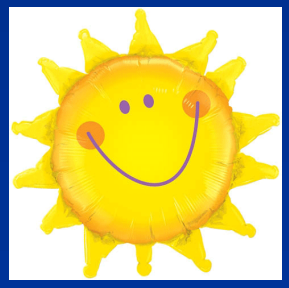
Vitamin D in Allergic and Immune Disorders

Mitchell R. Lester, MD

Fairfield County Allergy, Asthma, and Immunology Associates
Norwalk, CT

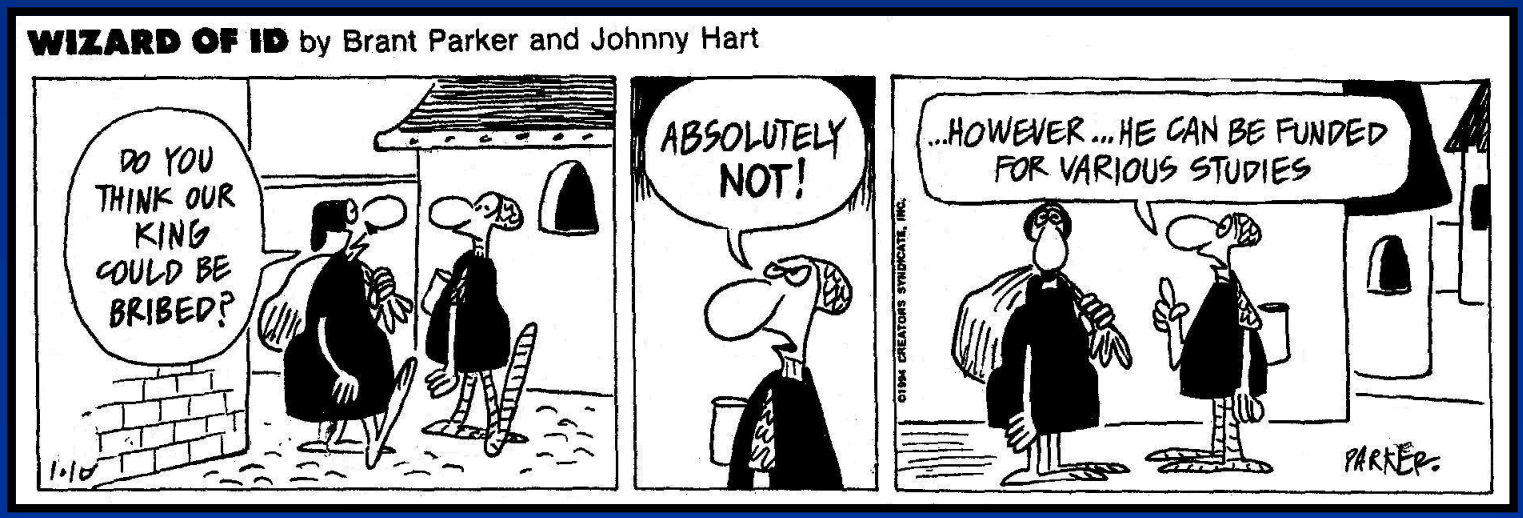
ACAAI Meet the Professor Breakfast (S3)
November 10, 2013



mrlester@optonline.net

Disclosure

I have no potentially relevant financial interests, conflicts of interest, or other affiliations with any corporate organizations relevant to the subject of my presentation. I do not intend to discuss off label use of medications or devices.



Disclosure

I take 1400 IU of vitamin D q.d.

Hopefully, this topic will interest you enough to read more on your own including some of the references.

The handout can serve as a framework for our discussion.

Learning Objectives

At the conclusion of this CME activity, the participant will be able to:

1. **Define levels of sufficient, insufficient, and deficient vitamin D.**
2. **Describe associations vitamin D levels and atopic diseases.**
3. **Identify the potential role of vitamin D in immune modulation.**

Vitamin D Synthesis

Sunlight (UVB)

Skin

7-dehydrocholesterol

Cholecalciferol
(Vitamin D3)

Liver

Dietary intake
Supplements

25-hydroxyvitamin D3

Kidney

1,25-dihydroxyvitamin D3
(calciferol)-active molecule

RDA for Vitamin D

Age (years)	0-1	1-13	14-18	19-50	51-70	>70
IU/d	400	600	600	600	600	800
Pregnancy and lactation			600	600		

ods.od.nih.gov/factsheets/vitamind-healthprofessional/ (6/24/11)

Sources of Vitamin D

Source	Serving size	IU per serving	% RDV (1-70 yrs.)
Milk, fortified	8 oz.	120	20
Cod liver oil	15 ml.	1360	227
OJ, fortified	8 oz.	137	23
Salmon	3 oz.	447	75
Egg, large	One	41	7
Skin	Up to 30’	20,000	3333

ods.od.nih.gov/factsheets/vitamind-healthprofessional/ (6/24/11)
NEJM. 2011;364:248-54., and others.

