

Vitamina D: un ormone multifunzione

Introduction
And Infections
Food Allergy
Asthma
Conclusions

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Napule è...
PEDIATRIA PREVENTIVA E SOCIALE



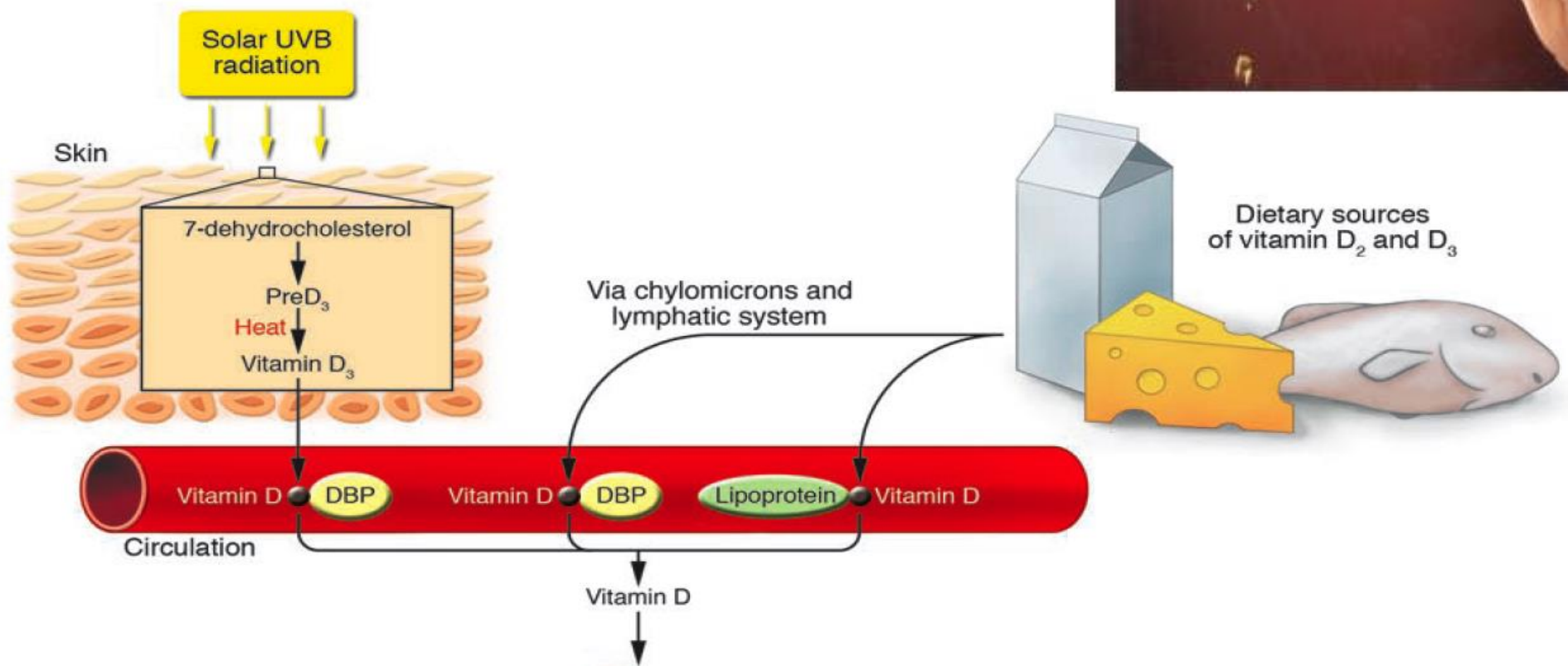
LUCI OMBRE ABBAGLI

Prevenzione Nutrizione

Allergologia Dermatologia

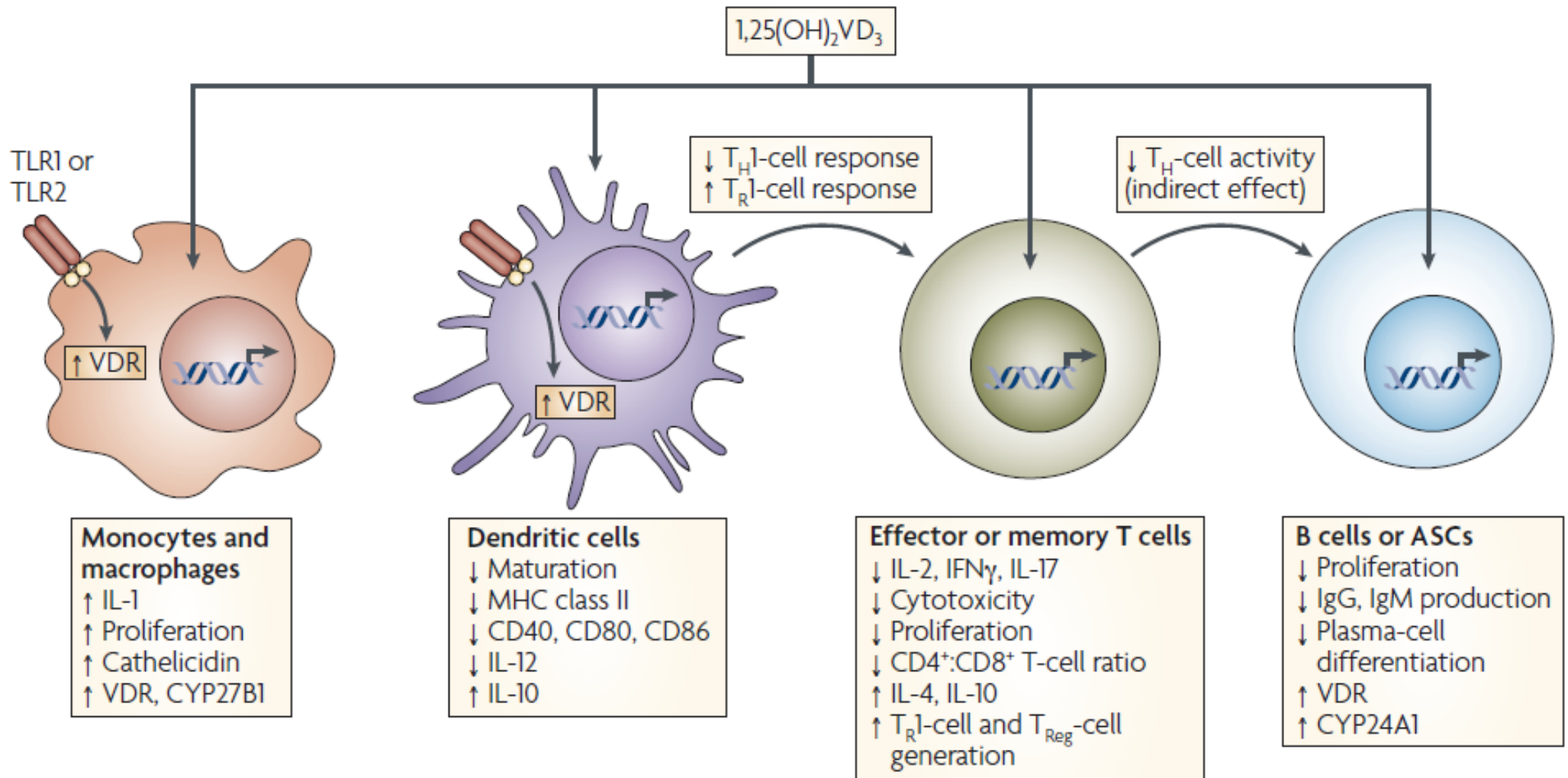
Gastroenterologia

30 APRILE - 3 MAGGIO 2015
Hotel Royal Continental, Napoli



Mechanisms of vitamin D immunomodulation

Moira Nat Rev Immunol 2008;8:685



Vitamin D status at birth: An important and potentially modifiable determinant of atopic disease in childhood?

Editorial Bacharier LB, JACI 2014;133:154

Vitamin D has been reported to:

1. affect the innate immune system through the induction of macrophage production of the antimicrobial peptides cathelicidin and β -defensins
2. Enhance skin barrier function
3. suppress Toll-like receptor production by monocytes
4. enhance IL-10 production by mast cells
5. inhibit dendritic cell activation and function induced by LPS
6. decrease T_H1 cytokine production
7. induce regulatory T cells
8. inhibit B-lymphocyte function, resulting in diminished IgE secretion

