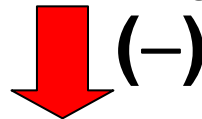
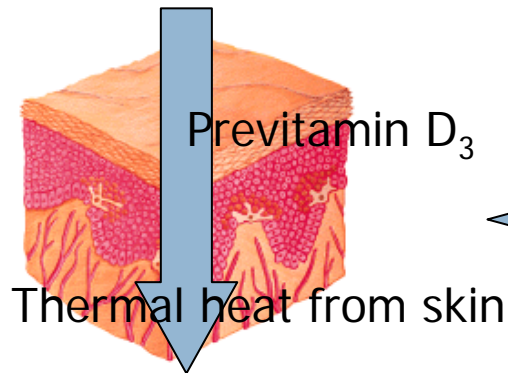
1. Parfitt AM et al. *Am J Clin Nutr.* 1982;36:1014–1031.

2. Lips P. *Endocr Rev.* 2001;22:477–501.

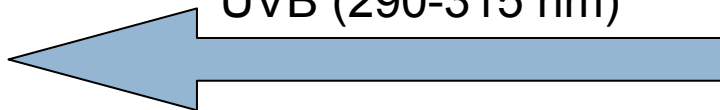
7-dehydrocholesterol in skin

(SPF \geq 8, clothes, glass)

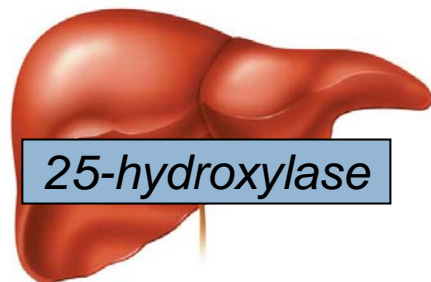
Major Source: Sun



UVB (290-315 nm)



Vitamin D₃ (Cholecalciferol)



25-hydroxylase



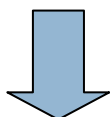
Minor Source: Dietary

Vitamin D₂ (ergocalciferol):

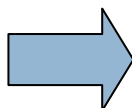
Plants/supplements

Vitamin D₃ (Cholecalciferol):

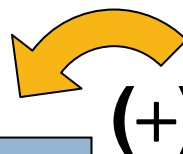
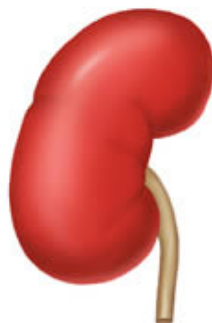
Fish (cod liver oil), meat, fortified milk, egg yolk, butter



25-hydroxyvitamin D₃
25(OH) D₃

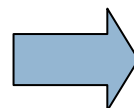


1-hydroxylase



Parathyroid hormone

1,25-dihydroxyvitamin D₃



↑Calcium absorption (small intestine)
↑Urinary calcium reabsorption (kidney)
↑Bone mineralization

THE DANGERS OF VITAMIN D



Committee on Nutrition, Pediatrics, 1963

Interesting Facts

- Concern in 1950's that vitamin D given to pregnant women was teratogenic
- Concern that even for some individuals doses of vitamin D above 400 IU/day could be toxic
 - In 1964, no quantitative means of assessing circulating concentrations of vitamin D
 - In fact, at that time, unproven that vitamin D was further metabolized within the body
- By 1967, vitamin D was viewed by the medical community as a significant causative factor in Supravalvular Aortic Stenosis Syndrome (SAS)
 - Taussig, H.B. 1966. Possible injury to the cardiovascular system from vitamin D. *Ann Intern Med* 65:1195-1200.
 - Friedman, W.F. 1967. Vitamin D as a cause of the supravalvular aortic stenosis syndrome. *Am Heart J* 73:718-720.

SAS Syndrome—the Dogma

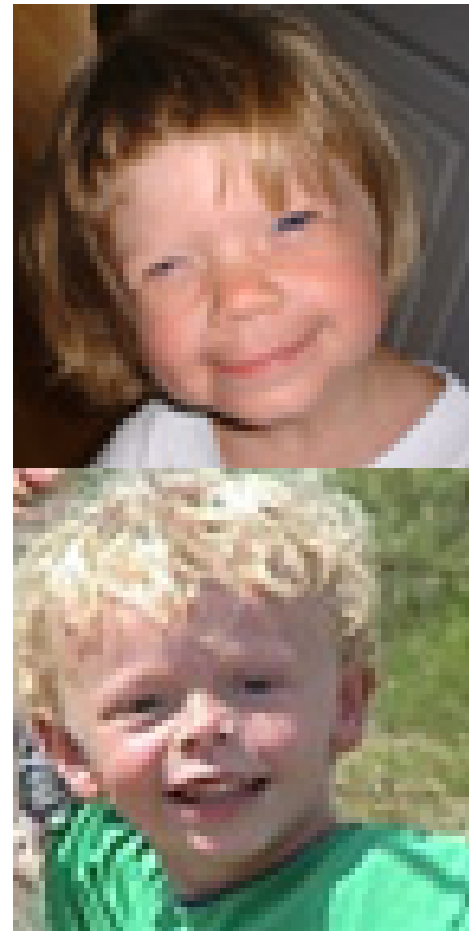
- **Premise: Maternal vitamin D supplementation during pregnancy caused SAS syndrome, the elfin facies and other findings described**
- Animal models were developed to show that toxic excesses of vitamin D during pregnancy would result in SAS
 - Antia, A.V., Wiltse, H.E., Rowe, R.D., Pitt, E.L., Levin, S., Ottesen, O.E., and Cooke, R.E. 1967. Pathogenesis of the supraaortic stenosis syndrome. *J. Pediatr* 71:431-441.
 - Seelig, M. 1969. Vitamin D and cardiovascular, renal and brain damage in infancy and childhood. *Ann NY Acad Sci* 147:537-582.
- Pharmacologic doses of vitamin D (hundreds of thousands of IU) were given to animals creating hypervitaminosis D with hypercalcemia.

What we were to find out...

- That SAS was not caused by too much vitamin D *per se*
 - But what, in fact, is a genetic disorder called Williams Syndrome

Williams Syndrome

- A severe genetic affliction related to elastin gene disruption
 - ▣ Caused by deletion of elastin and contiguous genes on chromosome 7q11.23
- Characterized by multiorgan involvement (including SAS), dysmorphic facial features, and a distinctive cognitive profile



Misattribution of vitamin D as the cause of SAS

- Williams Syndrome patients often exhibit abnormal vitamin D metabolism
 - Exaggerated response of circulating 25(OH)D to orally administered vitamin D
 - Susceptible to bouts of idiopathic hypercalcemia
 - Morris, C.A., and Mervis, C.B. 2000. William's syndrome and related disorders. *Ann Dev Genomics Human Genet* 1:461-484.
 - This relationship was suspected as early as 1976 but was not definitively made until 1991:
 - Becroft, D.M.O., and Chambers, D. 1976. Supravalvular aortic stenosis-infantile hypercalcemia syndrome: in vitro hypersensitivity to vitamin D and calcium. *J. Med. Genetics* 13:223-228.

Second Problem: What constitutes sufficiency?

- Even today we do not know full what is sufficiency for infants, children and adolescents—we are just beginning to learn
- View that vitamin D was needed most for growing bones, i.e. in children with little requirement beyond childhood
 - ▣ For adults, the requirement was set at 200 IU vitamin D/day—which was viewed as a ‘liberal amount’.
 - *National Academy of Sciences. Recommended dietary allowances.* 1989 Washington, D.C.: National Academy Press.
- The premise: all that one needed could be obtained from one glass of milk or sticking your arm out of the car window for 10 minutes three times a week.

What is the optimal circulating concentration of 25(OH)D in humans?

- An office worker, covered in sunscreen, inactive, general sun paranoia (2-15 ng/mL)
- Field worker (40-70 ng/mL)
- Lifeguard (60-90 ng/mL)
- A Pregnant woman and her developing fetus???
- A lactating woman and her breastfeeding infant???
- Children from early childhood through adolescence???

Haddad and Chyu, JCEM 1971, 33: 992-995

Group	No.	Age (years)	Consumption Of D Weekly (units)	Weekly Exposure to Sunlight (hours)	Plasma 25 – HCC (ng/ml)
Normal Adult Volunteers	40	30.2 ± 12.9	2230 ± 1041	8.8 ± 6.1	27.3 ± 11.8
Biliary Cirrhosis	4	1.5 - 55	2500 (est.)	_____	6.4 ± 2.6*
Lifeguards	8	18.5 ± 2.0	2895 ± 677	53.0 ± 10.3	64.4 ± 8.7*

* P < .001

+ values represent mean ± SD

Haddad and Chyu article

This article became the basis for “normal vitamin D status” in humans.

It was not powered to do so and was actually describing a method to measure 25(OH)D reliably and more easily in the laboratory.