25-OH-D3 Levels and Health

ng/mL	nmol/L**	Health status
<12	<30	**DEFICIENT:** Associated rickets in infants and children and osteomalacia in adults.
12–19	30–49	**INSUFFICIENT:** Generally considered inadequate for bone and overall health in healthy individuals
≥20	≥50	**SUFFICIENT:** Generally considered adequate for bone and overall health in healthy individuals
20-29 30-50	50-75 ≥75	**INSUFFICIENT** **SUFFICIENT**
>50	>125	Emerging evidence links potential adverse effects to such high levels, particularly >60 ng/mL (>150 nmol/L)

ods.od.nih.gov/factsheets/vitamind-healthprofessional/ (6/24/11)
NEJM. 2011;364:248-54.
Allergy Asthma Proc. 2011;32:438-44.

** Conversion: 1 ng/ml=2.496 nmol/L

Who is at Risk of Vitamin D Deficiency?

Dark complexion.
Older children/teenagers.
Girls.
Obesity.
More screen time.
More time indoors
Extremes of latitude.
Low milk consumption.
Breast fed babies.
Malabsorption.

Vitamin D Deficiency is More Common than You Think

Estimates of 30-80% deficiency reported.

NHANES (2001-2004) study of 6000 1-21 year olds:

- **9% vitamin D deficient (<15 ng/ml).**
- **61% vitamin D insufficient (<30 ng/ml).**
- **Lower in older children, female, African and Mexican Americans, drank milk < once/week, >4 hours per day in front of screens.**

Adolescents (72% Black or Hispanic):

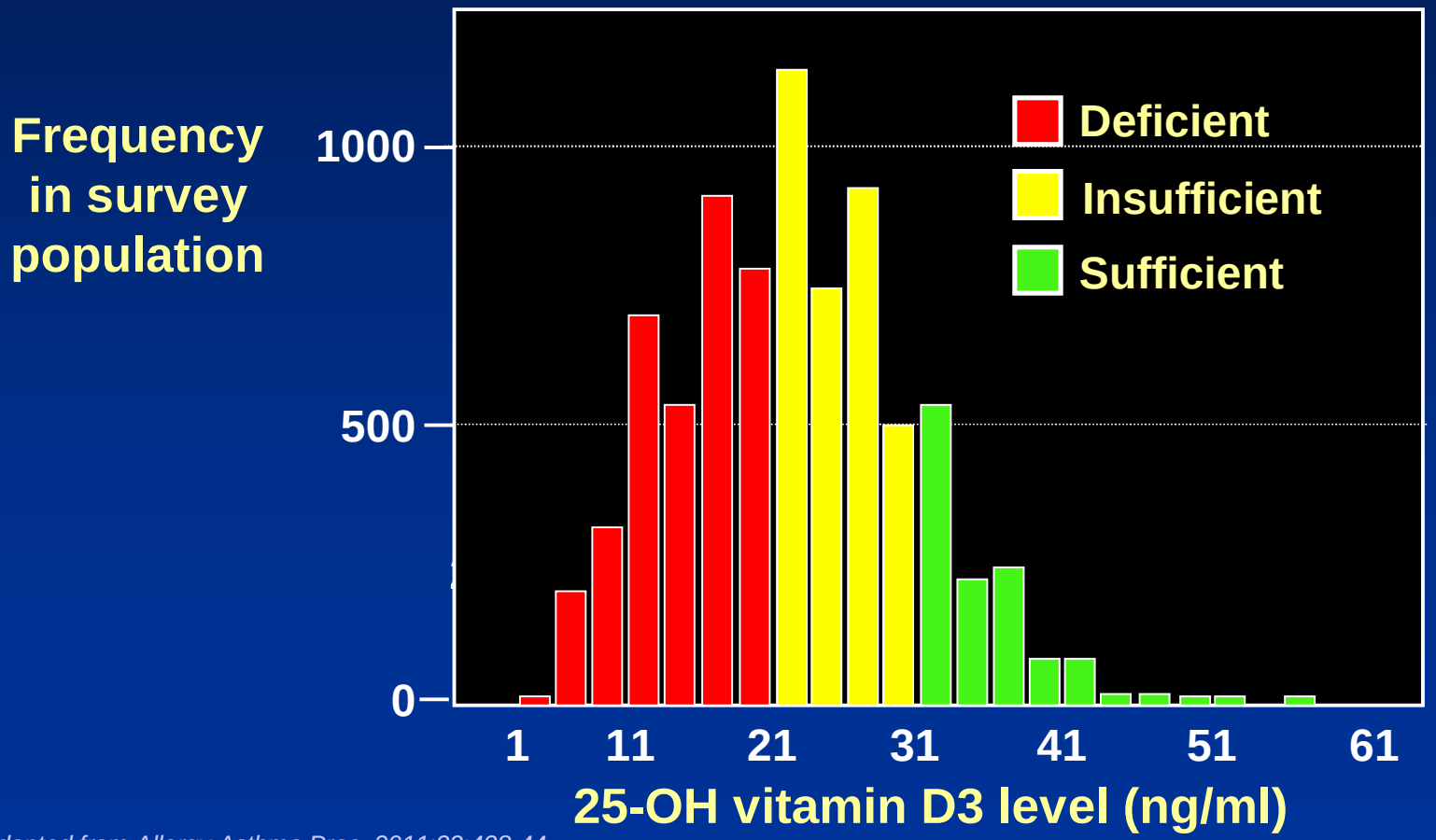
- **24% vitamin D ≤ 15 ng/ml.**
- **42% vitamin D ≤ 20 ng/ml.**