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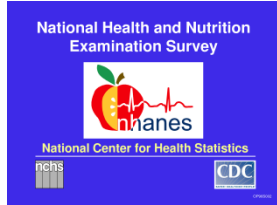
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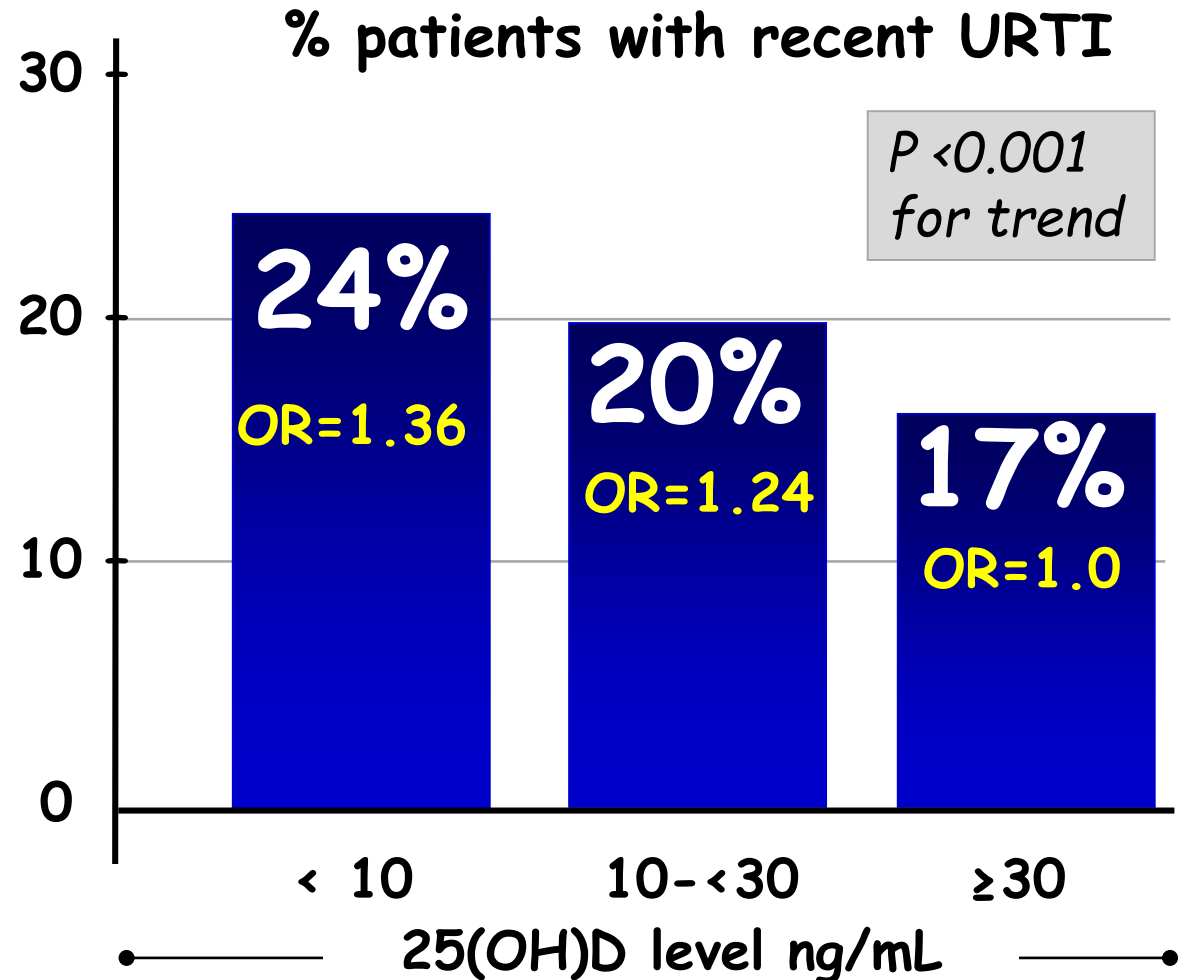
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Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey.

Ginde AA Arch Intern Med. 2009;169:384



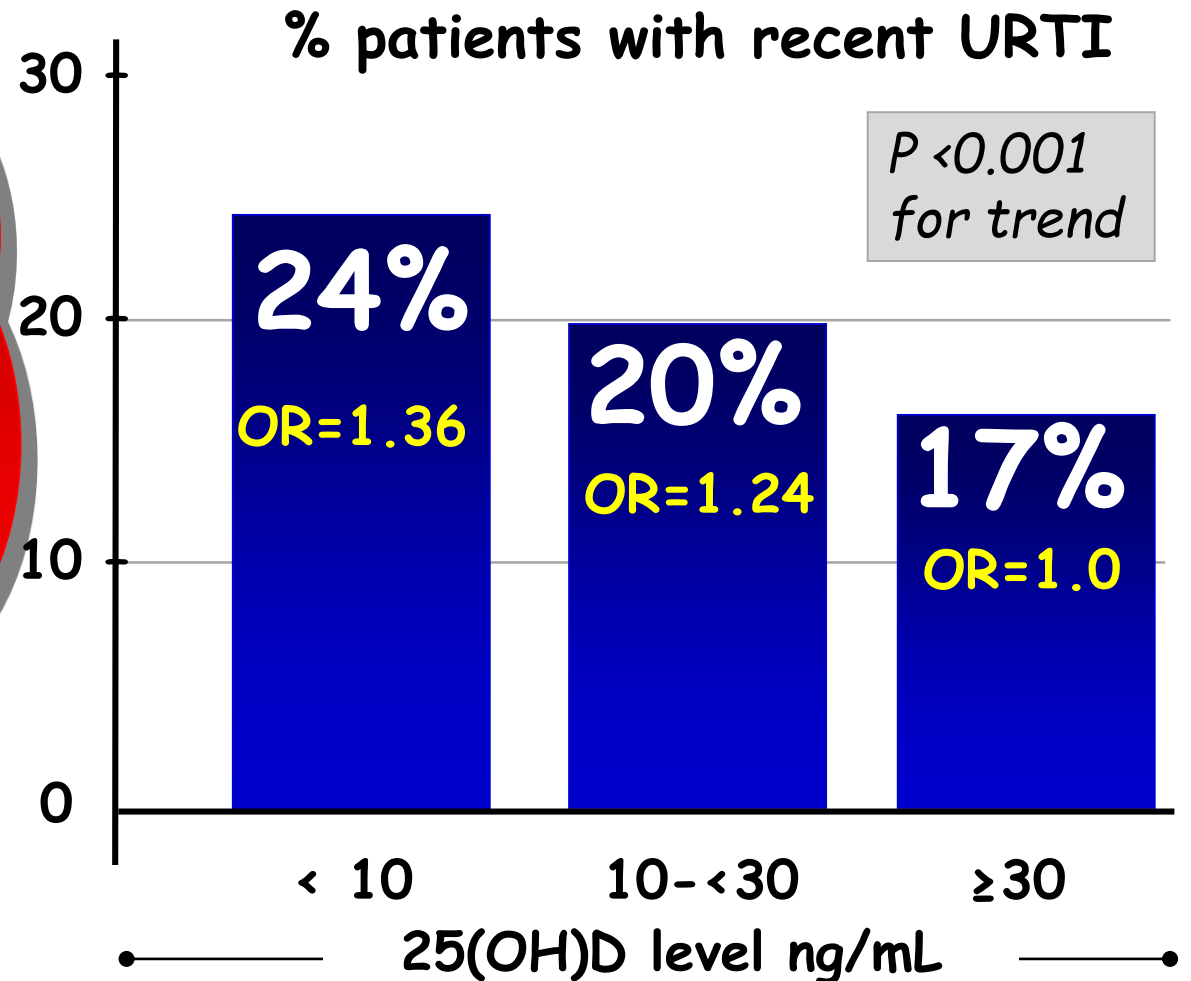
- ✓ Vitamin D levels in 18883 participants ≥ 12 years in the Third National Health and Nutrition Examination Survey in the USA;
- ✓ Symptoms suggestive of an URTI in the preceding few days.



Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey

Survey Ginde AA Arch Intern Med. 2009;169:384

✓ The association between 25(OH)D level and URTI seemed to be stronger in individuals with asthma (OR, 5.67) and chronic obstructive pulmonary disease (OR, 2.26).



Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia

Camargo, *Pediatrics* 2012;130(3):e561-7

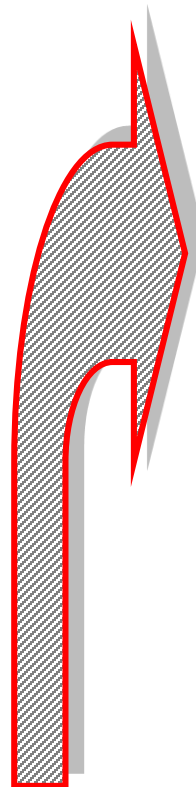


Vitamina

D



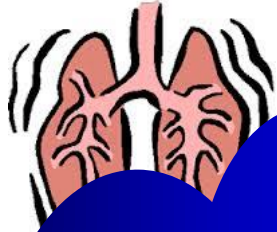
- ✓ 247 children who were assigned to daily ingestion of unfortified regular milk (control; n = 104) or milk fortified with 300 IU of vitamin D (n = 143) (Jan-March);
- ✓ number of parent-reported ARIs over the past 3 months.



- At baseline, the median serum 25(OH)D level was 7 ng/ml;
- The median 25(OH)D levels of children in the control versus vitamin D groups was significantly different (7 vs 19 ng/mL; $P < .001$);

Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia

Camargo, *Pediatrics* 2012;130(3):e561-7



Vitamina

D



✓ Vitamin D supplementation significantly reduced the risk of ARIs in winter among Mongolian children with vitamin D deficiency.

- Compared with controls, children receiving vitamin D reported significantly fewer ARIs during the study period with rate ratio of 0.52 (95% confidence interval: 0.31-0.89).



Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial.

Manaseki-Holland, Lancet 2012;379:1419

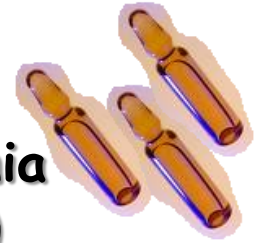


Background

- Vitamin D has a role in regulating immune function, and its **deficiency** is a suggested **risk factor for childhood pneumonia**.
- Our aim was to assess whether oral supplementation of Vitamin D₃ (cholecalciferol) **reduce the incidence and severity of pneumonia in a high-risk infant population**.