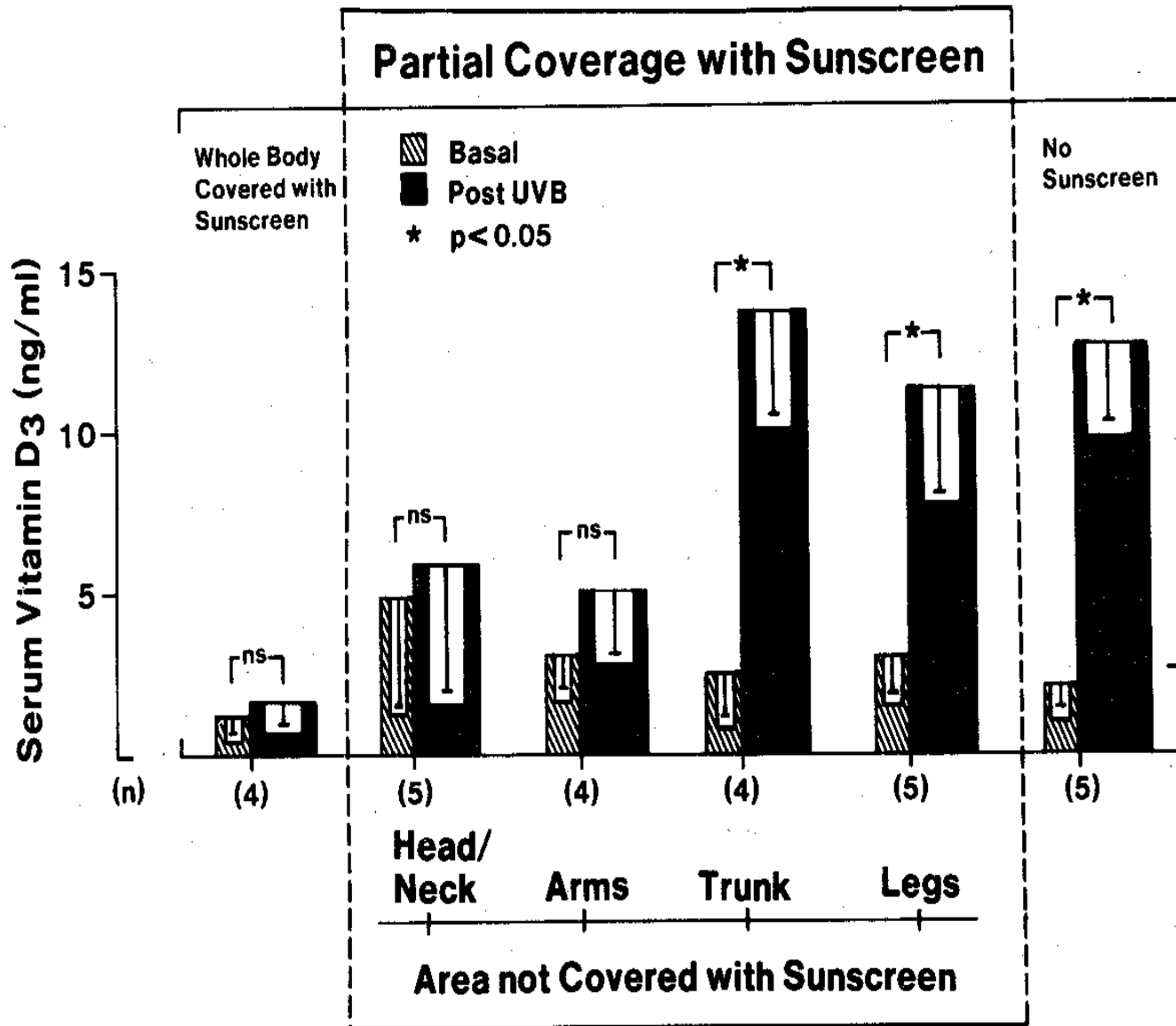
“Normal” Vitamin D Status

- Should NEVER have been defined by Gaussian distribution
- This is similar to defining “normal” estrogen levels by sampling a population of women who are primarily postmenopausal.
- There is a range that is associated with better health below which there are higher rates of disease states—we know this in 2009—we did not know this even five years ago.



Problem #3—

Sunscreen and Lifestyle
Changes



Matsuoka, L.Y., Wortsman, J., and Hollis, B.W. 1990. Use of topical sunscreen for the evaluation of regional synthesis of vitamin D₃. *J Amer Acad Dermatol* 22:772-775.

Adequate Intake for Vitamin D

- Children: 400 IU/d approximated from one teaspoon of cod-liver oil

(Park, JAMA 1940:115:370-9)

Even today, this is sound advice when you look at it on a per kilogram basis.

- Adults: One-half (200 IU)/d the infant dose to ensure that adults obtain some from the diet

(Blumberg et al, Pediatrics 1963;31:512-25)

- Considered a “generous allowance” in the 1989 version of the American recommended dietary allowances

Indoor Air Quality Act of 1989

- Average American spends 93% of their time indoors
- Profound implications for endogenous synthesis of vitamin D₃
 - 1989. Report to Congress on Indoor Air Quality, Volume II: Assessment and Control of Indoor Air Pollution. Office of Air and Radiation. U.S. Environmental Protection Agency EPA 400-1-89-001C, pp. I, 4-14

What determines your vitamin D status?

- Degree of skin pigmentation
- Sunlight exposure
- Dietary contribution (<10% total)
- Latitude
- Season/time of year and angle of sun's rays
- Use of sunscreen or protective or full clothing
- Outdoor exposure
- Body Mass Index
 - BMI >30 associated with decreased circulating 25(OH)D as fat serves as a vitamin D reservoir

What determines your vitamin D status if you are a fetus or neonate?

- Neonatal vitamin D status direct reflection of maternal status
- Neonatal levels are ~0.6-0.7 of maternal levels
- In Charleston, SC, 100 cord blood samples were collected at delivery:
 - Mean gestational age: 37.4 ± 3.2 weeks (range 27-41; median 38).
 - > 80% of the cohort delivered greater than 37 weeks' gestation.
- 25(OH)D mean \pm SD for the cohort: 13.5 ± 8.3 ng/mL.
- By race, there were significant differences between groups ($p < 0.0001$)

Cord Blood 25(OH)D by Season and Race

Group	All Year	April 1 – October 31	November 1 – March 31
All	13.5 ± 8.3 (n=100)	19.5 ± 9.6 (n=15)*	12.3 ± 7.7 (n=83)
African American	10.5 ± 6.0 (n=67)*	13.1 ± 4.0 (n=9)	10.1 ± 5.7 (n=58)*
Caucasian	19.5 ± 9.6 (n=33**)*	29.0 ± 7.0 (n=6)*	17.7 ± 9.2 (n=25)*

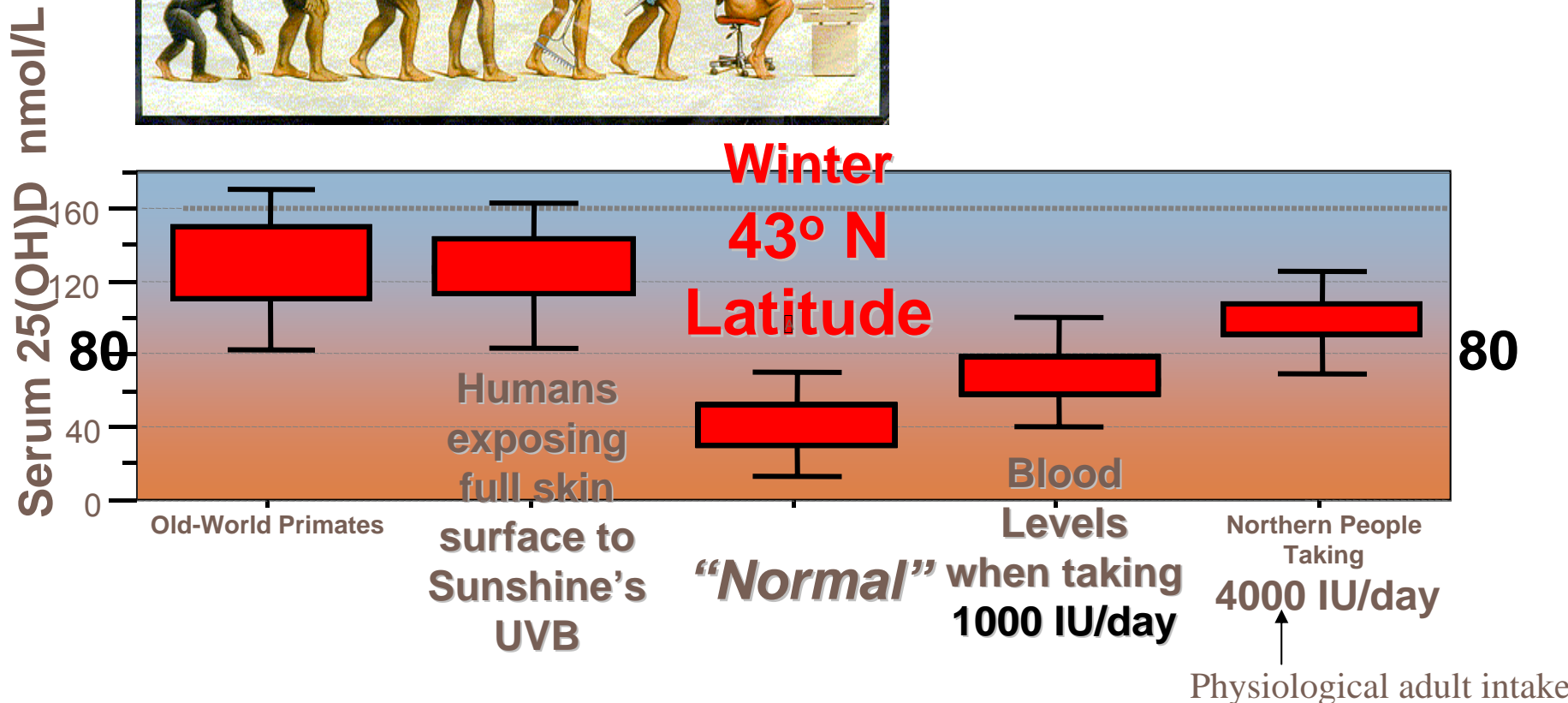
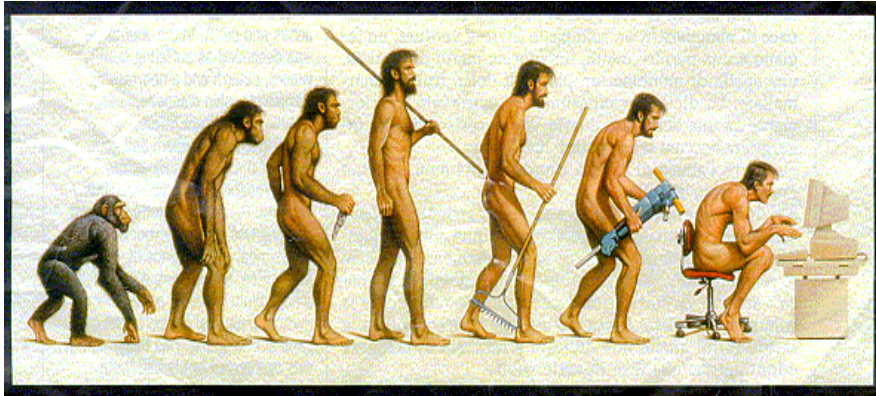
***p value < 0.0001; **season missing for 2 cases**

Basile L, Taylor S, Quinones L, Wagner C, Hollis B 2007 Neonatal vitamin D status at birth at latitude 32°72': Evidence of widespread deficiency. J Perinatology **27**(9):568-571.

Substrate Deprivation

- Why are maternal and neonatal vitamin D levels so low?
- The vitamin D endocrine system is the ONLY steroid endocrine system in the body that is almost always limited by substrate availability due to latitude, lifestyle, race etc.
 - Vitamin D conversion to 25(OH)D
 - 25(OH)D conversion to 1,25(OH)₂D in extra-renal sites

Vitamin D Status in Primates and Early Humans



Stages of Vitamin D Deficiency in Infants

Stage I: Hypocalcemia & euphosphatemia

Stage II: Eucalcemia, hypophosphatemia, & slight increase in skeletal alkaline phosphatase

Stage III: Hypocalcemia, hypophosphatemia, & increased alkaline phosphatase

Consequences of Vitamin D Insufficiency

Calcium absorption¹

- ❑ When vitamin D status is sufficient, absorption of dietary calcium is approximately 30% to 40%.
- ❑ As vitamin D status declines, absorption of dietary calcium declines to about 10% to 15%.

PTH

- ❑ Low levels of vitamin D leads to increased release of PTH,² which increases bone resorption and decreases bone mass.