Infants and toddlers 8-24 months (90% Black or Hispanic):

- **12% vitamin D ≤ 20 ng/ml.**
- **40% vitamin D ≤ 30 ng/ml.**

Pediatrics. 2009;124:e362-70.
Arch Pediatr Adolesc Med. 2004;158:531-7.
Arch Pediatr Adolesc Med. 2008;162:505-12.

Vitamin D Levels in a Random Population (NHANES 2005-06)



Adapted from Allergy Asthma Proc. 2011;32:438-44.

Non-Calcemic Roles of Vitamin D

Vitamin D receptor (VDR) and α-1-hydroxylase have been found on and in most cell types and tissues of the body.

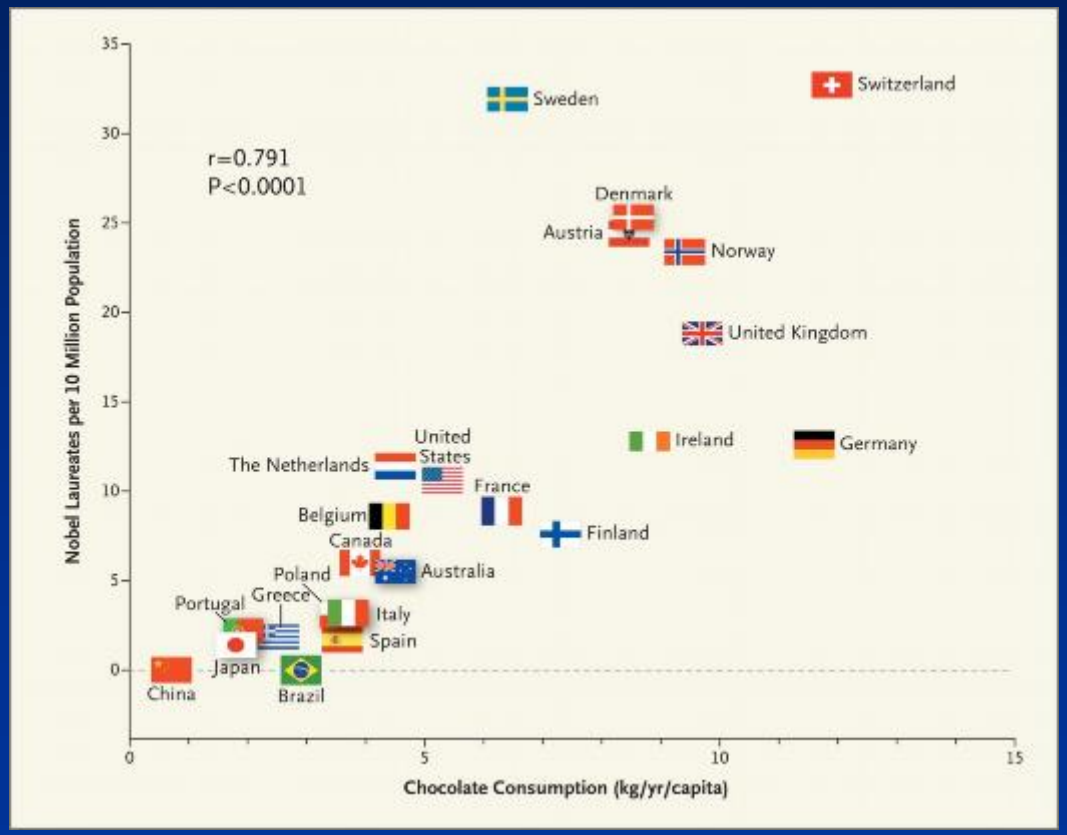
Numerous conditions have been associated with vitamin D deficiency:

- **Atherosclerosis.**
- **Cardiac contractility.**
- **Autoimmunity.**
- **Neoplasm**
  - **Breast**
  - **Colon**
  - **Prostate**
- **Impaired insulin synthesis.**
- **In the PICU:**
  - **More critical illness**
  - **Longer admission.**
  - **Pressor need.**
  - **Risk of septic shock**

Associations of Vitamin D Status with Things We Do for a Living

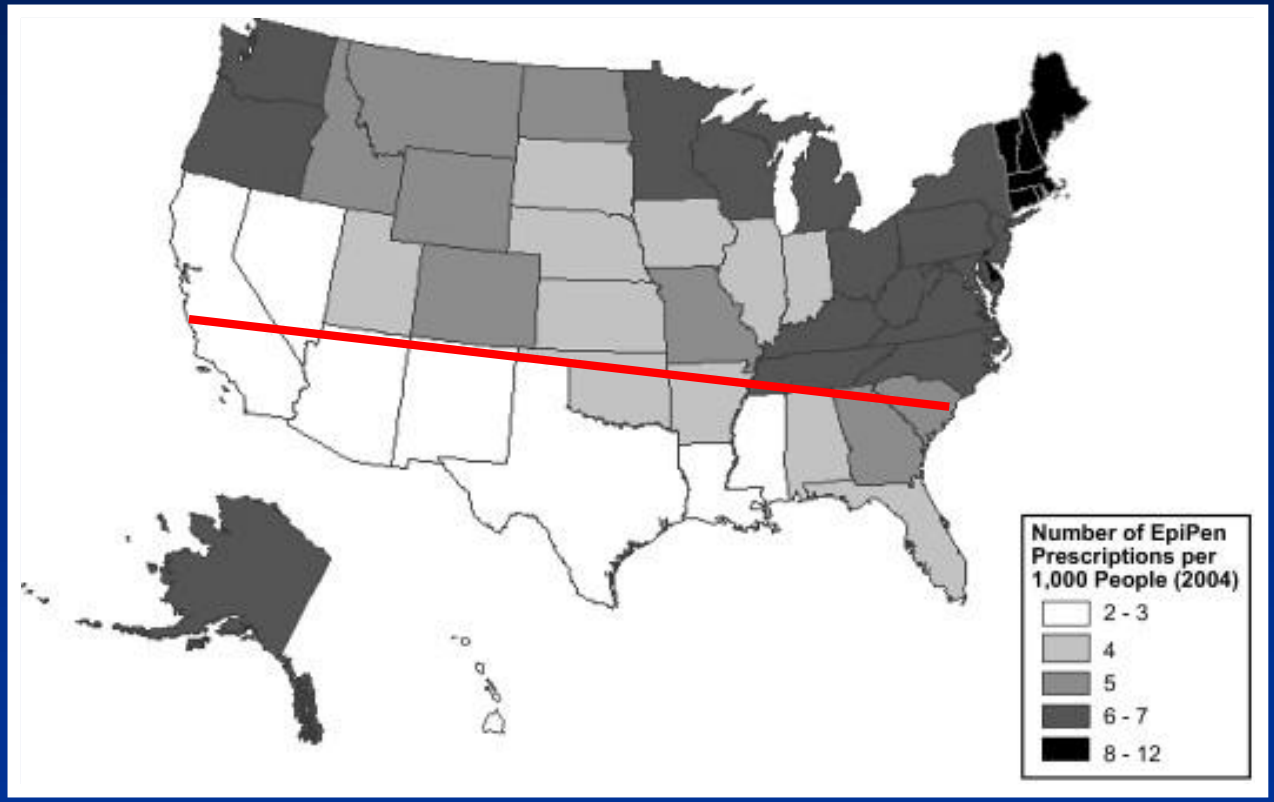
- **Atopic diseases**
  - Total and specific IgE
  - Asthma
  - Atopic dermatitis
- **Anaphylaxis**
- **Food Allergy**
- **Chronic urticaria?**
- **Infections**
  - Atopic dermatitis
  - Influenza, resp. viruses
  - Tuberculosis, HIV
- **Autoimmunity**
  - Type 1 diabetes mellitus
  - Multiple sclerosis
  - Rheumatoid arthritis

An Association Does not Imply Cause and Effect. It is Merely a Place to Start Your Research.



