

Vitamin D, Food Allergy, and Food-induced Anaphylaxis

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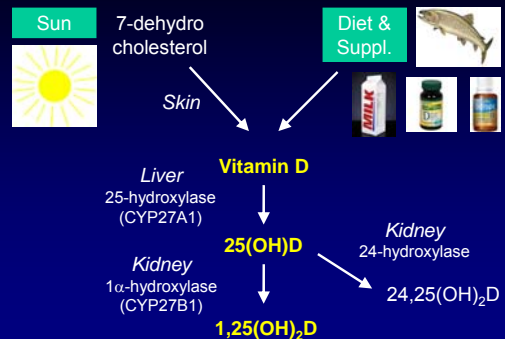
Presentation

1. Food allergy / anaphylaxis
2. Vitamin D
3. Observational studies
4. Potential mechanisms
5. Summary

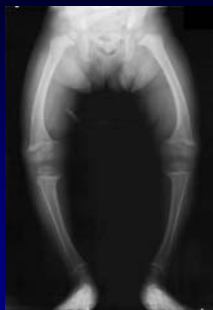
Food Allergy / Anaphylaxis

- Surveillance complicated by false-positives (proxy measure: Rx epinephrine autoinjector)
- Prevalence of food allergy rising in many developed nations. Likewise, frequency of food-induced anaphylaxis also rising – though unpublished data suggest plateau or decline
- Causes of food allergy epidemic are unclear
 - Hygiene hypothesis?
 - Early exposure to food allergens?

Vitamin D Synthesis & Metabolism

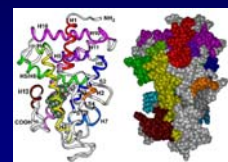


Severe Vitamin D Deficiency → Rickets

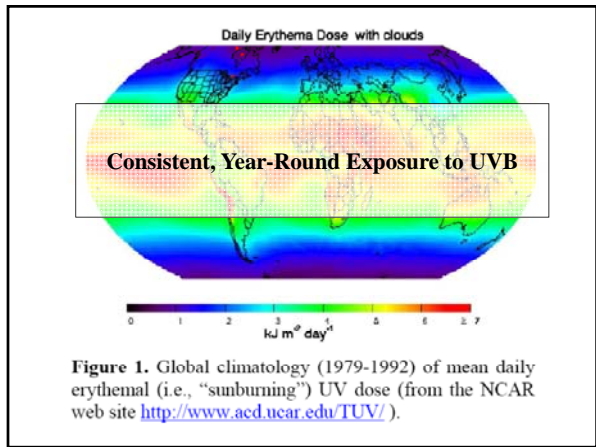
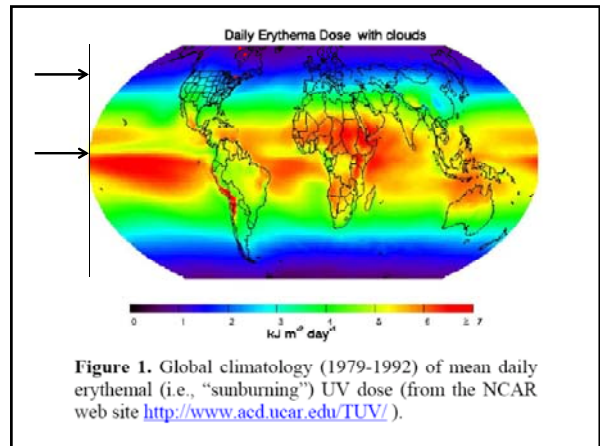
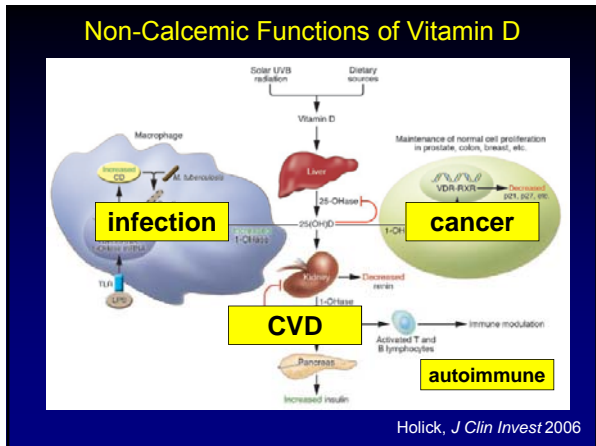


Vitamin D Receptor (VDR)

- VDR present in most tissues and cells of body
- Growing recognition that many different cells have the enzymatic machinery to convert 25(OH)D to the active hormone, 1,25(OH)₂D
- >2,700 binding sites for VDR along genome
- Significant effects on activity of 229 genes