Bone Mass

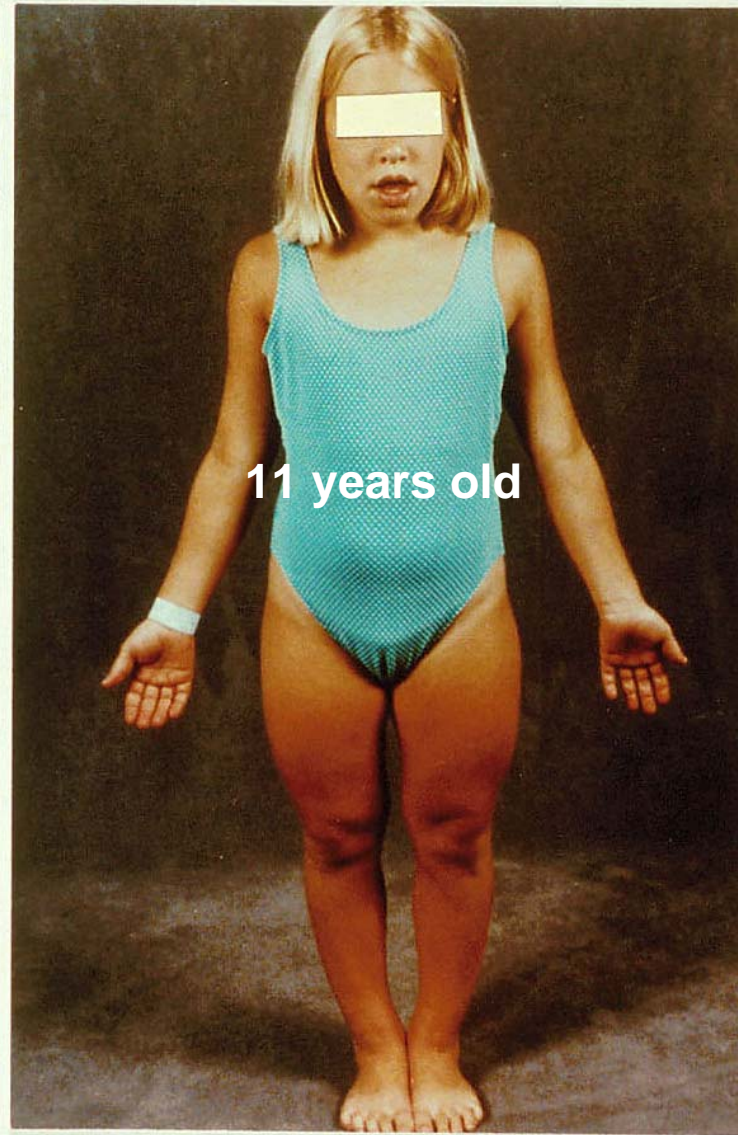
- ❑ Given its effect on calcium absorption, vitamin D insufficiency is associated with bone loss and an increased fracture risk.

1. Holick MF. *Curr Opin Endocrinol Diabetes*. 2002;9:87–98; Lips P. *Endocr Rev*. 2001;22:477–501.
2. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357(3): 266-281.

Vitamin D Deficiency

- Rickets
 - Enlargement of skull, joints of long bones and rib cage, curvature of spine and thighs, generalized muscle weakness
- Osteomalacia
- Immune
 - Immunomodulatory actions
 - Potent stimulator of innate immune system acting through toll-like receptors on monocytes and macrophages
 - Cancers – leukemia, prostate & breast cancer, psoriasis, diabetes mellitus

Classic Rickets: Obvious deformities correctable but what about other risks?



Photos courtesy of Dr. Lyndon Key, MUSC

How toxic is vitamin D?

- The U.S. Nutrition Guidelines state that the lowest observed adverse effect level (LOAEL) for humans is 2,000 IU vitamin D/day

Finland - Historical

Recommended intake of Vitamin D for Infants in Finland

- 1950s – 1964 4000-5000 IU/d
- 1964 2000 IU/d
- 1975 1000 IU/d
- 1992 400 IU/d

*No infantile hypercalcemia reported

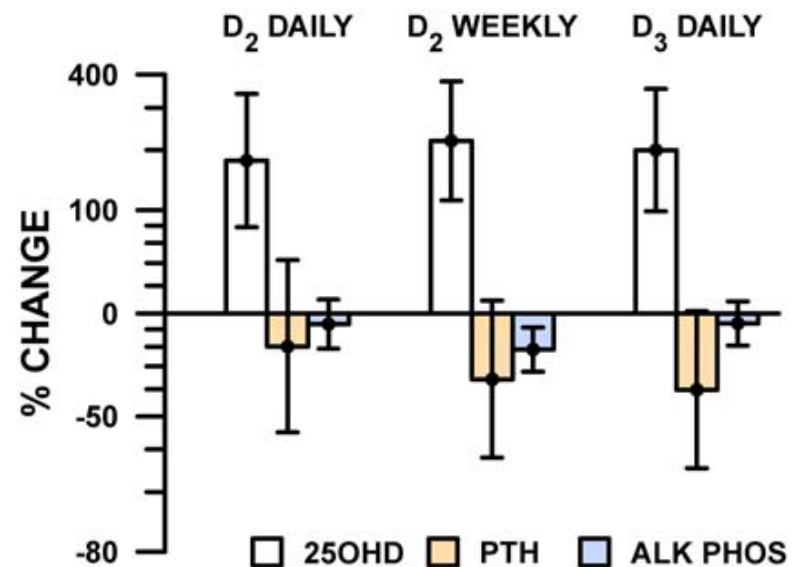
- Follow-up of these children 30+ years later shows lower rates of type I diabetes in those who received at least 2000 IU vitamin D/day as infants

A series of landmark studies—focus on safety and redefining the LOAEL

- Vieth, R. 1999. Vitamin D supplementation, 25-hydroxy-vitamin D concentrations, and safety. *Am J Clin Nutr* 69:842-856.
- Vieth, R., Chan, P.C.R., and MacFarlane, G.D. 2001. Efficacy and safety of vitamin D₃ intake exceeding the lowest observed adverse effect level (LOAEL). *Amer J Clin Nutr* 73:288-294.
- Heaney RP, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003; 77:204-210.

Gordon CM et al: Treatment of hypovitaminosis D in infants and toddlers. J Clin Endocrinol Metab 2008

- 6-wk supplementation with 2000 IU D₂/day, 50000 IU D₂ weekly or 2000 IU D₃/day
- Three regimen were equivalent in raising 25(OH)D levels with minimal change in serum calcium and equivalent decreases in PTH



Biomarkers for Vitamin D Sufficiency

- 25(OH)D
- Intact PTH
- Bone Mineral Density (BMD)
- Intestinal Calcium Absorption
- Mobility responsiveness
- Insulin sensitivity
- Beta cell function
- Immune function
- ??? Presence or absence of long-latency diseases such as diabetes, rheumatoid arthritis, MS, prostate and breast cancers, cardiovascular diseases

Acute and Long Latency Diseases

- Flu, acute respiratory infections, tuberculosis
- Various types of cancers, including colon, prostate, and breast cancers
- Autoimmune diseases such as Lupus, Multiple Sclerosis, Rheumatoid Arthritis, Scleroderma
- Type 1 Diabetes; Type 2 diabetes, insulin resistance and obesity
- Osteopenia, osteomalacia and rickets
- Cardiovascular disease
- Fetal growth, fetal dentition, and bone mass
 - And the list goes on...

CHRONIC DISEASES

Disease	Status of Evidence
□ osteoporosis	++++
□ osteoarthritis	+
□ falls/neuromusc fcn	++++
□ multiple sclerosis	++
□ fibromyalgia-like syndrome	++
□ type I diabetes	++
□ insulin sensitivity	++
□ cardiovascular disease	+++
□ pregnancy outcomes	++++
□ periodontal disease	++++
□ various cancers	++++
□ tuberculosis	++++
□ hypertension	++++

What do these diverse groups of disease states all have to do with vitamin D?

Vitamin D and the Innate Immune System

- In 1903, Niels Ryberg Finsen was awarded the Nobel Prize for his work, demonstrating that UV light was beneficial to patients with Lupus vulgaris.
- The beneficial effects of UV exposure to tuberculosis patients is also known.

Yet, what went wrong with sanatoriums?

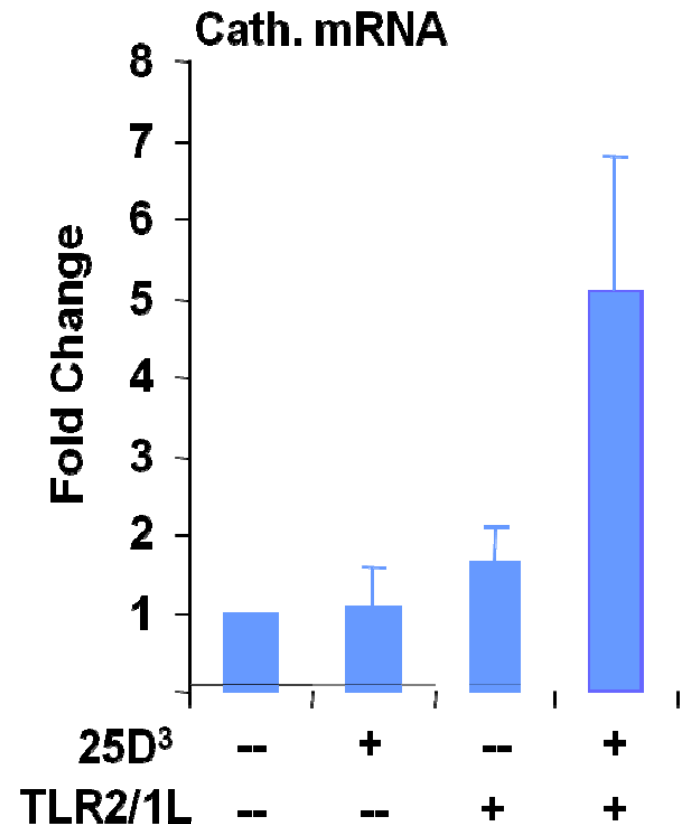
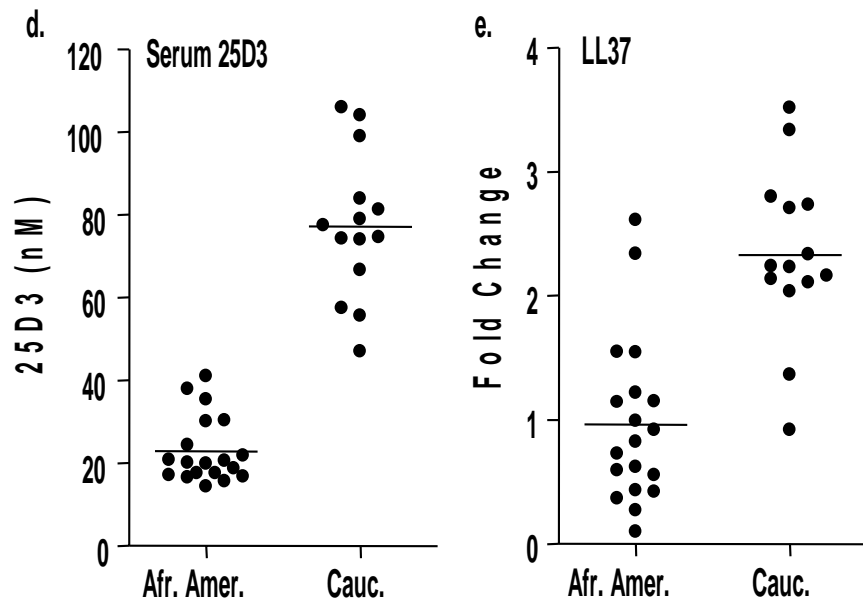


Cathelicidin (LL-37)

- An endogenous antimicrobial peptide
- Generated by innate immune system in response to microbial invasion thru Toll 2 surface receptor on monocytes and macrophages
 - Vitamin D Responsive Element (VDRE) also contained in gene regulatory region of these cell types

Sera taken from AA subjects with low 25(OH)D inefficient in supporting cathelicidin mRNA induction

Addition of 25(OH)D₃ restores ability of sera from AA to mediate induction of cathelicidin mRNA



Liu P, et al. Toll-like receptor triggering of a vitamin-D mediated human antimicrobial response. Science 2006; 311

- Support a link between TLRs and vitamin D–mediated innate immunity
- Suggest differences in ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection

It also explains these findings— of rickets and infection

- Rickets is not only associated with skeletal abnormalities but also respiratory infections.
- In 1994 a brief study demonstrated that respiratory infections in children with elevated alkaline phosphatase levels were eliminated by supplementing them with 60,000 IU vitamin D/wk for a period of 6 wks.