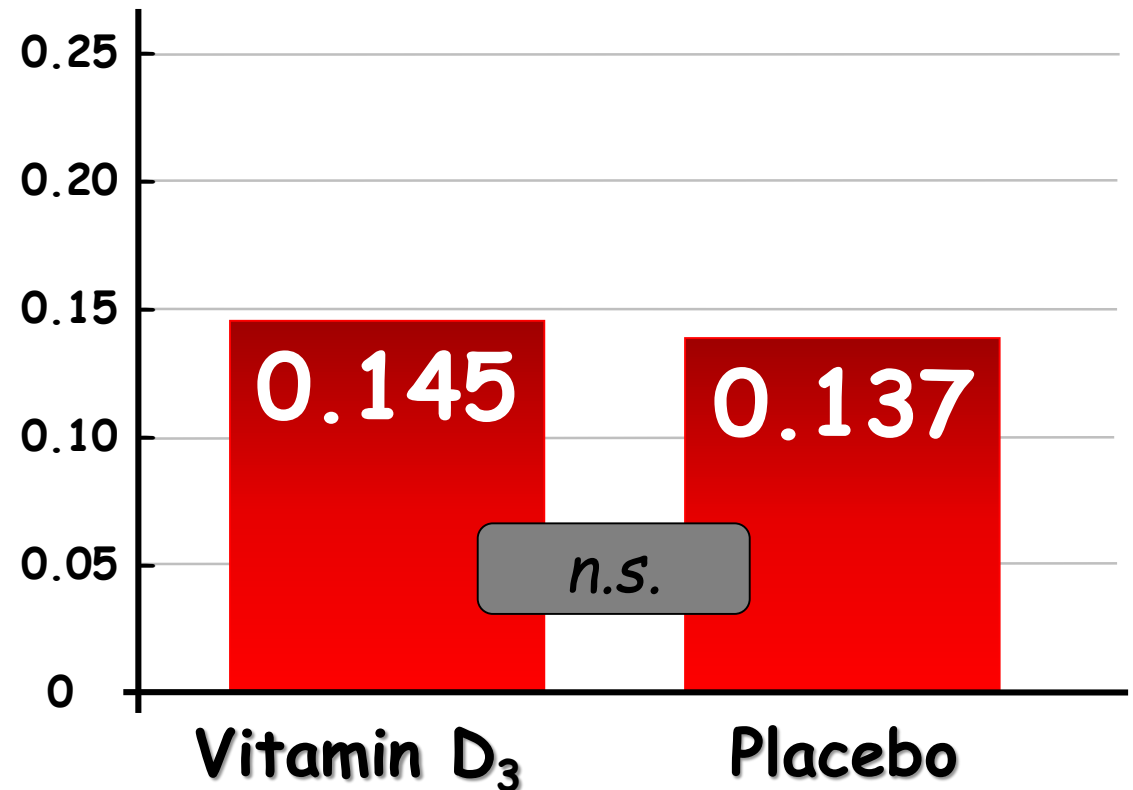
Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial.

Manaseki-Holland, Lancet 2012;379:1419



Incidence of pneumonia
(n° per child per yr)

- ✓ 3046 children (1-11 mo);
- ✓ 1524 children Vitamin D₃ (oral 100.000 IU);
- ✓ 1522 children placebo;
- ✓ Administration once every 3 mo for 18 mo.



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Potential links between the emerging risk factors for food allergy and vitamin D status

Vuillermin CEA 2013;43:560

Possible mechanisms by which the emerging food allergy risk factors may also be associated with low vitamin D status

(i) Sun exposure and cutaneous synthesis of vitamin D

Higher latitude [22, 23]

Winter birth [5]

Black American ethnicity [10]

Absence of pets [41, 42]

Obesity [11,12]

Not living on a farm [43]

(ii) Dietary intake of vitamin D

Australian residence [3, 17]

Lower maternal intake of oily fish [9]

Delayed (or absent) introduction of infant formula [44, 45]

Delayed introduction of hen's eggs [8]

Potential links between the emerging risk factors for food allergy and vitamin D status

Vuillermin CEA 2013;43:560

Possible mechanisms by which the emerging food allergy risk factors may also be associated with low vitamin D status

(iii) Bioavailability or metabolism of vitamin D

Obesity [11,12]

CYP24A1 gene polymorphisms [46]

(iv) Biological activities of vitamin D

May promote the induction of immune tolerance [47, 48]

Modifies intestinal barrier function [49–52]

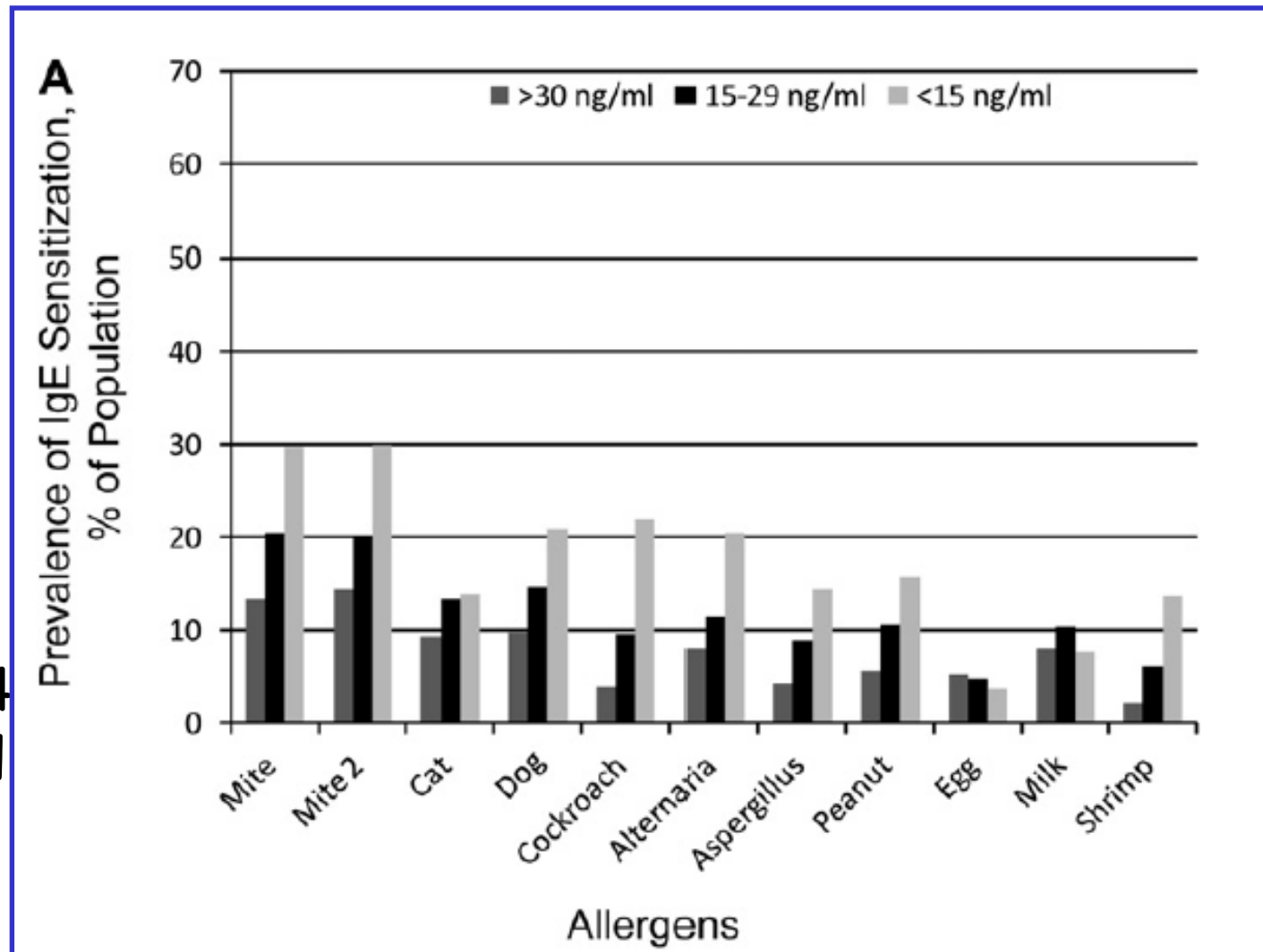
Modifies immune response to microbial exposure [46, 53]

May alter composition of the gut microbiome [51, 54]

Vitamin D levels and food and environmental allergies in the United States: Results from the National Health and Nutrition Examination Survey 2005-2006. Sharief, JACI 2011;127:1195

25-hydroxyvitamin D deficiency (<15 ng/mL) and insufficiency (15-29 ng/mL) and allergic sensitization

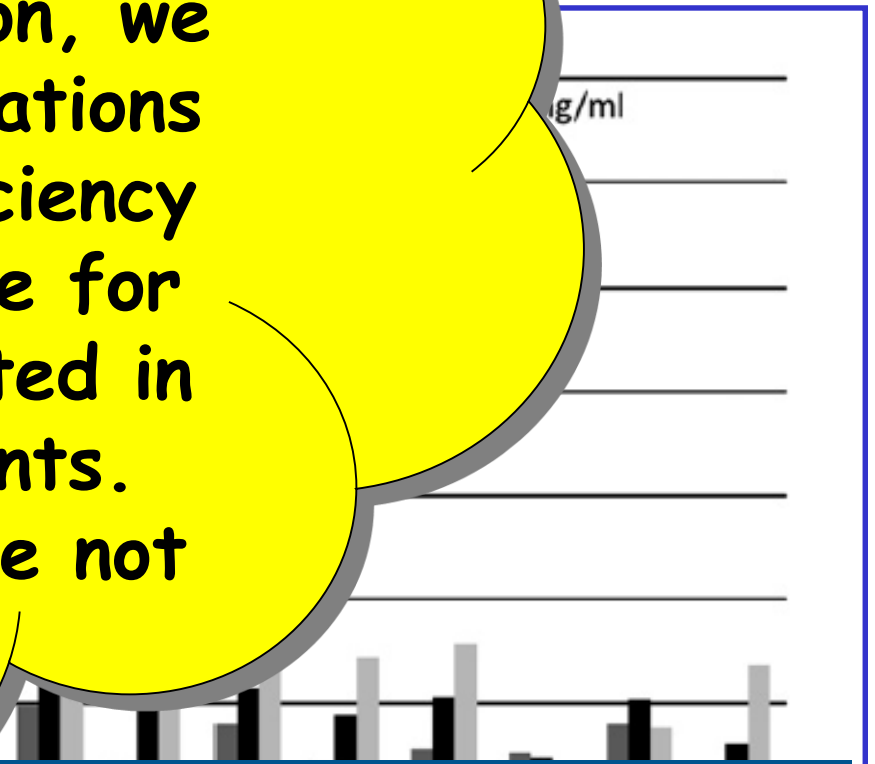
Serum IgE levels in a sample of 3136 children and adolescents and 3454 adults in the National Health and Nutrition Examination Survey 2005-2006



Vitamin D levels and food allergy in the United States: Results from the National Health and Nutrition Examination Survey

In this nationally representative population, we found consistent associations between 25(OH)D deficiency and a higher prevalence for 11 of 17 allergens tested in children and adolescents. These associations were not seen in adults

25-hydroxyvitamin D
deficiency
ng/ml
insulin
ng/ml
sensitized
Serum
sample
3136 children



Clinical implications: We found an association between vitamin D deficiency and the prevalence of IgE sensitization. Low vitamin D levels might be a risk factor for allergies, and patients with allergies might be at risk for low vitamin D levels.