A. Norman, 2006; Ramagopalan, *Genom Res* 2010



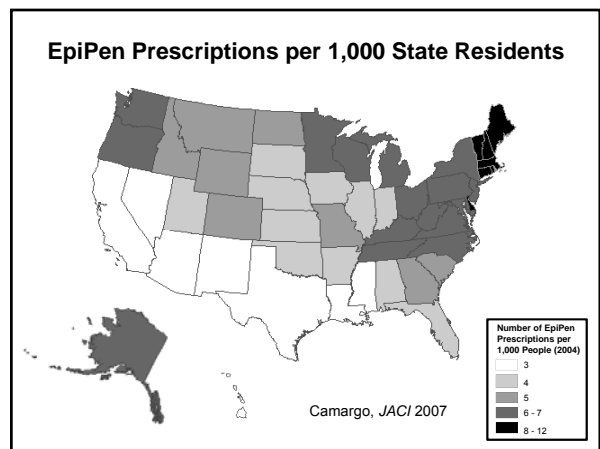
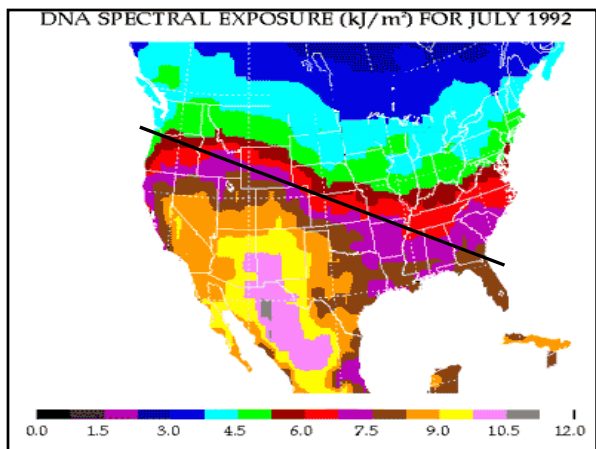
Serum 25(OH)D (cut-points controversial)

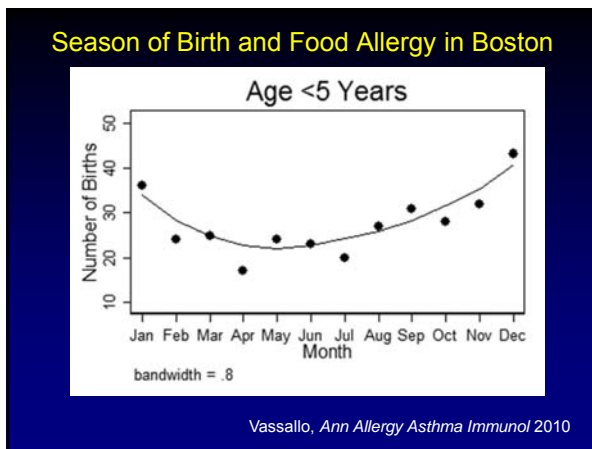
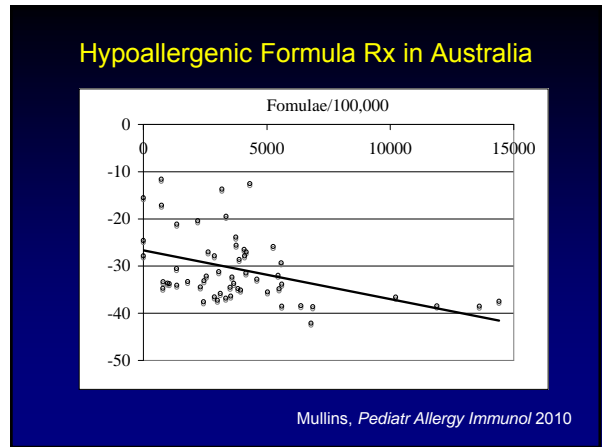
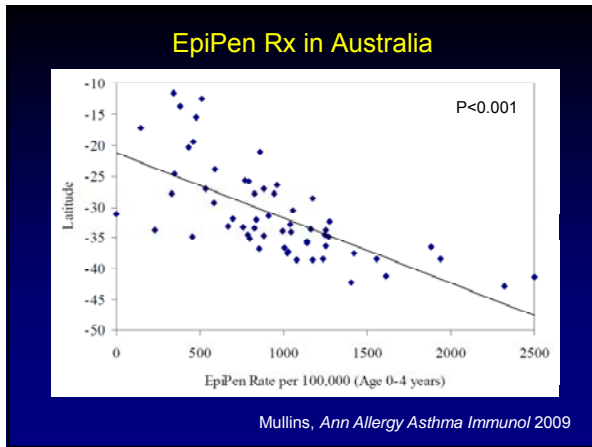
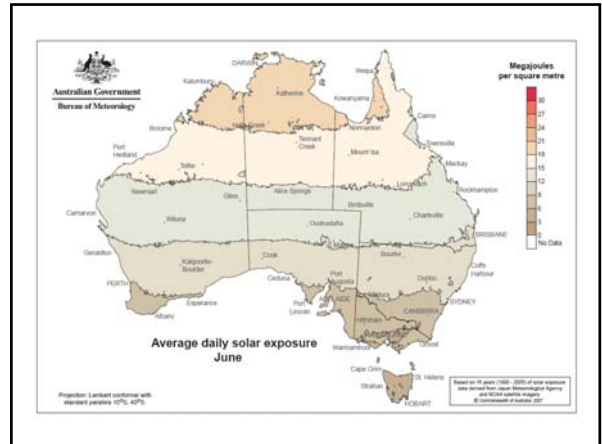
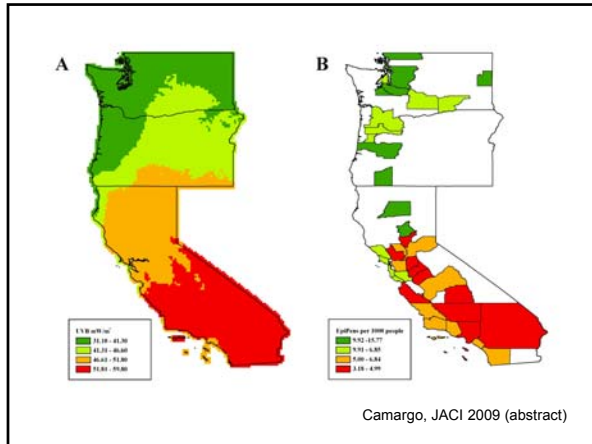
- Conversion factor: 1 ng/ml = 2.496 nmol/L
- US average: ~25 ng/ml 60-65
- "Inadequate" vitamin D
 - <10 ng/ml (everyone)
 - <20 ng/ml (AAP, IOM)
 - <30 ng/ml (many researchers)
 - <40 ng/ml (few researchers)