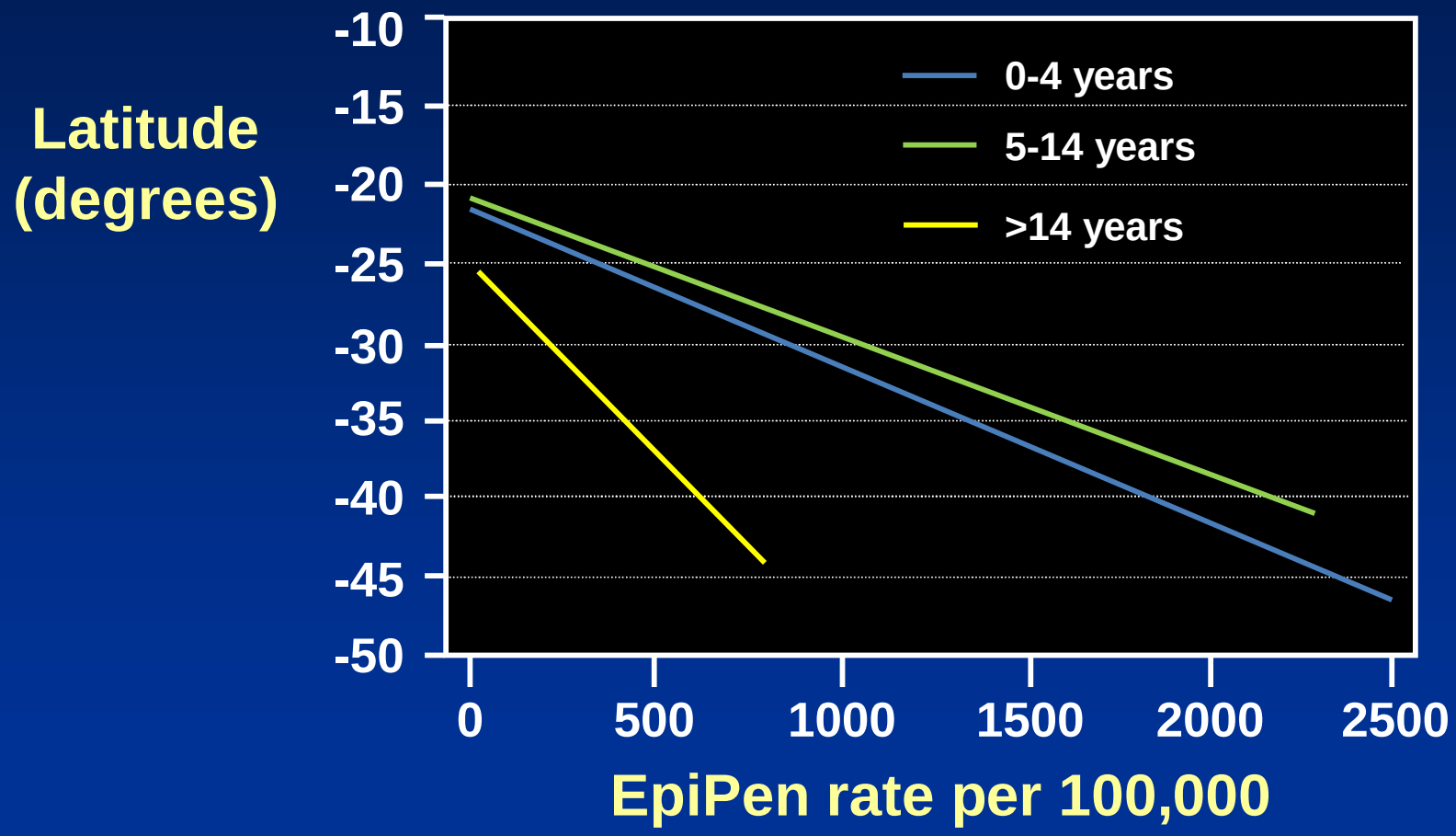
N Engl J Med 2012;367:1562-1564.