Vitamin D insufficiency is associated with challenge-prove food allergy in infants.

K Allen, 2013;131:1109

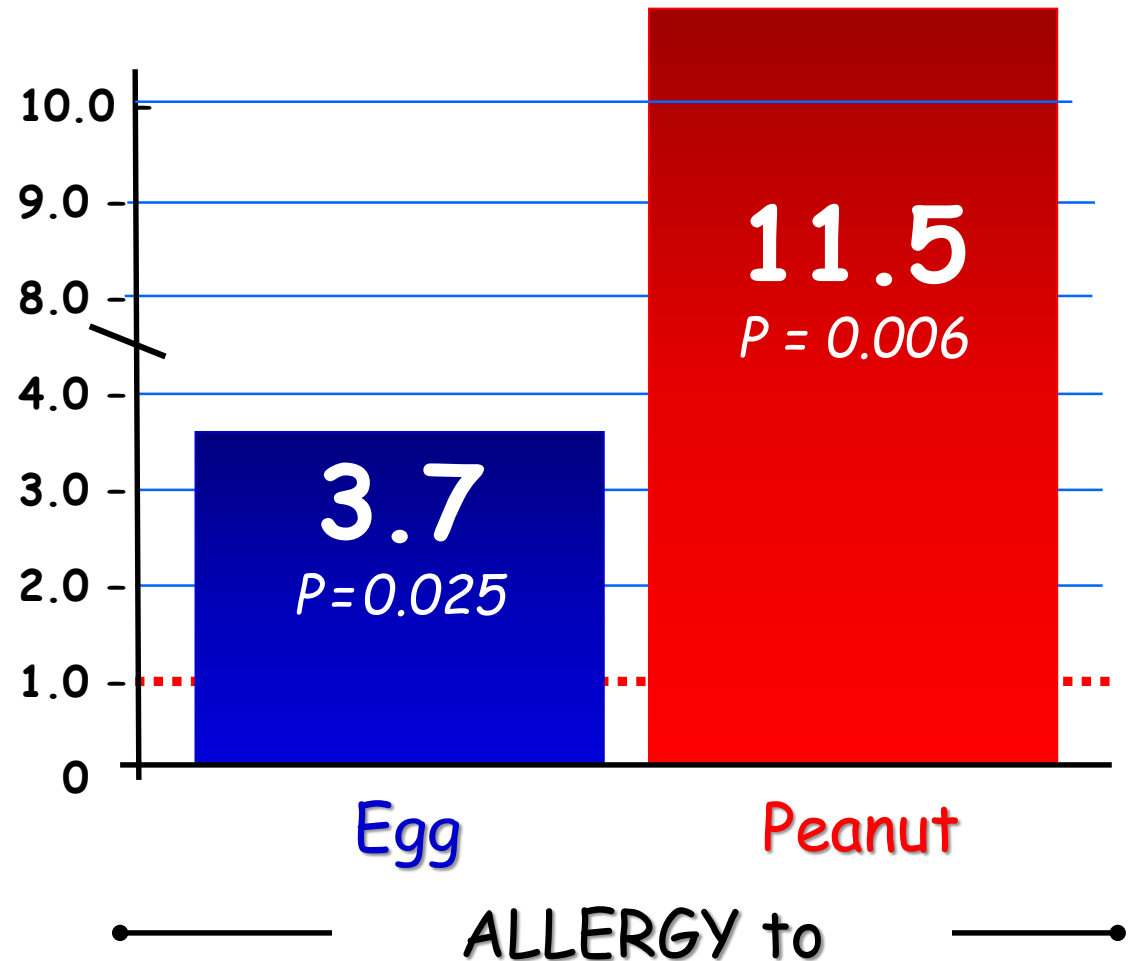
5276 infants SPT to peanut, egg, sesame, and cow's milk or shrimp.

Detectable SPT underwent wheal food challenge clinic.

Serum 25-hydroxyvitamin D levels

Associations between serum 25-hydroxyvitamin D and food allergy

with vitamin D insufficiency (<50 nmol/L) AOR for



Vitamin D insufficiency is associated with challenge-prove food allergy in infants.

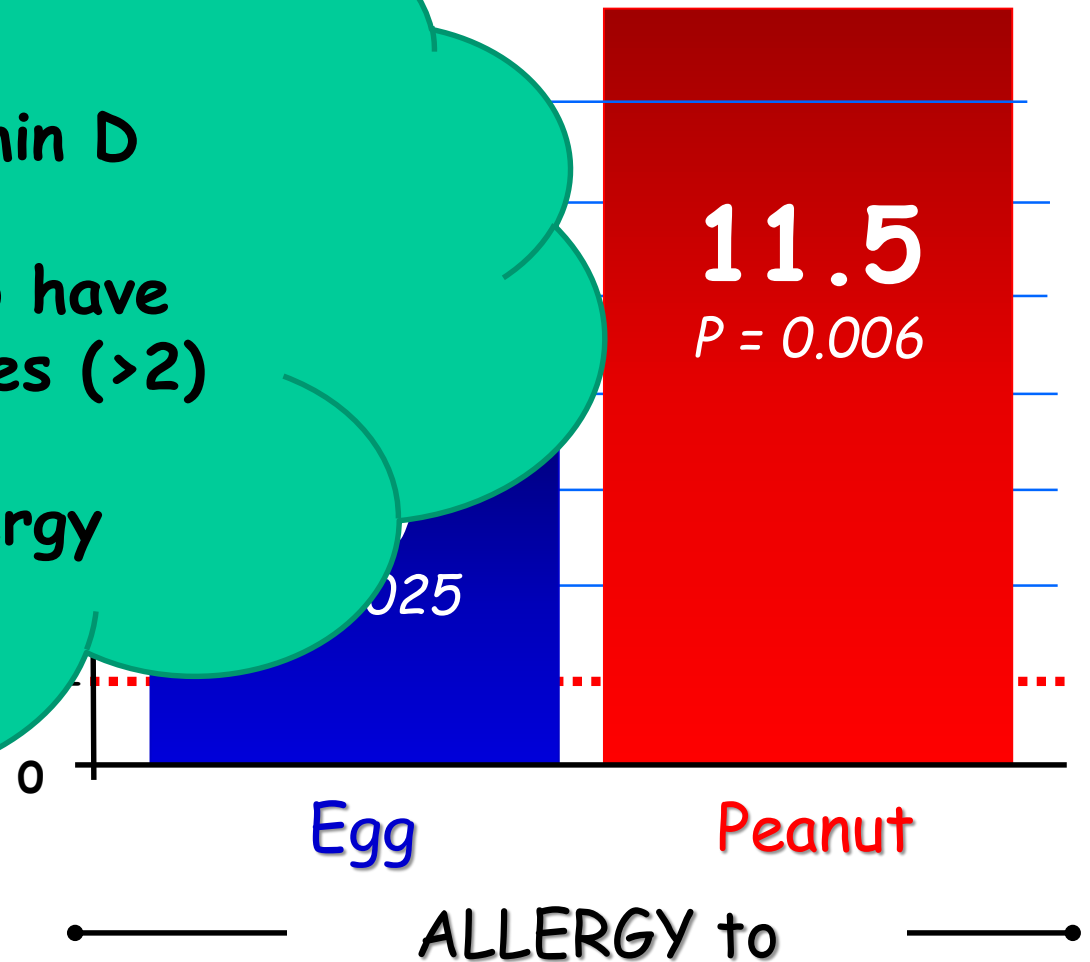
K Allen, 2013;131:1109

5276 infants SPT to peanut and cow's milk

Infants with vitamin D insufficiency were more likely to have multiple food allergies (>2) rather than a single food allergy

with vitamin D insufficiency (<50 nmol/L) AOR for

Association between serum 25-hydroxyvitamin D and food allergy



Vitamin D insufficiency is associated with challenge-prove food allergy in infants.