Optimal level also controversial ...

- ≥30 ng/ml
- 40 ng/ml
- 40-60 ng/ml
- 60-80 ng/ml

Bischoff-Ferrari, *Osteopor Int* 2010; Canadian Paediatric Society 2007; Wagner, *Pediatrics* 2008; Institute of Medicine 2011; www.grassrootshealth.net





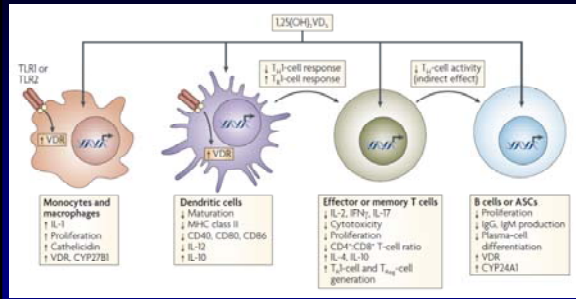
Maternal Vitamin D Intake During Pregnancy and Food Allergen IgE in Offspring at Age 5y

Nutrients (from foods)	Any food allergen	
	Unadjusted† OR (95% CI)	Adjusted‡ OR (95% CI)
Total fat	1.01 (0.29–3.58)	0.68 (0.17–2.76)
Saturated fatty acids	1.05 (0.44–2.52)	0.91 (0.34–2.43)
Vitamin A	0.83 (0.58–1.21)	0.84 (0.55–1.27)
α-Carotene	0.88 (0.70–1.09)	0.98 (0.76–1.26)
β-Carotene	0.85 (0.63–1.14)	0.94 (0.67–1.32)
Vitamin C	0.81 (0.57–1.16)	0.83 (0.56–1.22)
Vitamin D	0.56 (0.37–0.86)*	0.56 (0.35–0.91)*
α-Tocopherol	0.80 (0.37–1.73)	0.62 (0.26–1.52)
γ-Tocopherol	1.05 (0.644–1.70)	0.99 (0.58–1.70)
Zinc	0.81 (0.25–2.62)	0.92 (0.25–3.37)
Copper	0.94 (0.35–2.53)	1.21 (0.40–3.69)
Iron	1.08 (0.42–2.79)	1.47 (0.51–4.23)

OR (95% CI), odds ratio (95% confidence interval).
†p < 0.05.