Latitude and Epinephrine Prescriptions



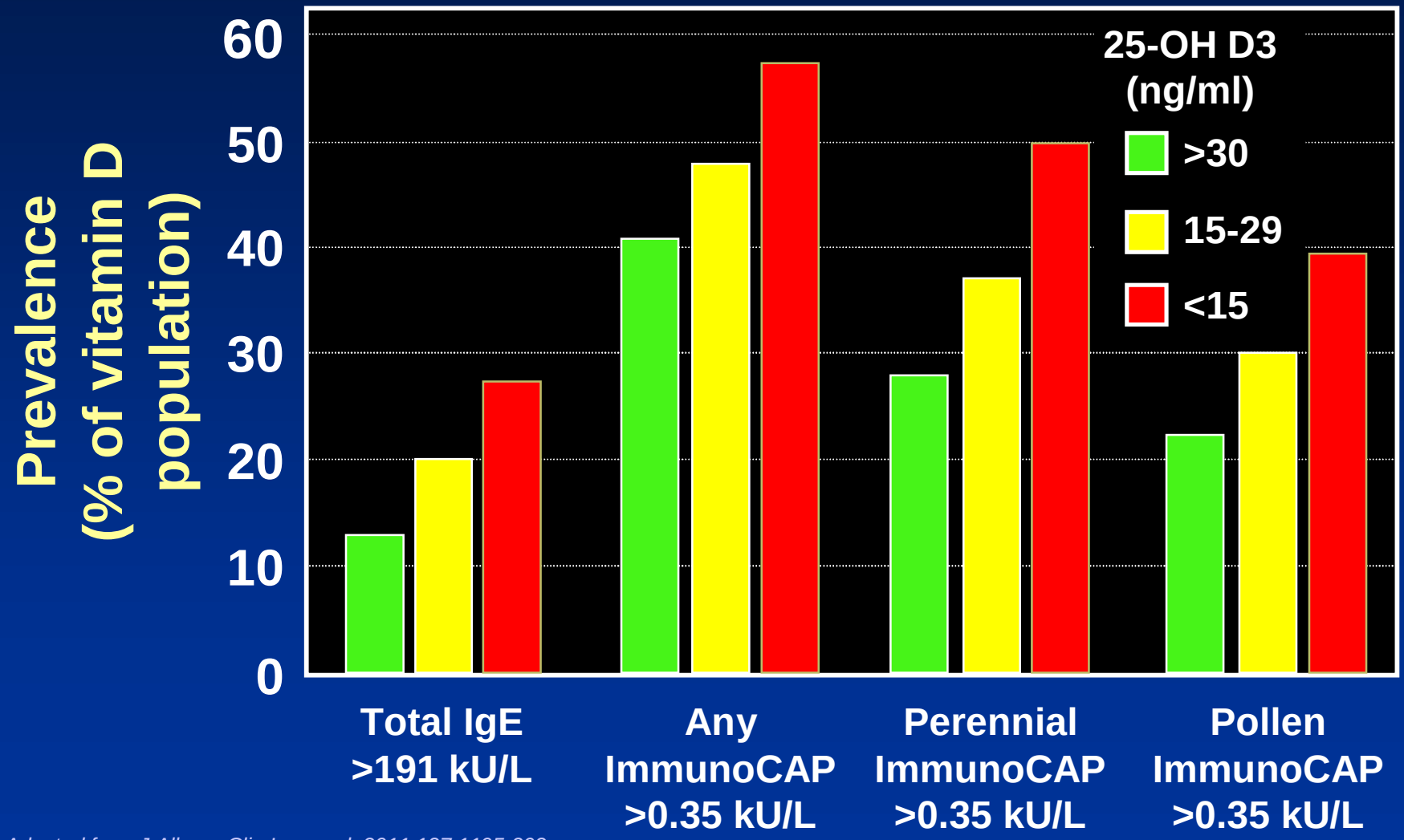
J Allergy Clin Immunol. 2007;120:131-6..

Latitude and Epinephrine (Southern Hemisphere)



Adapted from Ann Allergy Asthma Immunol. 2009;103:488-95.

Vitamin D Levels and Atopy



Adapted from J Allergy Clin Immunol. 2011;127:1195-202.