Rehman P 1994 Sub-clinical rickets and recurrent infection. J Tropical Pediatr **40**:58.

Vitamin D and Pregnancy



Much consternation—Vitamin D deficiency is not limited to children

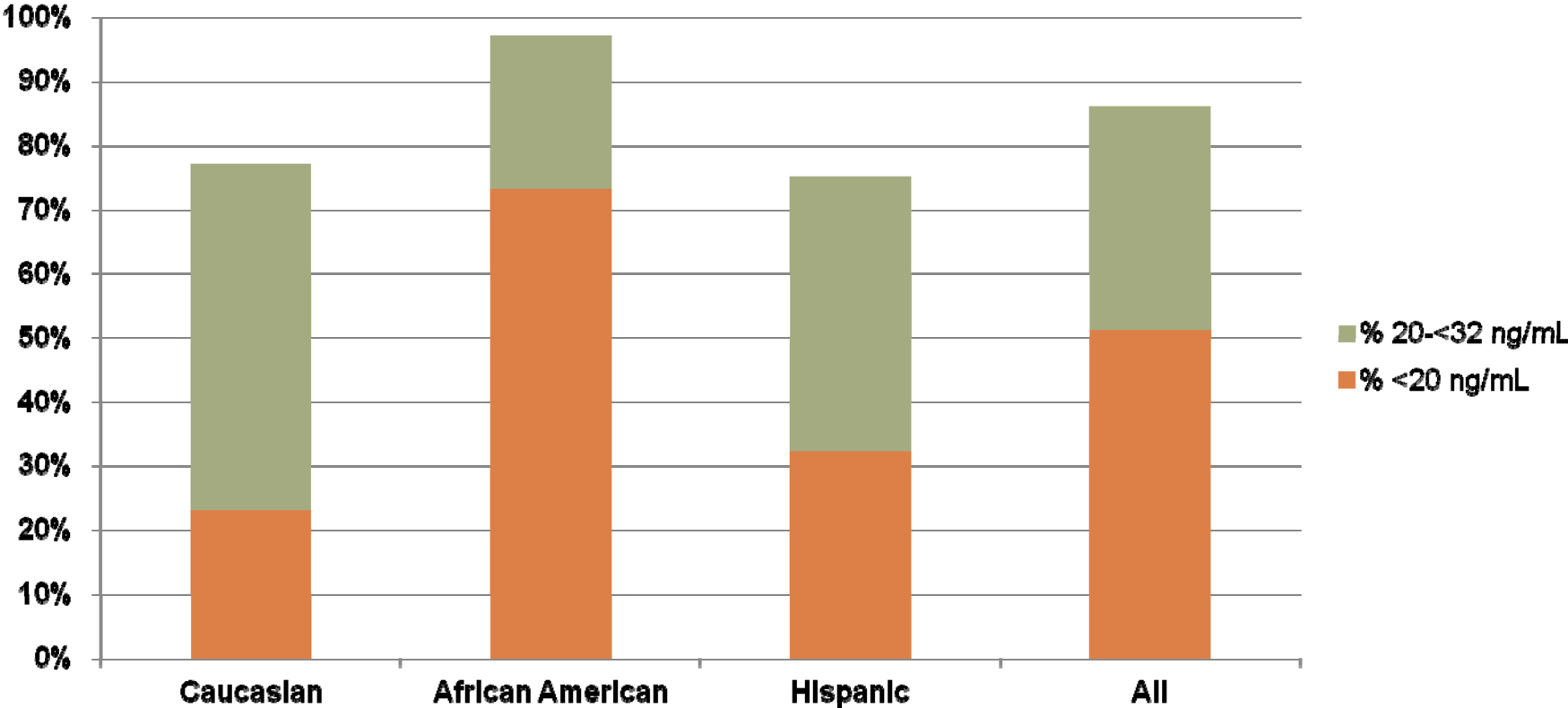
- Nesby-O'Dell, S., Scanlon, K., Cogswell, M., Gillespie, C., Hollis, B., Looker, A., Allen, C., Dougherty, C., Gunter, E., and Bowman, B. 2002.
- Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey: 1988-1994. *Am J Clin Nutr* 76:187-192.

What was known in 2002...

- A subset of pregnant women had or developed vitamin D deficiency during their pregnancy
 - ▣ Adverse effects known in terms of impaired fetal growth, dentition, lighter/less dense bones, and rarely, neonatal seizures from profound hypocalcemia
- Supplementation with vitamin D beyond 400 IU/day was unnecessary and risky—
 - ▣ Remember the teratogenicity data
- A scientific review committee at NIH reviewed our grant to evaluate the vitamin D requirements of the pregnant woman and thought the study worthy of doing.
 - ▣ It began a cascade of events that has changed the way we view vitamin D today.

Evidence of the Epidemic: Our Data in South Carolina

Baseline Circulating 25(OH)D Levels



Public Health Issue

- Evident that vitamin D deficiency during pregnancy is a serious public health issue that affects both mother and fetus.
- Need to establish the vitamin D requirements of the pregnant woman seen as vital in preventing vitamin D deficiency.
- **Objective:** Evaluate the safety and effectiveness of high dose vitamin D supplementation in decreasing pregnancy comorbidity risks in a randomized clinical trial

Deficiency during Fetal & Infant Development

□ Higher risk of maternal preeclampsia

- Halhali A, Tovar AR, Torres N, Bourges H, Garabedian M, Larrea F 2000 Preeclampsia is associated with low circulating levels of insulin-like growth factor 1 and 1,25-dihydroxyvitamin D in maternal and umbilical cord compartments. *J Clin Endocrinol* **85**(5):1828-2833.
- Hypponen E 2005 Vitamin D for the prevention of preeclampsia? A hypothesis. *Nutr Rev* **63**(7):225-32.
- Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM 2007 Maternal Vitamin D Deficiency Increases the Risk of Preeclampsia, vol. 92, pp 3517-3522.

□ Impaired fetal growth

- Brooke OG, Brown IRF, Bone CDM, Carter ND, Cleeve HJW, Maxwell JD, Robinson VP, Winder SM 1980 Vitamin D supplements in pregnant Asian women: Effects on calcium status and fetal growth. *Brit Med J* **1**:751-754.
- Brunvand L, Quigstad E, Urdal P, Haug E 1996 Vitamin D deficiency and fetal growth. *Early Human Development* **45**:27-33.

□ Impaired dentition

- Purvis RJ, Barrie WJ, MacKay GS, Wilkinson EM, Cockburn F, Belton NR 1973 Enamel hypoplasia of the teeth associated with neonatal tetany: a manifestation of maternal vitamin-D deficiency. *Lancet* **2**(7833):811-4.

□ Increased risk of gingivitis and periodontal disease

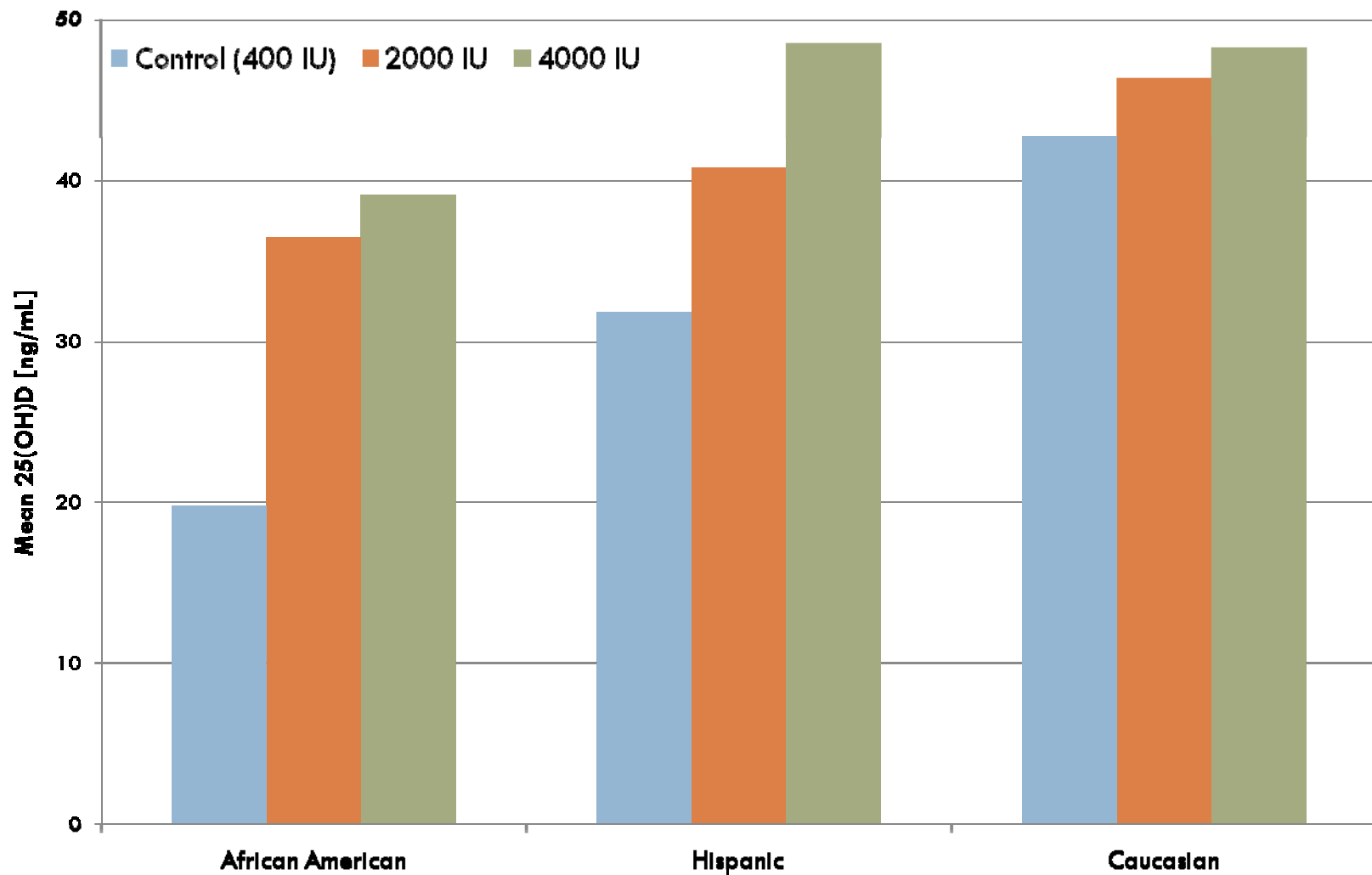
- Dietrich T, Nunn M, Dawson-Hughes B, Bischoff-Ferrari HA 2005 Association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation. *Am J Clin Nutr* **82**:575-580.
- Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA 2004 Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. *Am J Clin Nutr* **80**(1):108-13.