Nwaru, *Pediatr Allergy Immunol* 2010

Immunologic Effects of Vitamin D



Mora, *Nature Rev Immunol* 2008

Rostrum

Potential mechanisms for the hypothesized link between sunshine, vitamin D, and food allergy in children

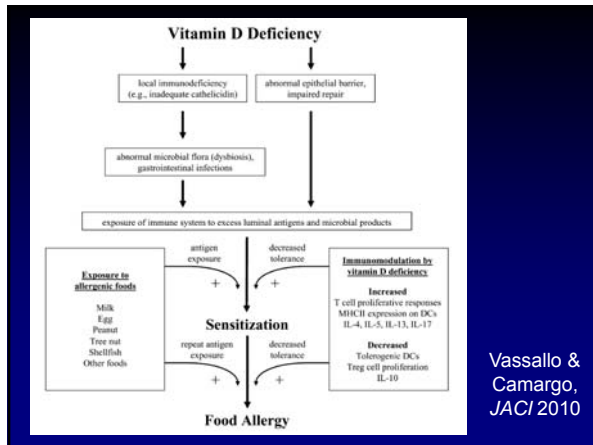
Milo F. Vassallo, MD, PhD¹ and Carlos A. Camargo, Jr, MD, DPH, FAAP^{1,2,3,4} Boston, MA¹

Epidemiologic data suggest that the incidence of food allergy (FA) is increasing among children, yet a satisfactory model of the pathogenesis remains elusive. FA is the consequence of maladaptive immune responses to common and otherwise innocuous food antigens. Concurrent with the increase in FA is an epidemic of vitamin D deficiency (VDD) caused by several factors, especially decreased sunlight/UVB exposure. There is growing appreciation of the importance of the pleiotropic hormone vitamin D in the development of tolerance, immune system defenses, and epithelial barrier integrity. We propose a "multifactorial" model in which VDD in a developmentally critical period increases susceptibility to colonization with altered microbial flora and gastrointestinal infections, contributing to abnormal intestinal barrier permeability and excess and inappropriate exposure of the immune system to dietary allergens. A compensating effect (and additional "hit") of VDD is the promotion of a pro-inflammatory immune imbalance that might compromise immunologic tolerance and contribute to FA. We propose that early correction of VDD might promote mucosal immunity, healthy microbial ecology, and allergen tolerance and thereby blunt the FA epidemic in children. *J Allergy Clin Immunol* 2010;126:217-221.

Abbreviations used:
FA: Food allergy
25(OH)D: 25-hydroxyvitamin D
Treg: T regulatory cell
UVB: Ultraviolet B-wave radiation
VDD: Vitamin D deficiency

Despite recent advances in our understanding of FA, many basic questions remain unanswered. Why is the incidence of FA increasing? Who will have FA? Why are young children at particular risk? How and why do some children outgrow FA? Moreover, effective interventions for FA are lacking. Primary prevention of FA by modifying the maternal diet during pregnancy appears ineffective.¹ At present, the only recommended preventive measure, with increasing support, is exclusive breast feeding until 4 to 6 months of age.² The mainstay of secondary prevention is allergen avoidance, which can be extremely challenging. Methods to desensitize patients to food allergens are being explored, but as critical as this will be to some patients, such approaches have yet to achieve consistently safe and broadly applicable results.³

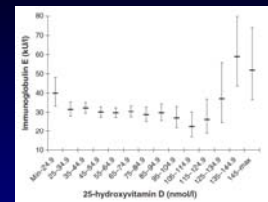
Vassallo & Camargo, *JACI* 2010



Vassallo & Camargo, *JACI* 2010

Curvilinear Association with IgE ?

- UK (Hyponnen, *Allergy* 2009):
 - Cross-sectional study, n=9377 adults, age 45y
 - Low & high 25(OH)D associated with higher levels of total IgE



- Arizona (Rothers, *JACI* 2011):
 - Birth cohort study, n=219 newborns → age 5 years
 - Low & high 25(OH)D associated with higher risk of aeroallergen sensitization

Summary & Clinical Implications

- For unclear reasons, the prevalence of food allergy is rising in many developed nations
- Definition of vitamin D deficiency is controversial but most experts agree that population levels are low
- ↓ UVB exposure, and possibly ↓ 25(OH)D, are associated with ↑ prevalence of food allergy/anaphylaxis
- Observational data and mechanisms remain unclear ... Further research needed
- *My best guess for target 25(OH)D?*
Age 1 year and older: ~40 ng/ml ~100 nmol/L