Vitamin D and Asthma Control

- **Vitamin D levels are correlated with FEV_1, FVC, asthma control, and steroid responsiveness.**
- **Vitamin D level is inversely correlated with asthma symptoms, bronchial hyperreactivity, asthma exacerbations, steroid requirement, and bronchial smooth muscle mass.**
- **Vitamin D deficiency is a risk for asthma hospitalization and airway remodeling, and is associated with steroid resistant asthma.**

Allergy Asthma Proc. 2011;32:438-44.
J Allergy Clin Immunol. 2007;120:1031-5.
Am J Clin Nutr. 2007. 85:788-95.
Br J Nutr. 2010;104:1051-7.
Ann Allergy Asthma Immunol. 2010;105:191-99.
J Allergy Clin Immunol. 2007;120:1031-5.
J Allergy Clin Immunol. 2010;125:995-1000.
J Allergy Clin Immunol. 2010;126:52-8.
Am J Resp Crit Care Med. 2011;184:1342-9.
Eur Resp J. 2011;38:1320-7.

Asthma and Vitamin D Supplementation

- **Vitamin D enhances T cell steroid responsiveness *in vitro*.**
- **Supplementation at 1 (cod liver oil) decreases risk of allergies and asthma at 31 years.**
- **In established and newly diagnosed asthma, vitamin D supplementation leads to better asthma control.**

J Allergy Clin Immunol. 2010;125:995-1000.
J Allergy Clin Immunol. 2007;120:1031-5.
J Allergy Clin Immunol. 2011;1294-6.
Ann Allergy Asthma Immunol. 2012;108:281-2.

Pre-, Peri, and Neonatal Vitamin D and Risks for Atopy

- VDR polymorphisms.
- Low maternal vitamin D intake and levels and low cord levels of 25-OH-D3 are associated with increased risk of atopic dermatitis in infancy and for wheeze and/or asthma at 3, 5, and 9 years old.
- Breast fed babies at risk.

Allergy Asthma Proc. 2011;32:438-44.
J Allergy Clin Immunol. 2007;120:1031-5.
Am J Clin Nutr. 2007. 85:788-95.
Am J Resp Crit Care Med. 2011;184:1342-9.
J Allergy Clin Immunol. 2007;120:1031-5.
J Allergy Clin Immunol. 2010;125:995-1000.
J Allergy Clin Immunol. 2010;126:52-8.
Ann Allergy Asthma Immunol. 2010;105:191-99.
Pediatrics. 2012 ;130(5):1128-35.
Eur Resp J. 2011;38:1320-7.
Br J Nutr. 2010;104:1051-7.

Vitamin D and Infections

- **Vitamin D supplementation maintains epithelial barrier and improves control of atopic dermatitis.**
- **Deficiency is associated with increased risk of sinusitis and increased rate of viral respiratory illnesses.**
- **Supplementation decreases rate of URIs and influenza (dose dependent).**
- **Vitamin D enhances immunity to M. tuberculosis.**

Br J Dermatol. 2008;159:245-7.
J Allergy Clin Immunol. 2008;122:415-7.
Pediatrics. 2011;127:180-7.
J Epidemiol Infect. 2007;135:1095-8.
Clin Exp Med. 0012;8 (epub ahead of print)
Clin Devel Immunol. 2012:430972. epub 7/5/12.
PLoS One. 2012;7(7):e40692

National Jewish Hospital for Consumptives

How Can We Make Sense of All That?

It's easy…..

VDR and α-1-hydroxylase are everywhere!

They have to be there for a reason, not by accident.

VDR and α-1-hydroxylase are everywhere

- APCs (Dendritic cells, monos, macros, etc.):
  - Exposure to lipopolysaccharide up-regulates VDR and α-1-hydroxylase.
  - Vitamin D3 up-regulates toll-like receptors (TLR) for better response to microbes.
  - Vitamin D3 up-regulates antimicrobial proteins, maintains epithelial barrier integrity in AD.
  - Vitamin D3 enhances tolerance in adaptive immunity by up-regulating IL-10, IL-19, and TGF-β (enhances Treg [FoxP3+] cell development).
  - Vitamin D3 down-regulates co-stimulatory molecules CD40 and CD80/86.