□ At this time, not known about other rates of infection or other long-term markers

Public Health Issue

- Evident that vitamin D deficiency during pregnancy is a serious public health issue that affects both mother and fetus.
- Need to establish the vitamin D requirements of the pregnant woman seen as vital in preventing vitamin D deficiency
- **Objective:** Evaluate the safety of high dose vitamin D supplementation during pregnancy in a randomized control trial starting at 12 weeks of gestation.

Mean Circulating 25(OH)D at 1 Month Prior to Delivery by Race/Ethnicity



Treatment Effects on Circulating 25(OH)D Levels in Offspring

- Neonatal 25(OH)D was significantly correlated with both treatment group and maternal 25(OH)D levels at various points during pregnancy:
 - Significantly different by treatment group at delivery
 - 18.2 ± 10.2 ng/mL (45.5 nmol/L) (control)
 - 22.8 ± 9.8 ng/mL (57.0 nmol/L) (2000 IU)
 - 26.5 ± 10.3 ng/mL (66.3 nmol/L) (4000 IU)
 - ($p < 0.0001$)
 - Maternal 25(OH)D correlated with neonatal 25(OH)D at delivery
 - Maternal baseline ($r = 0.68$; $p < 0.0001$)
 - Maternal one month prior to delivery ($r = 0.6$; $p < 0.0001$)
 - Maternal area under the curve (chronic level; $r = 0.68$; $p < 0.0001$)
 - Maternal level at delivery correlated with ($r = 0.77$; $p < 0.0001$)

Thrasher Research Fund Community- Based Study in Columbia , SC

- Diverse group of women randomized to 1 of 2 tx groups at <16 weeks' gestation:
 - 257 women were enrolled; 160 women completed the study; Randomized to 2000 or 4000 IU vitamin D₃/day irrespective of baseline 25(OH)D
 - Confirms NIH/NICHD study findings
 - No adverse events associated with vitamin D supplementation
- Analysis of pregnancy complications as function of Δ 25(OH)D from baseline, chronic vitD status (area under curve), and 1-month prior to delivery:
 - Rates of infection were inversely related to all 3 measures of vitD status, an effect that persisted even after controlling for race.
 - Preterm labor/birth was inversely associated with initial (p=0.001) and month prior to delivery 25(OH)D (p=0.008).

2010 Perspective on Vitamin D during Pregnancy

- Vitamin D supplementation with 4,000 IU vitamin D/day for pregnant women was safe and effective in achieving vitamin D sufficiency in a racially diverse group.
- To normalize vitamin D metabolism in the pregnant woman, a circulating 25(OH)D level of at least 40 ng/mL (100 nmol/L) is required.
- Higher maternal circulating 25(OH)D was associated with lower risk of co-morbidities of pregnancy.
- Therefore, we recommend for all pregnant women:
 - Checking 25(OH)D levels at the start of pregnancy
 - Achieve a 25(OH)D level of at least 40 ng/mL (100 nmol/L) for optimal conversion of to 1,25(OH)₂D
 - This can be achieved through vitamin D supplementation of 4000 IU/day starting at 12 weeks' gestation

VITAMIN D IN LACTATION



It is widely known that human milk is deficient in vitamin D.



- Dogma of the 20th Century


Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents

Carol L. Wagner, MD, Frank R. Greer, MD, and the Section on Breastfeeding and Committee on Nutrition

Pediatrics 2008;122:1142–1152

Beyond Current Recommendations

- AAP recommends that all breastfed infants receive vitamin D supplementation starting within the 1st few days after delivery
 - Wagner CL, Greer FR, Section on Breastfeeding, Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008;122:1142–1152.
- Addresses the infant but not mother's status:
 - Could maternal supplementation at higher doses provide adequate levels in breast milk without toxicity to mother?
 - This would effectively treat mother and breastfeeding infant.



Will direct maternal vitamin D supplementation meet the requirements of both the mother and her nursing infant?

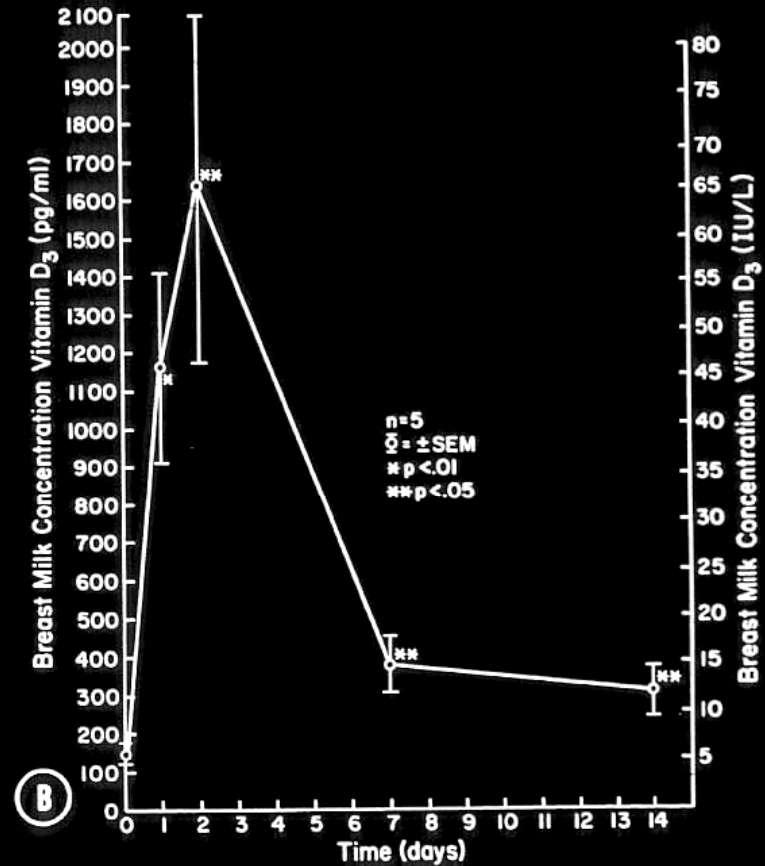
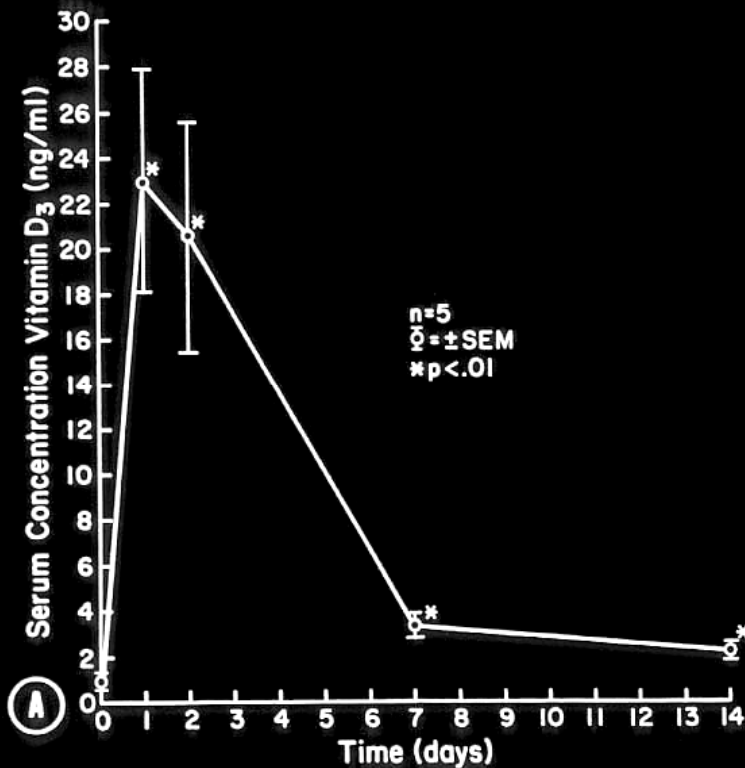
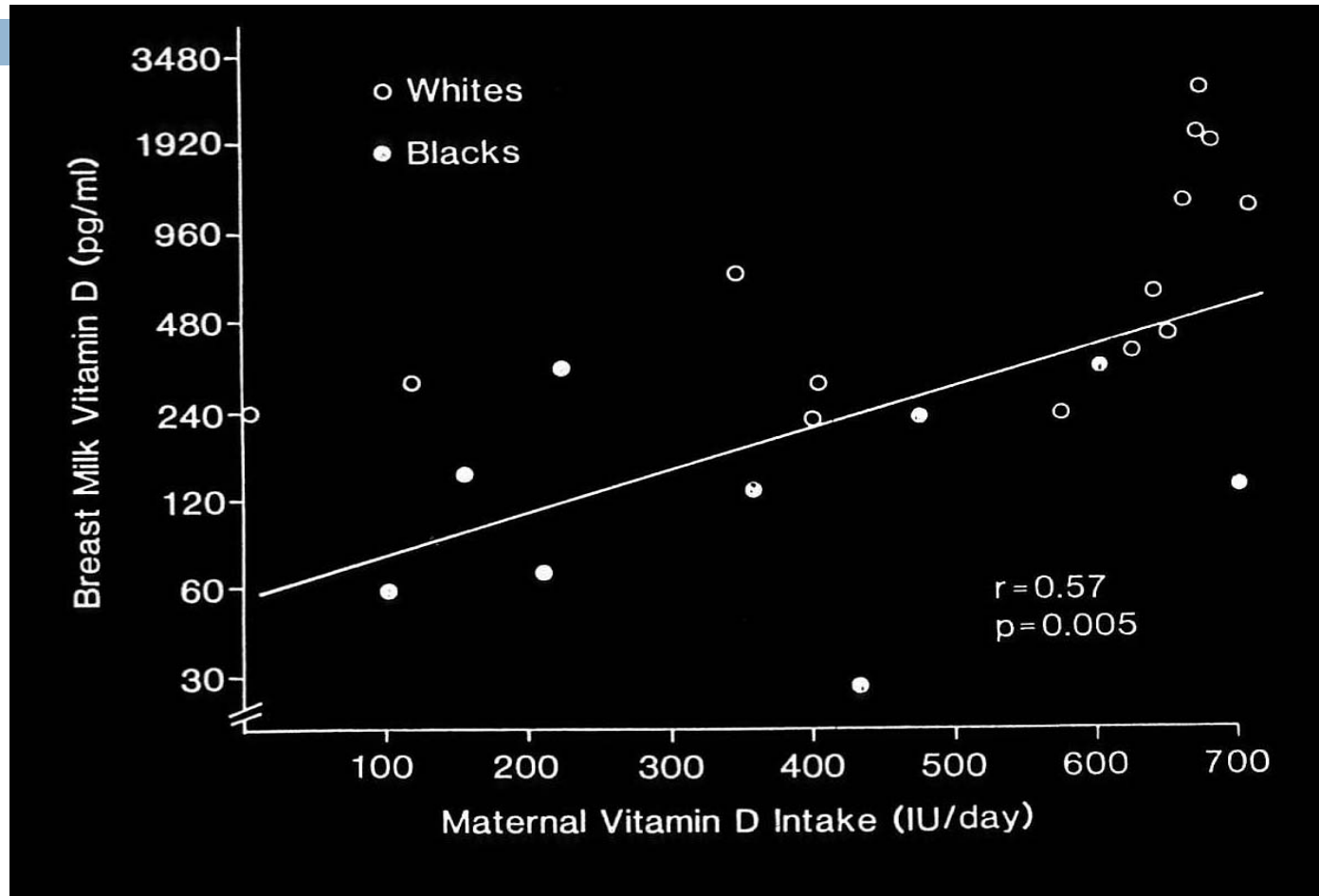


Figure. Serum (A) and milk (B) concentrations of vitamin D₃ in five white lactating women before and after 1.5 minimal erythemic dose of total body ultraviolet B irradiation.