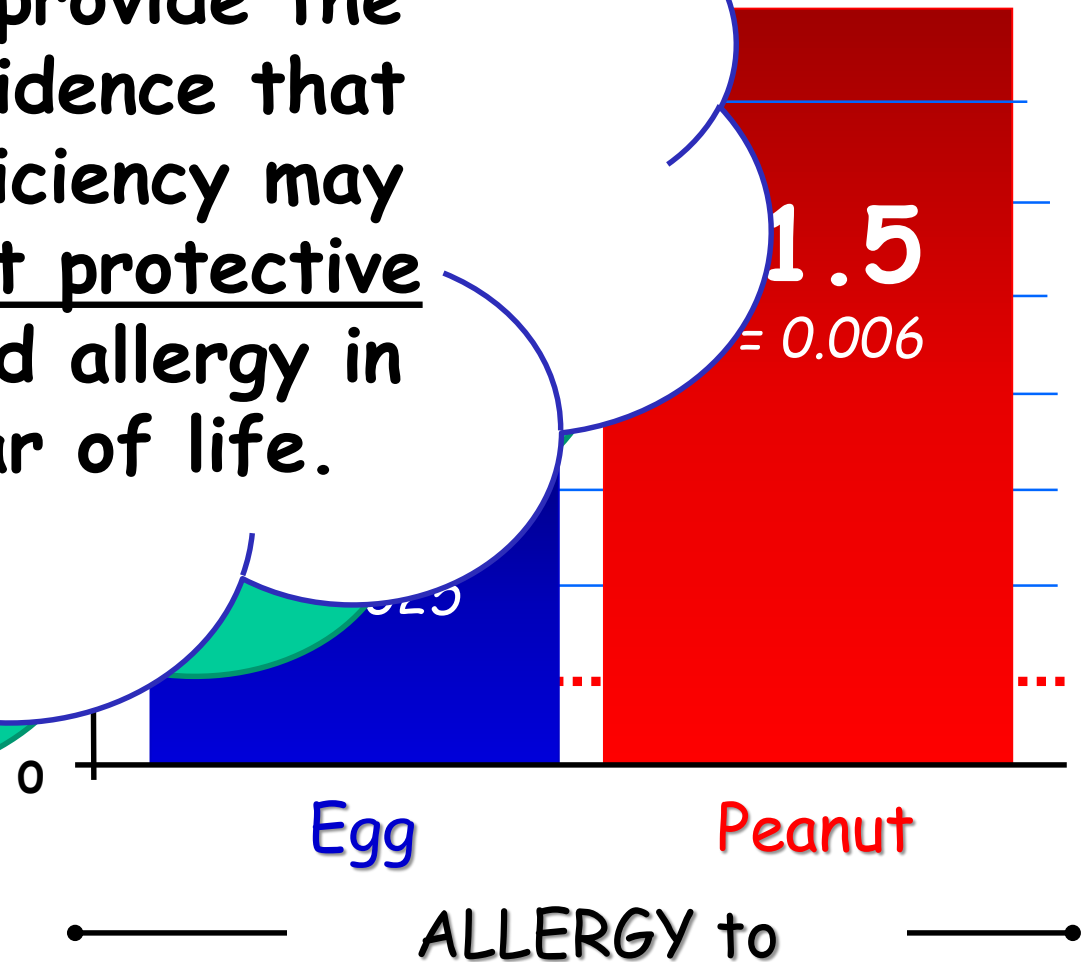
K Allen, 2013;131:1109

These results provide the first direct evidence that vitamin D sufficiency may be an important protective factor for food allergy in the first year of life.

5276 infants
peanut
cow's

Association
serum 25-
hydroxyvitamin D and
food allergy

insufficiency (<50
OR for



Cord serum 25-hydroxyvitamin D and risk of early childhood transient wheezing and atopic dermatitis. Baiz N, JACI; 2014; 133:147

aim was to investigate in 239 newborns the associations between cord serum 25(OH)D levels and asthma, wheezing, allergic rhinitis, and atopic dermatitis in the offspring from birth to 5 years.

Outcome	OR (95% CI)	
	Unadjusted	Adjusted*
Wheeze		
Early transient	0.77 (0.69-0.95), <i>P</i> = .01	0.67 (0.54-0.81), <i>P</i> = .0002
Late onset	0.94 (0.77-1.16), <i>P</i> = .58	0.86 (0.67-1.11), <i>P</i> = .24
Persistent	1.10 (0.70-0.95), <i>P</i> = .50	1.15 (0.79-1.691), <i>P</i> = .46
Atopic dermatitis		
By the age of 1 y	0.88 (0.76-1.00), <i>P</i> = .08	0.84 (0.71-1.00), <i>P</i> = .05
By the age of 2 y	0.86 (0.77-1.00), <i>P</i> = .05	0.82 (0.70-0.95), <i>P</i> = .02
By the age of 3 y	0.87 (0.76-1.00), <i>P</i> = .05	0.82 (0.68-0.97), <i>P</i> = .02
By the age of 5 y	0.82 (0.71-0.91), <i>P</i> = .003	0.75 (0.63-0.88), <i>P</i> = .0005
Early onset	0.82 (0.70-0.95), <i>P</i> = .01	0.73 (0.62-0.90), <i>P</i> = .002
Late onset	0.82 (0.68-0.98), <i>P</i> = .03	0.75 (0.60-0.94), <i>P</i> = .01
Asthma at 5 y	1.09 (0.87-1.38), <i>P</i> = .42	1.07 (0.78-1.45), <i>P</i> = .69
Allergic rhinitis at 5 y	1.06 (0.84-1.34), <i>P</i> = .62	0.99 (0.72-1.38), <i>P</i> = .98

Cord serum 25-hydroxyvitamin D and risk of early childhood transient wheezing and atopic dermatitis. Baiz N, JACI; 2014; 133:147

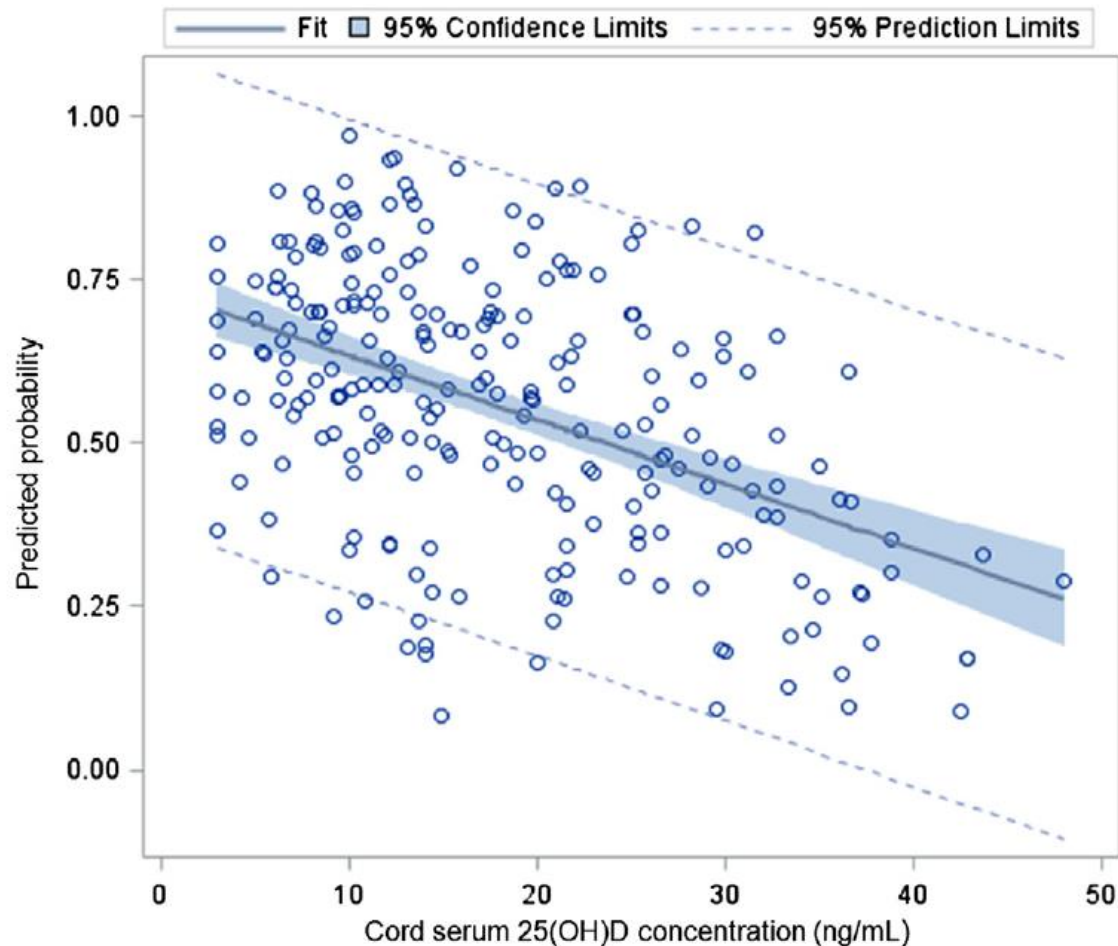
aim was to investigate in

239 newborns the

associations between cord serum 25(OH)D levels and

asthma, wheezing, allergic rhinitis, and atopic dermatitis in the offspring from birth to 5 years.