VDR and α-1-hydroxylase are everywhere

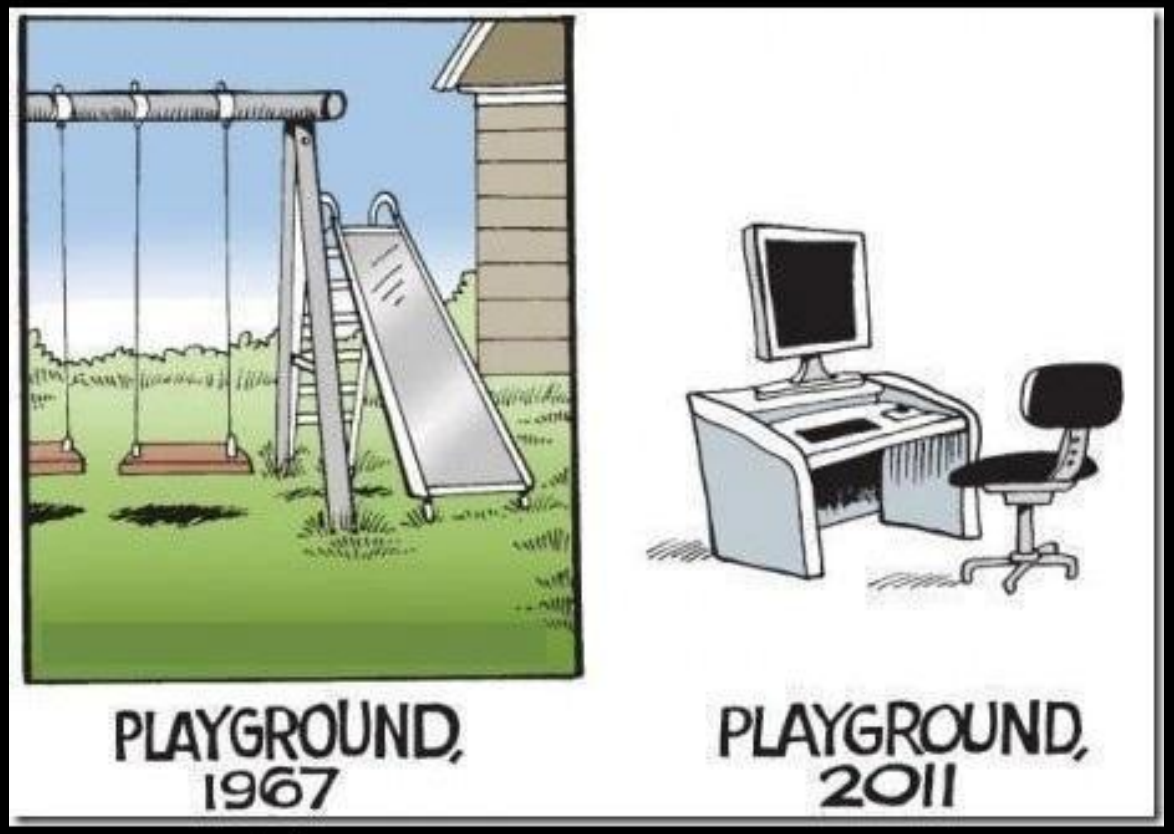
- **Lymphocytes:**
  - **Decreased proliferation.**
  - **Inhibition of Th1 and Th2 cytokines by naïve (cord) T cells with enhanced Treg phenotype.**
  - **Vitamin D3 enhances IL-2 production.**
  - **Enhances steroid responsiveness and immunosuppressive effects.**
  - **Decreased IL-6, decreased IL-12 induced IFN-γ synthesis.**
  - **Decreased CD40 and CD80/86 on B cells→ Decreased T cell activation.**
  - **Better response to SCIT.**

VDR and α-1-hydroxylase are everywhere

Other cells we think about everyday:

- **Mast Cells**
  - **Inhibition of maturation.**
  - **Apoptosis.**
- **Decreased eosinophil recruitment.**
  - **Respiratory epithelium and smooth muscle.**
- **Inhibits smooth muscle proliferation.**
- **Decreased RANTES (CCL5) production.**
- **Decreases matrix metalloproteinase production.**
- **Helps fetal lung growth (mice).**

Complex Problem.
Simple Solution?



Selected References

1. Frieri M and Valluri A. Vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms. *Allergy Asthma Proc*. 2011;32:438-44.
2. Sandhu MS and Casale TB. The role of vitamin D in asthma. *Ann Allergy Asthma Immunol*. 2010;105:191-99.
3. Litonjua AA and Weiss ST. Is vitamin D to blame for the asthma epidemic? *J Allergy Clin Immunol*. 2007;120:1031-5.
4. Muehleisen B and Gallo RL. Vitamin D in allergic disease: Shedding light on a complex problem. *J Allergy Clin Immunol.* 2013;131:324-9.
5. Rosen CJ. Vitamin D insufficiency. *N Eng J Med.* 2011;364(3):248-54.
6. Vassalo MF and Camargo CA. Potential mechanisms for the hypothesized link between sunshine, vitamin D, and food allergy in children. *J Allergy Clin Immunol 2012;126:217-22.*