Cancela, L., LeBoulch, N., and Miravet, L. 1986. Relationship between the vitamin D content of maternal milk and the vitamin D status of nursing women and breastfed infants. *J Endocrinol* 110:43-50.

Cancela et al. (J Endocrinol 1986;110:43-50.)



- Circulating 25(OH)D concentrations in breastfed infants are directly related to the vitamin D content of the mothers' milk

Available evidence indicates that if vitamin D status of the lactating mother is adequate, her breastfeeding infant will maintain a “minimally normal” vitamin D status.

Greer FR, Marshall S. Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without vitamin D2 supplements. J Pediatr 114 (2) 1989 p:204 -12

Additional Data...

- Data suggest that doses exceeding 1000 IU vitamin D/d (2,000-10,000 IU/d) required to achieve a robust normal concentration of circulating 25(OH)D
 - Vieth et al. Am J Clin Nutr 2001;73:288-94.
 - Heany et al. Am J Clin Nutr 2003;77:204-10.
 - Hollis & Wagner. Am J Clin Nutr 2004.
 - Hollis & Wagner. J Clin Nutr 2004.
 - Wagner, et al. Breastfeeding Med 2006; 2: 59-70

Two Finnish Studies


- Maternal supplements with 1000 IU vitamin D/d resulted in a minimal increases in circulating 25(OH)D concentrations in breastfeeding infants
- Repeated study with 2000 IU vitamin D/d found the vitamin D status of the breastfeeding infants improved significantly
 - Ala-Houhala M. J Pediatr Gastroenterol Nutr 1985;4:220-6.
 - Ala-Houhala et al. Arch Dis Child 1986;61:1159-63.

Important Considerations Regarding Vitamin D Status

- When a woman is deficient in vitamin D, her developing fetus is deficient.
- Similarly, a lactating woman who is deficient in vitamin D, provides breast milk that is deficient in vitamin D--
 - therefore, unless her breastfeeding infant is supplemented, her breastfeeding infant will be deficient.

Main Concerns of High Dose Vitamin D Supplementation

- Toxicity to both mother and her breastfeeding infant
- Or that mother would become toxic but that there would be little transfer to infant
 - ▣ Human milk is deficient theory
- There would be a reduction in bone demineralization in mother due to the direct of vitamin D on PTH, with lower levels of calcium to be transferred to the breastfeeding infant.



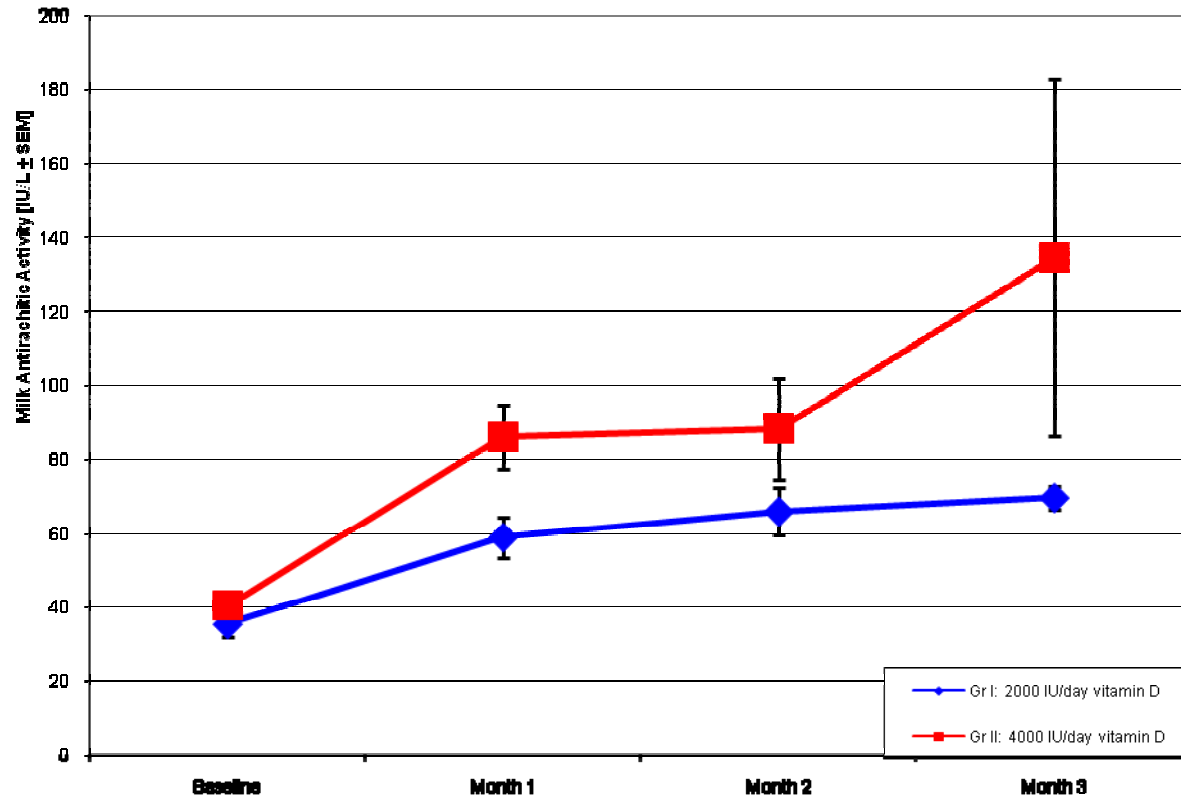
Vitamin D Requirements during Lactation: High-Dose Maternal Supplementation as Therapy to Prevent Hypovitaminosis D in Both Mother and Nursing Infant.

Hollis & Wagner. *Am J Clin Nutrition* 2004; 80S: 1752S-
1758S.

Vitamin D Supplementation During Lactation

- 1. To increase the nutritional vitamin D status of the mother
- 2. To improve the vitamin D nutriture of the breastfeeding infant

Longitudinal Assessment of Milk Antirachitic Activity as a Function of Supplementation Regimen In Lactating Women (n=18)



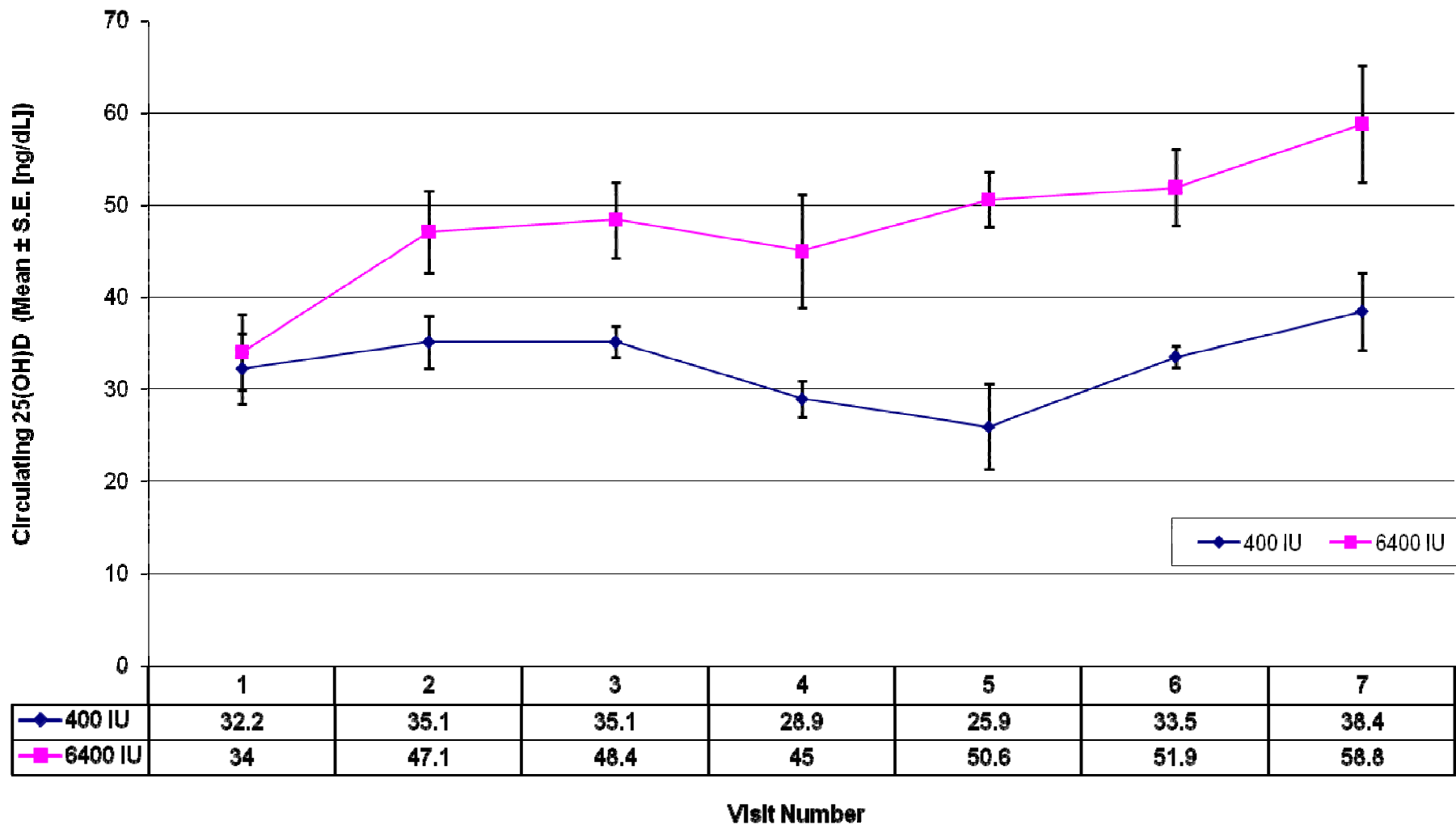
Pilot Study #2: Vitamin D Supplementation Trial of Lactating Mothers and Their Infants