Adjusted associations between cord serum 25(OH)D levels and predicted probabilities of atopic dermatitis by age of 5 years

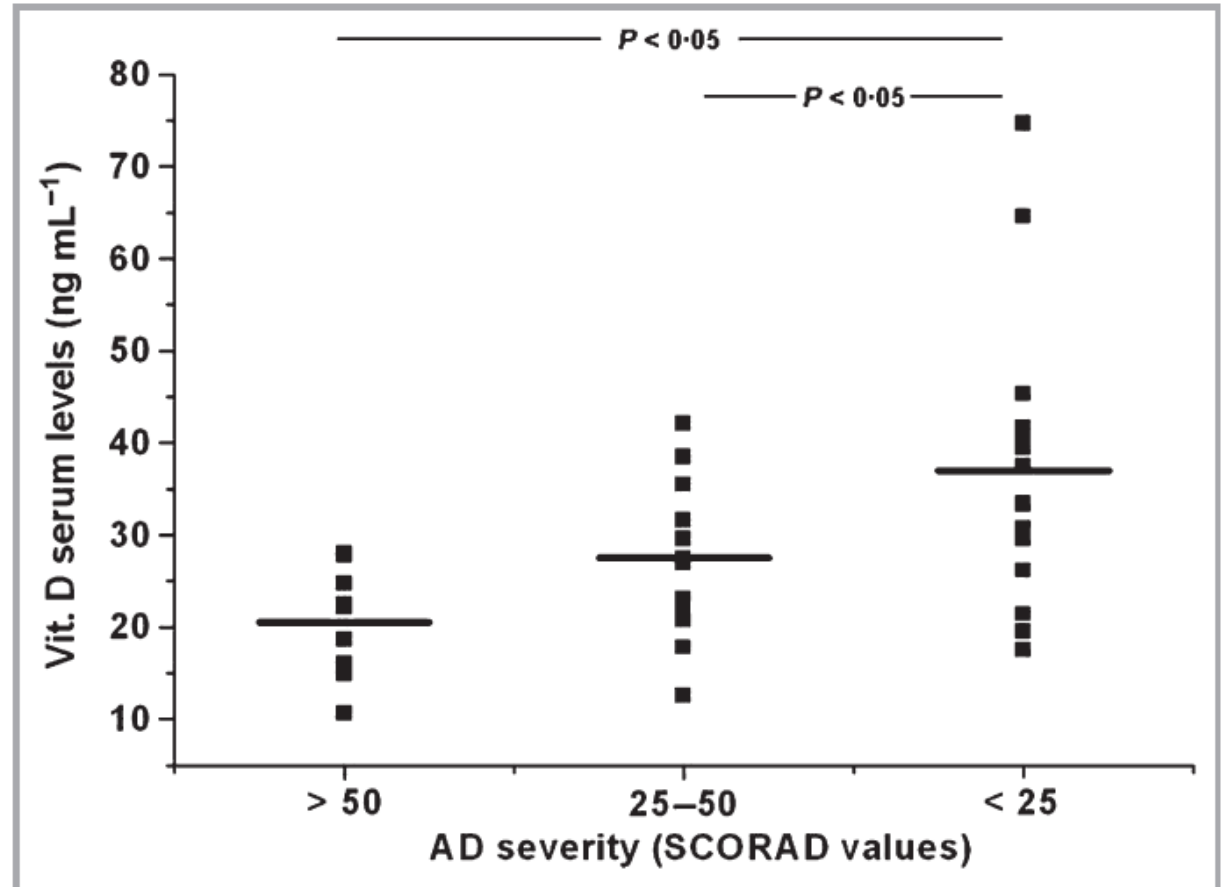


Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children.

Peroni DG, Br J Dermatol. 2011;164:1078

Mean serum vitamin D levels in relation to different threshold values of AD severity.

- ✓ 37 children (8 months and 12 years) with AD,
- ✓ SCORAD index,
- ✓ Serum levels of 25-hydroxyvitamin D
- ✓ sIgE to *S.aureus* and to *M. furfur*



Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children.

Peroni DC

Microorganism-induced exacerbations in atopic dermatitis: a possible preventive role for Vitamin D?

Peroni et al.

Allergy Asthma Proc 2015

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Mil
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)
4 (27)
5 (38)
6 (67)

SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; SEC, staphylococcal enterotoxin C.

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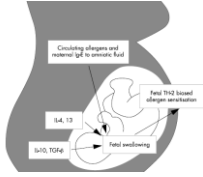
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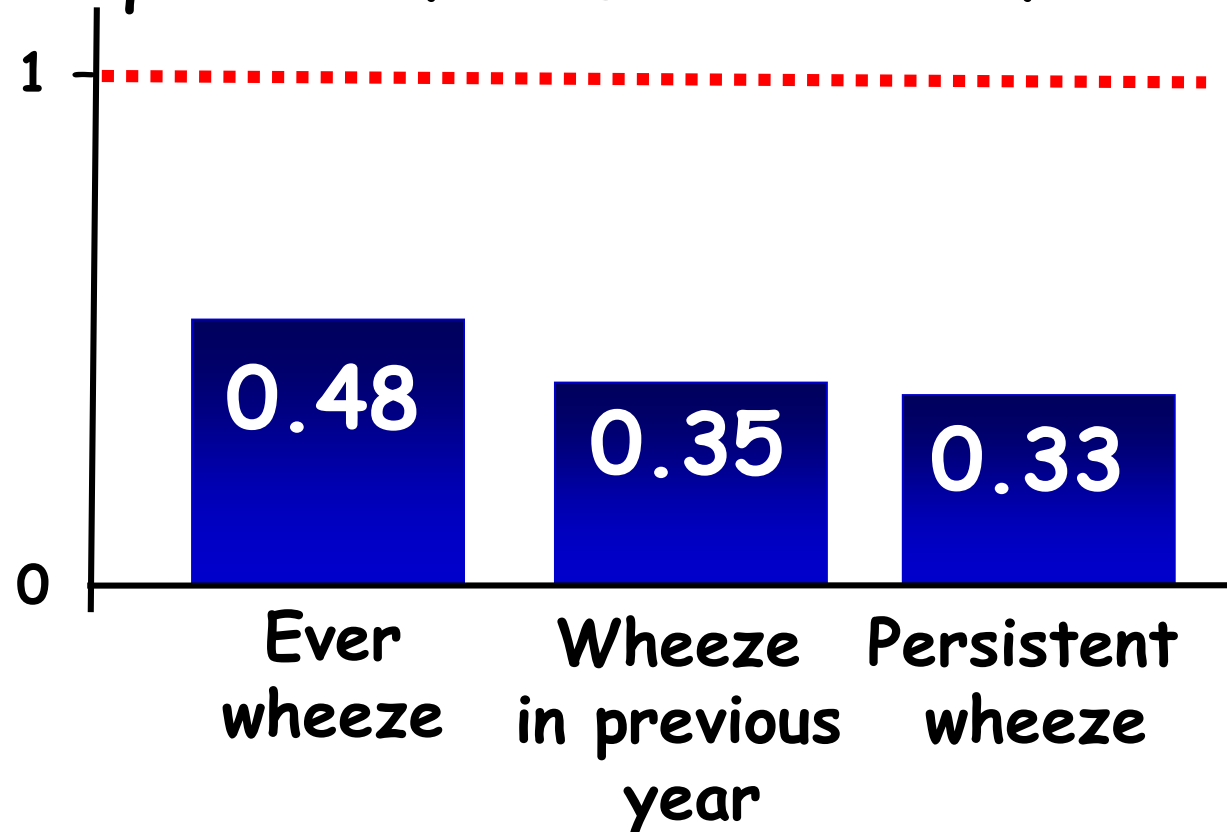


Maternal vitamin D intake during pregnancy and early childhood wheezing. Devereux G, Am J Clin Nutr. 2007;85:853



- ✓ Random sample of 2000 healthy Scottish pregnant women at approximately 12 wk gestation
- ✓ Maternal vitamin D intake ascertained at 32 wk of gestation with FFQ

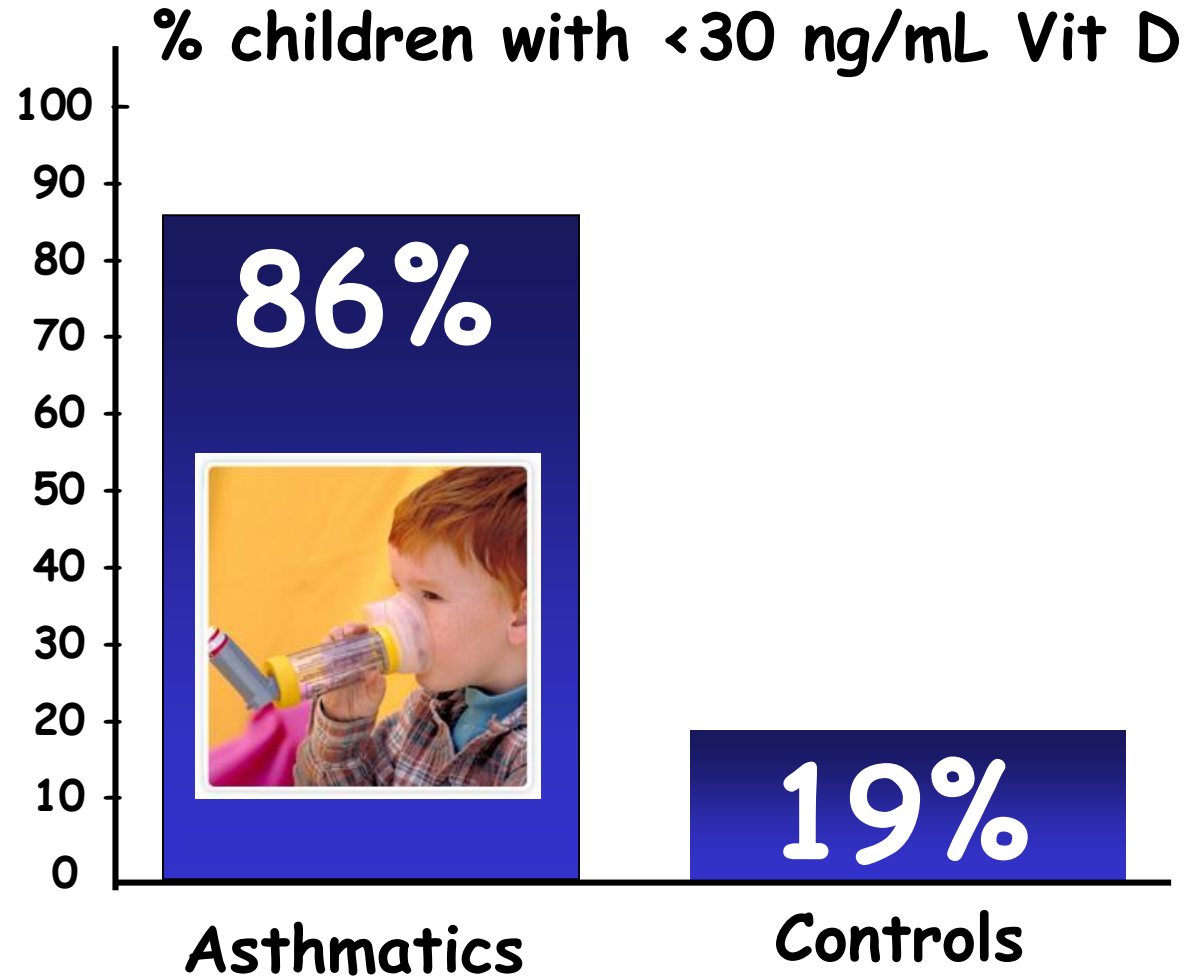
In 5 year old children of mothers in the highest versus the lowest quintiles of vit D intake OR for



High Prevalence of Vitamin D Deficiency among Inner-City African American Youth with Asthma in Washington

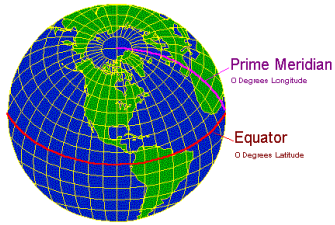
Freishtat J Pediatr 2010;156:948-52

- ✓ Urban African-American (AA) youth with asthma (=92)
- ✓ control subjects without asthma (=21).
- ✓ 25-hydroxyvitamin D insufficiency (<30 ng/mL) and deficiency (<20 ng/mL).

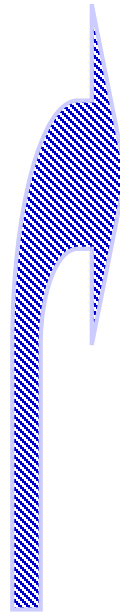


Serum Vitamin D Levels and Markers of Severity of Childhood Asthma in Costa Rica

Brehm Am J Respir Crit Care Med 2009;179:765



- ✓ 25-hydroxyvitamin D levels
- ✓ 616 asthmatic children
- ✓ Vitamin D levels deficient (<20 ng/ml), insufficient (≥ 20 and <30 ng/ml), and sufficient (≥ 30 ng/ml)



Vitamin D levels were significantly and inversely associated with:

- 1) total IgE and eosinophil count
- 2) any hospitalization in the previous year ($p=0.03$),
- 3) any use of anti-inflammatory medications in the previous year ($p=0.01$),
- 4) increased airway responsiveness ($p = 0.05$).

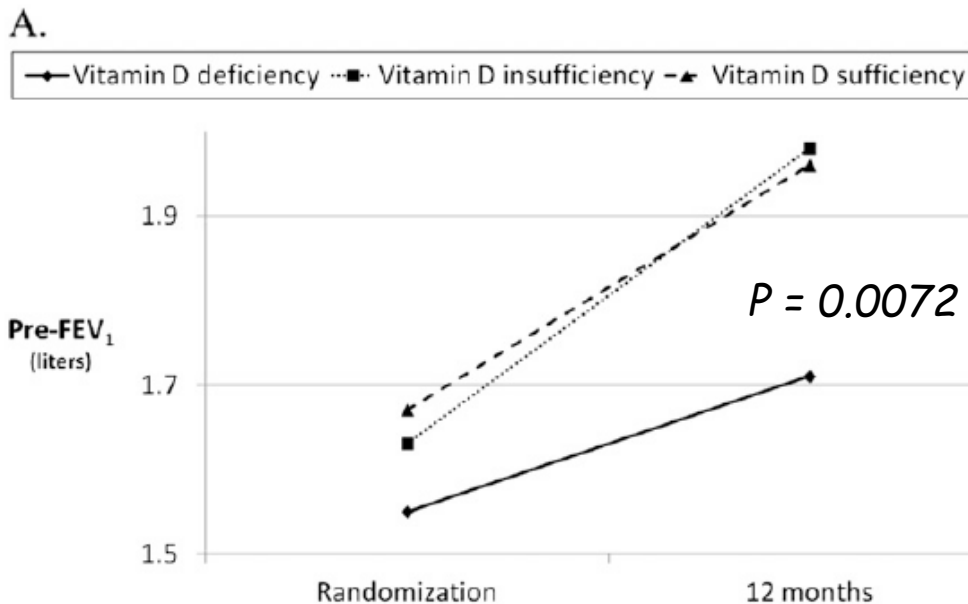
Effect of Vitamin D and Inhaled Corticosteroid Treatment on Lung Function in Children

Treatment on Lung Function in Children

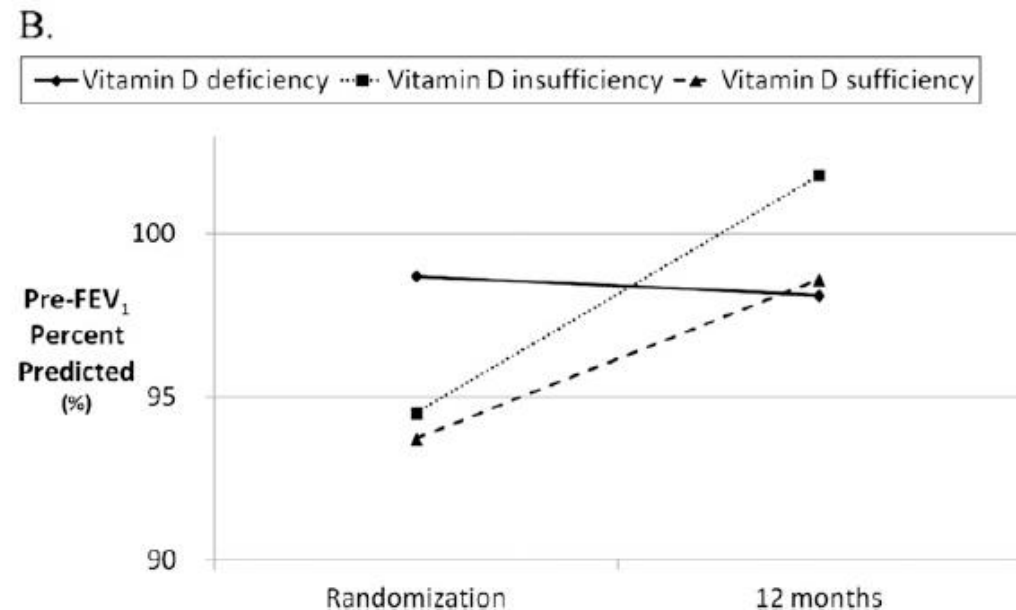
Chen Wu A., *AJRCCM* 2012; 186: 508-513



Change in prebronchodilator FEV₁



Change in prebronchodilator FEV₁ % predicted



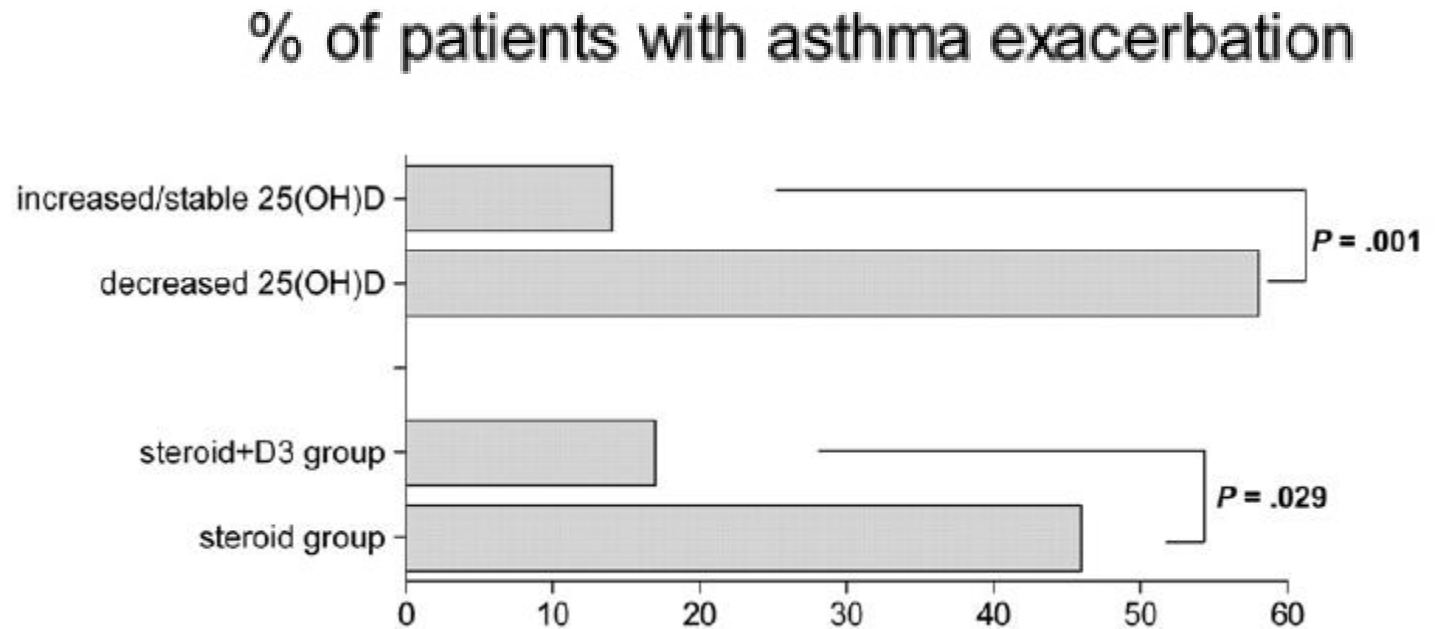
vitamin D sufficiency (>30 ng/ml), insufficiency (20-30 ng/ml), deficiency (<20 ng/ml)

Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection.