- Mothers were randomized to 1 of 2 treatment groups:
 - ▣ 400 vs. 6,400 IU vitamin D₃/day for 6 months starting at 1 month postpartum
- Investigators and study team blinded to assignment group:
 - ▣ Infants whose mothers were randomized to 400 IU/d received 300 IU vitamin D₃/day
 - ▣ vs. Infants whose mothers were in the 6,400 IU/day group received placebo

Results

- There were no adverse events in any mother or infant related to vitamin D
- Compliance with the regimen was higher in the mothers (>90%) than the corresponding infant
 - ▣ **Mothers said that they were more often likely to forget to give their infant vitamins than take their own pills**

**Figure 1. Maternal 25(OH)D Status:
400 IU vs. 6,400 IU Vitamin D₃/day Supplementation Regimen**



**Figure 3. Milk Antirachitic Activity as a Function of Maternal Vitamin D₃ Dose:
400 vs. 6,400 IU/day**

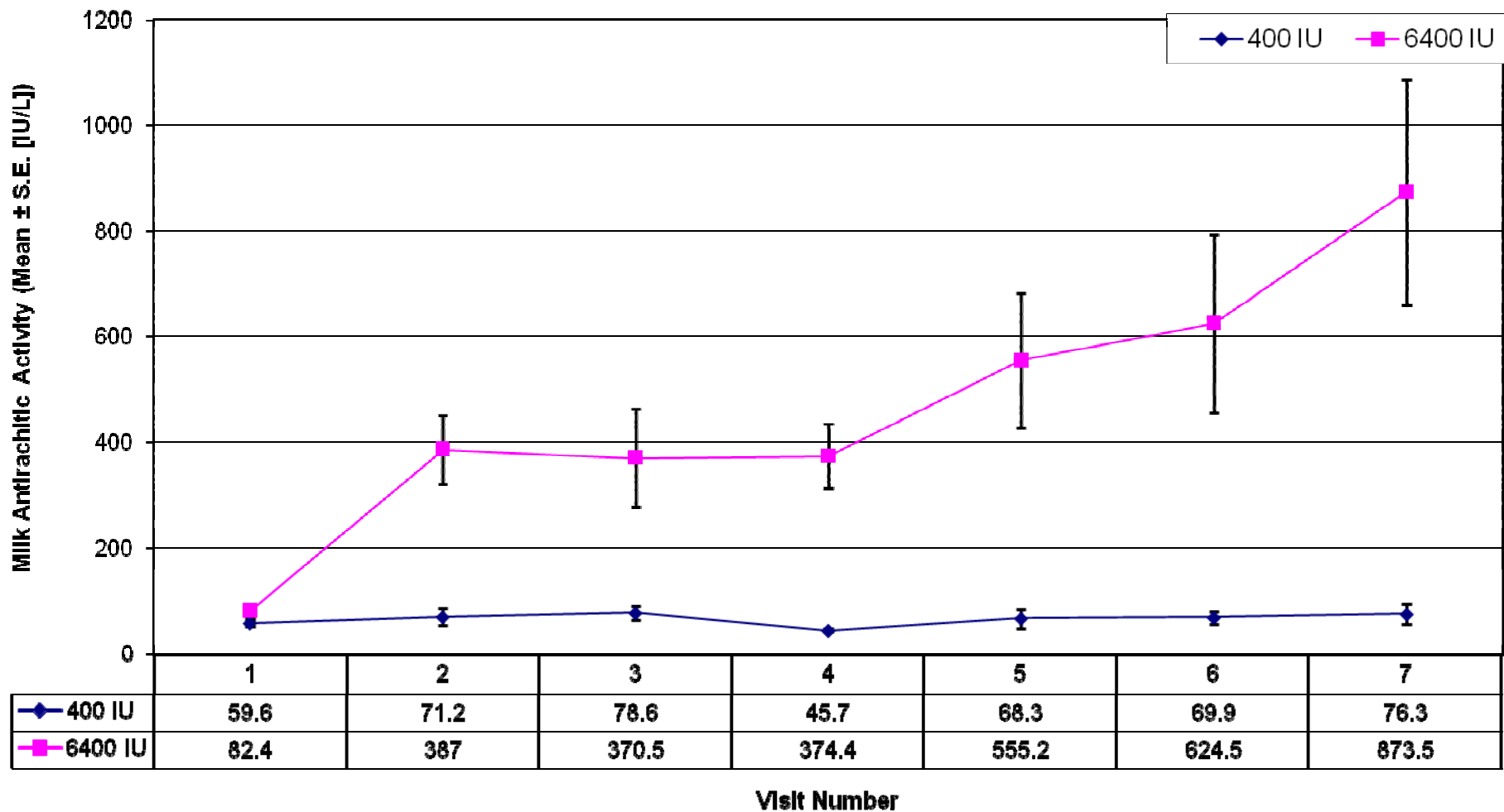
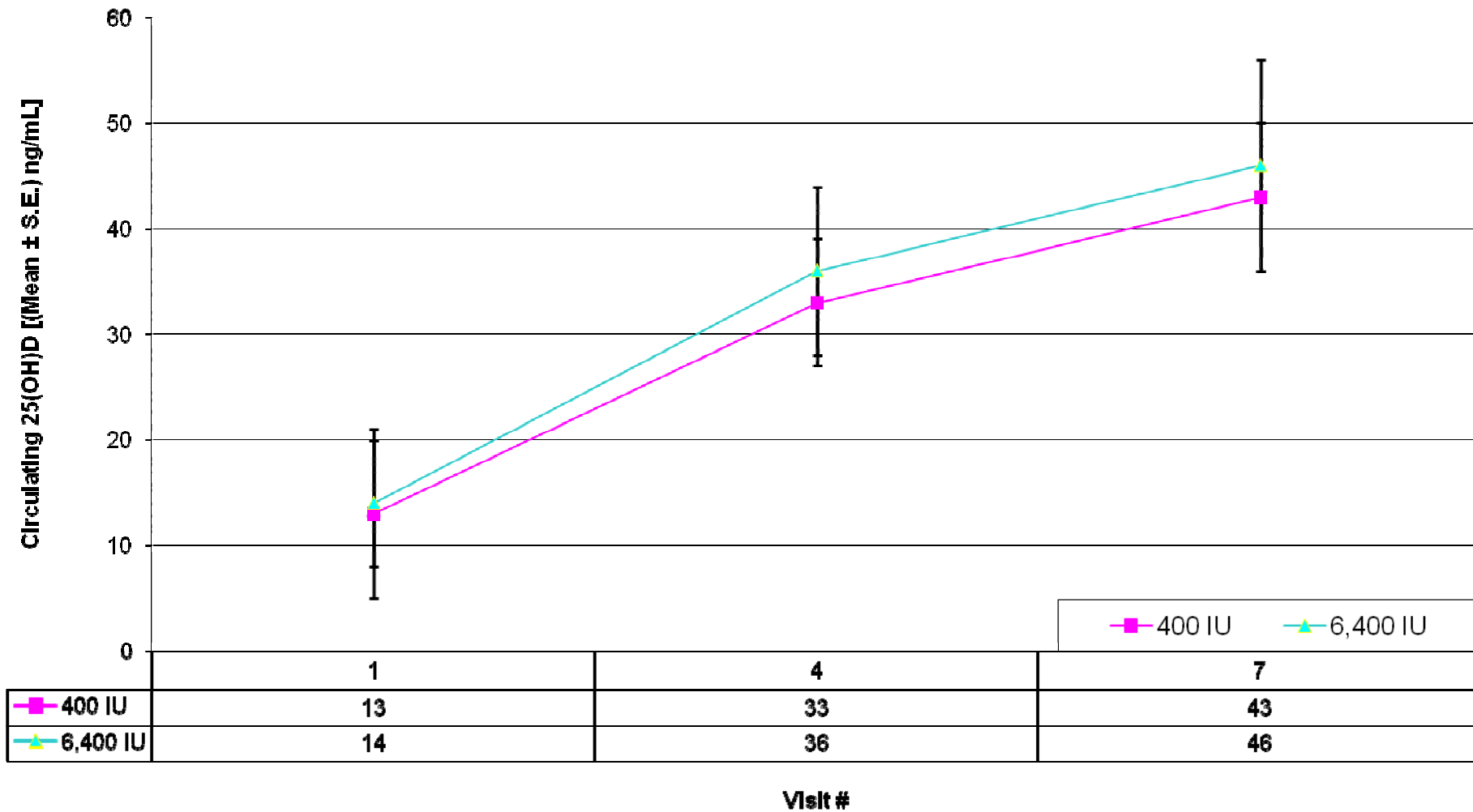


Figure 4. Infant Circulating 25(OH)D as a Function of Maternal Supplementation (400 vs. 6,400 IU vitamin D₃/day) & Infant Supplementation (300 vs. 0 IU vitamin D₃/day)



Results of 2nd pilot study

- Vitamin D supplementation of mother with higher doses improved maternal vitamin D status, and in so doing, increased her milk antirachitic activity, and thus, the transfer of vitamin D to her nursing infant.
- We showed both efficacy and effectiveness—
- What we have to show now is safety and effectiveness on a larger scale....

NIH-Sponsored Vitamin D Supplementation Trial of Lactating Women and Their Infants

- Two site study: MUSC and University of Rochester
- Began enrollment November 2006 in Charleston and January 2007 in Rochester
- Mothers recruited by 4-6 weeks postpartum (n=567)
 - ▣ Rochester: Lactating Mother/Infant Dyad only (n=189)
 - ▣ Charleston: Lactating Mother/Infant Dyad (n=189) & Non-lactating Mothers (n=189)
- Mother and infant dyad followed for 6 mos
 - ▣ Following vitamin D status, bone mineralization and safety parameters with visits monthly
- Recently ended 2000 IU arm of study as treatment failed to increase infant levels and a disproportionate number of infants required open label supplementation with 400 IU/day compared with 400 and 6000 IU groups

Effectiveness of Oral Vitamin D Supplementation in Breastfeeding Infants

- Design:
 - As part of larger, ongoing vitamin D supplementation trial of fully lactating women, infants of mothers assigned to the control group received 400 IU vitamin D₃ in one drop per day dosing starting at one month of age.
 - Subjects were enrolled throughout the year.
 - The change in circulating 25(OH)D levels in those infants was measured.
 - As part of our data safety and monitoring process, levels of those infants randomized to the control group in a blinded fashion were analyzed to determine effectiveness of the daily one drop/day vitamin D dosing method.
 - Infant 25(OH)D levels (mean ± S.D.) were measured by radioimmunoassay at Visits 1 (~1 month of age; baseline), 4 and 7.
 - Data were analyzed by Paired Student's t-test and repeated measures ANOVA; significance was set at 0.05 *a priori*.

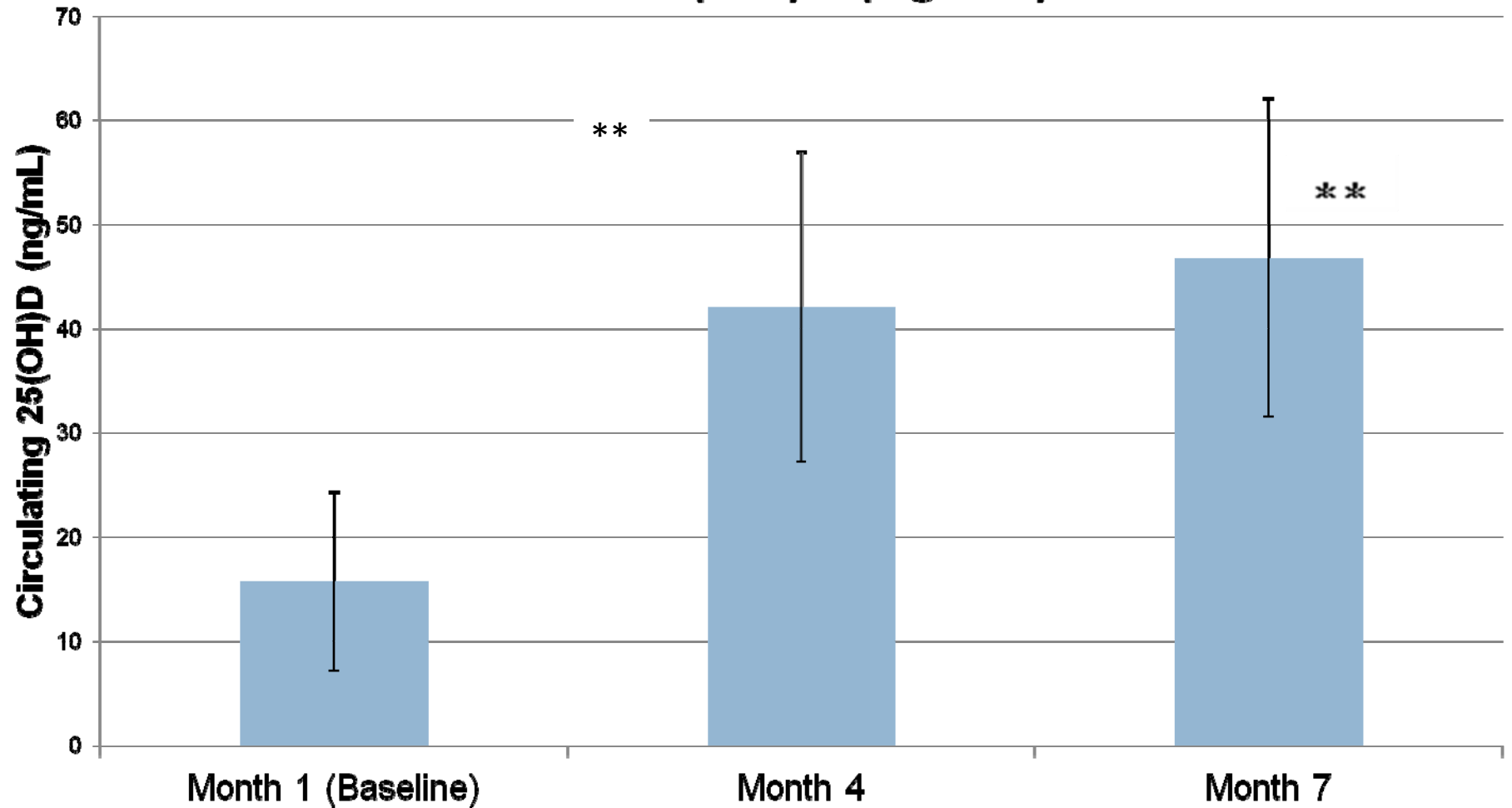
Results

- 54 mothers and their infants were enrolled in the study and randomized to the control group in a blinded fashion; 33 have completed the study through visit 7.
- The mean \pm S.D. 25(OH)D at one month (baseline) for the infants was:
 - 16.0 ± 9.3 ng/mL (range 1.0-40.8; n=33)
 - 24 (72.7%) had baseline levels <20 ng/mL (consistent with deficiency)
- Mean levels increased to 43.6 ± 14.1 (range 18.2-69.7) at 4 months and remained relatively unchanged at month 7: 42.5 ± 12.1 ng/mL (range 18.9-67.2).
 - Change in values between 1 and 4 months, 1 and 7 months was statistically significant ($p \leq 0.0001$).
- As predicted, there were no statistically significant differences between months 4 and 7 ($p=0.66$).
- Even with changes in season, the results remained significant. On an IU/kg basis, at visit 1, the infants were receiving 88.9 ± 10.5 IU/kg; at visit 4, they were receiving 59.7 ± 6.6 IU/kg; and at visit 7, they were receiving 50.5 ± 6.0 IU/kg ($p < 0.0001$).
- Despite the decrease in dose on a per kilogram basis, the infant mean circulating 25(OH)D levels were not significantly different between visit 4 and 7.

Infant Weight, Vitamin D Status and Dosage per Body Weight

Variable	Visit 1 (n=54)	Visit 4 (n=27)	Visit 7 (n=22)
Infant wt (mean ± S.D.)	4.6 ± 0.44 kg	6.8 ± 0.79 kg	8.0 ± 1.03 kg
Total circulating 25(OH)D [ng/mL]	16.3 ± 8.9	43.3 ± 13.7	42.2 ± 12.3
IU Vitamin D/body wt (kg)	87.3 ± 8.3	59.5 ± 7.0	50.8 ± 6.2

Total Infant Circulating 25(OH)D (ng/mL)



**p<0.0001

Conclusions

- Oral vitamin D₃ supplementation as an oil emulsion (400 IU/drop) was associated with significant and sustained increases in circulating 25(OH)D from baseline in fully breastfeeding infants through 7 months of age.
- We educated parents how to give the vitamin D before leaving the clinic.
- Caveat: It is essential that you show parents how to dispense any medication—whether it is acetaminophen or vitamin D.
 - ▣ If a parent can demonstrate how to give a med, then the chances of overdosing diminish.

For pregnant women

- 4,000 IU vitamin D/day was found to be safe and effective in raising maternal circulating 25(OH)D levels
 - ▣ Higher 25(OH)D was associated with lower risk of preterm labor/birth and overall infections during pregnancy
- As a clinician, you can check a circulating 25(OH)D level to ascertain that patient's status and prescribe accordingly, with the goal to achieve a total circulating 25(OH)D level of 40 ng/mL, the level where there is adequate substrate to convert 25(OH)D to 1,25(OH)₂D

For Lactating Women

- Maternal circulating 25(OH)D levels could be checked—
 - if levels >60 ng/mL, there is **likely** no need for supplementation of breastfeeding infant as maternal milk will have good levels.
 - **HOWEVER, DON'T ASSUME SUFFICIENCY:** you would have to check both maternal and infant levels to assure sufficiency.
- Supplement lactating mother with high dose vitamin D and treat both mother and infant:
 - ▣ **Unproven/experimental** at this time
- Achieve circulating 25(OH)D levels of at least 30 ng/mL in all your patients, and don't forget yourself!
- When in doubt, check a level...

For the breastfeeding infant

- Supplement breastfeeding infant with 400 IU vitamin D₃/day to ensure adequate intake
 - ▣ Either achieved through vitamin D only preparations or as part of a multivitamin preparation
 - Instruction on how to dose vitamin D is essential: one drop, one dropper, one mL: specific to each vitamin preparation
- Combination fed infants should receive vitamin D supplementation as well
- Exclusively formula-fed infants do not require supplementation if they are taking in greater than 1 liter formula per day
- Ongoing research will assess the safety and effectiveness of maternal supplementation with the premise that making mother replete in vitamin D will allow adequate transfer of vitamin D in her milk and thus adequate levels in her breastfeeding baby

Table 4. Suggested Vitamin D Supplementation Regimen for Infants, Children and Pregnant and Lactating Women

Age Group	Recommended Daily Vitamin D Intake (IU/day)	Caveats to ponder
Neonates	400 IU/day	This includes premature neonates and infants.
Infants < 1 year	400 IU/day up to 10 kg; then 25-50 IU/kg	
Children 1-2 yrs	25-50 IU/kg	For example, a child weighing 20 kg would be given 500-1,000 IU/day. Another child weighing 25 kg would be given 625-1,250 IU/day. One could give the lower dose during summer months and the higher dose during winter months.
Children 2-5 years	25-50 IU/kg up to 30 kg	
Children 5-12 years	25 IU/kg up to 50 kg	
Children 12-17 years	>50 kg	2,000-4,000 IU/day depending on BMI
Pregnant woman	>45 kg	4,000 IU vitamin D/day [This recommendation is based on our two RCT that were completed in 2009 (C. Wagner, D. Johnson, et al., 2010; C. Wagner, R. McNeil, et al., 2010; C. L. Wagner, et al., 2010)]
Lactating Woman		4,000 IU/day with refinement of recommendation once Lactation RCT vitamin D studies have been completed and analyzed.

From: Wagner CL, et al. New Insights into Vitamin D during Pregnancy, Lactation and Early Pregnancy. 2010; Hale Publishers

Indication for Measurement

- When nutritional deficiency of vitamin D is suspected
 - ▣ Intestinal malabsorption syndromes
 - ▣ Patients on chronic anti-epileptic drugs
 - ▣ Limited exposure to the sun: the average American in 1989 spent 93% of their time indoors—imagine the stats in 2009!
 - This happens even in San Diego, especially for those who work indoors such as a medical center!
 - ▣ Limited intakes of oral vitamin D supplements
 - ▣ Aged, homebound patients
 - ▣ Darkly pigmented individuals
 - ▣ Thorough use of sunscreen

Conclusions

- We are in the midst of a **vitamin D deficiency epidemic.**
- There are many reasons why, not the least of which is that we made too many assumptions about vitamin D.
- It is quite likely that chronic nutritional vitamin D deficiency puts all of us at risk for developing debilitating, long latency chronic diseases such as insulin resistance/diabetes, cardiovascular disease, cancer and autoimmune diseases.
- Society will need to understand the role that vitamin D plays in health—beyond bones and mandate policy changes at the national level.
 - ▣ That mechanism of change begins with you.

The children...they are our future.





Thank you

- How do I know if the infants and toddler in my practice have Vitamin D deficiencies?
 - What are the stages of Vitamin D deficiency? the clinical signs? the potential latent disease processes associated with Vitamin D deficiency?
 - What patients might be at risk?
 - Who should I screen, how often, and what kind of screening tests should I do for Vitamin D deficiency?
 - How do I treat patients with Vitamin D deficiencies?
- Sun exposure and Vitamin D
 - How much sun should infants and toddler get?
 - What do SPF sunscreens do to Vitamin D absorption?