Majak P, J Allergy Clin Immunol 2011;127:1294

- ✓ 48 children (5-18 yrs) with newly diagnosed asthma and sensitive only to house dust mites
- ✓ budesonide 800 $\mu\text{g}/\text{d}$ administered as a dry powder and vitamin D placebo (steroid group, $n = 24$), or budesonide 800 $\mu\text{g}/\text{d}$ and vitamin D3-500 IU (steroid + vit D group $n=24$).

- ✓ Follow-up: 6 months



The effects of vitamin D supplementation on airway functions in mild to moderate persistent asthma

Arshi S, Ann All AI 2014

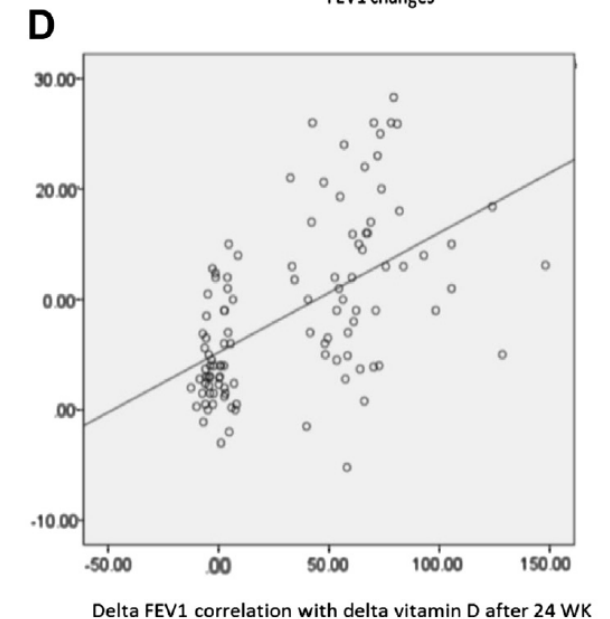
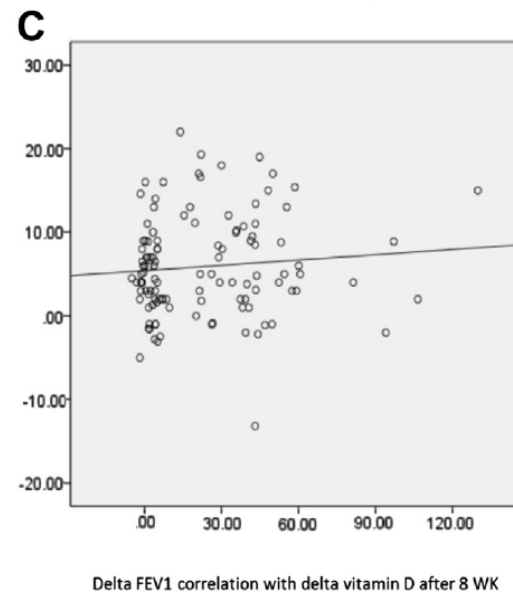
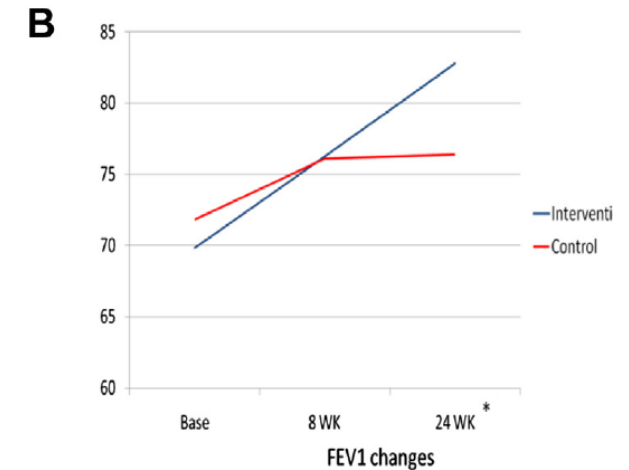
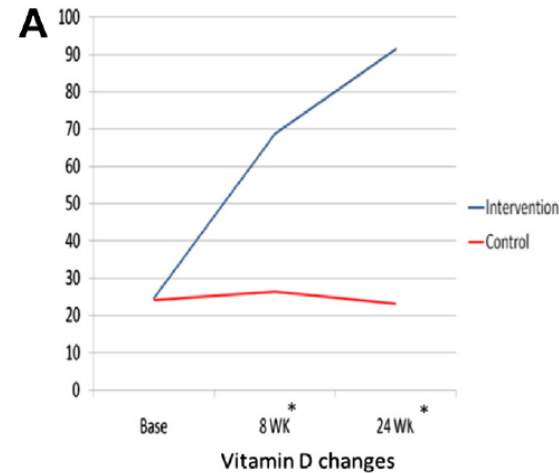
130 pts aged 10 to 50 yrs during a 24-week period.

FEV1 and FEV1/FVC and serum vitamin D

before and 8 and 24 weeks after the intervention.

Both groups received asthma controllers (budesonide or budesonide plus formoterol)

Active group received vitamin D supplementation (100,000-U bolus intramuscularly plus 50,000 U orally weekly) in addition to asthma controllers



Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial.

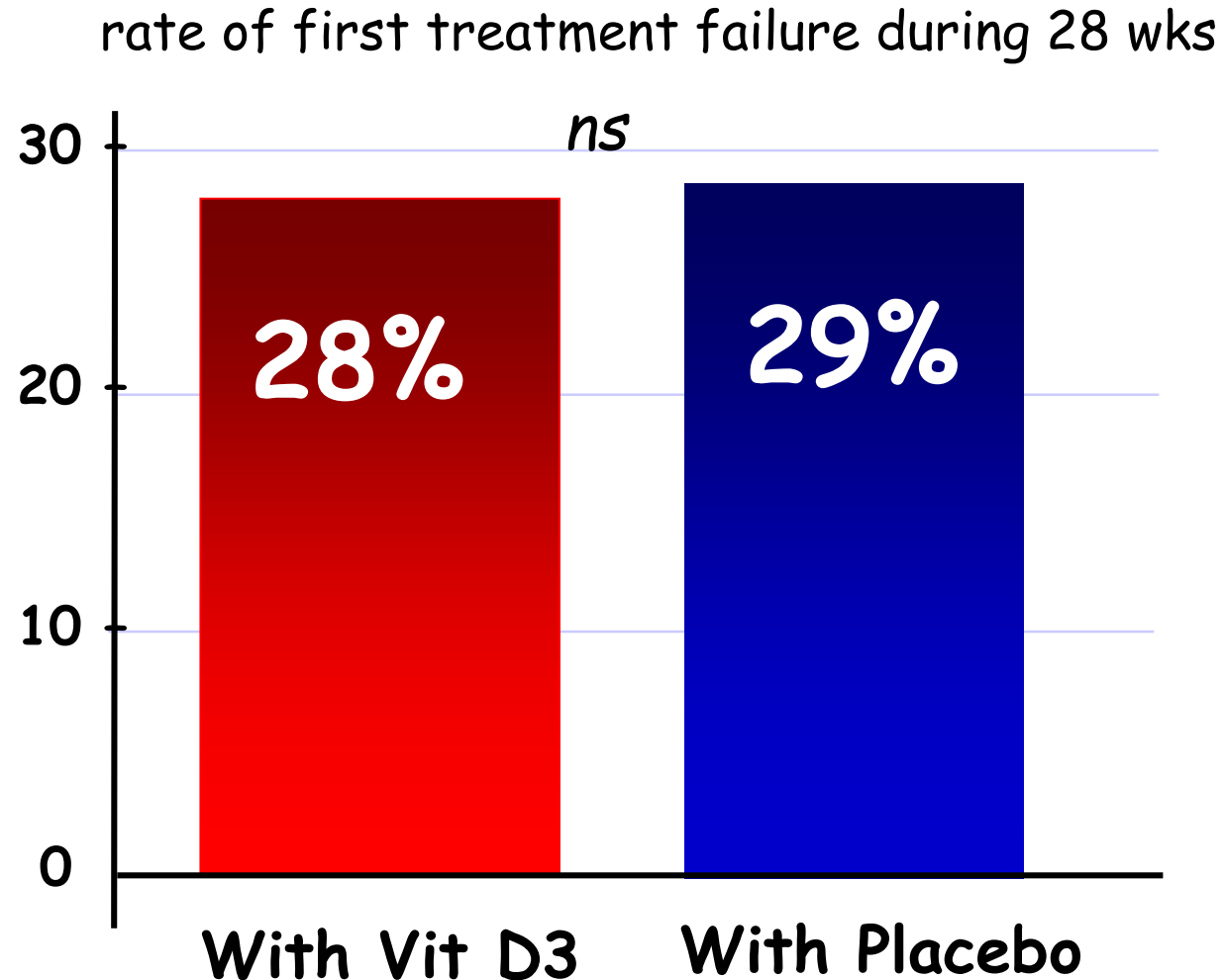
Castro, JAMA 2014;311:2083

The VIDA (Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma) randomized, double-blind, parallel, placebo-controlled trial

Adult patients with symptomatic asthma and a D3 <30 ng/mL

Oral vitamin D3 (100,000 IU once, then 4000 IU/d for 28 weeks) or placebo was added to inhaled ciclesonide (320 µg/d).

Primary outcome was time to first asthma treatment failure



Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial.

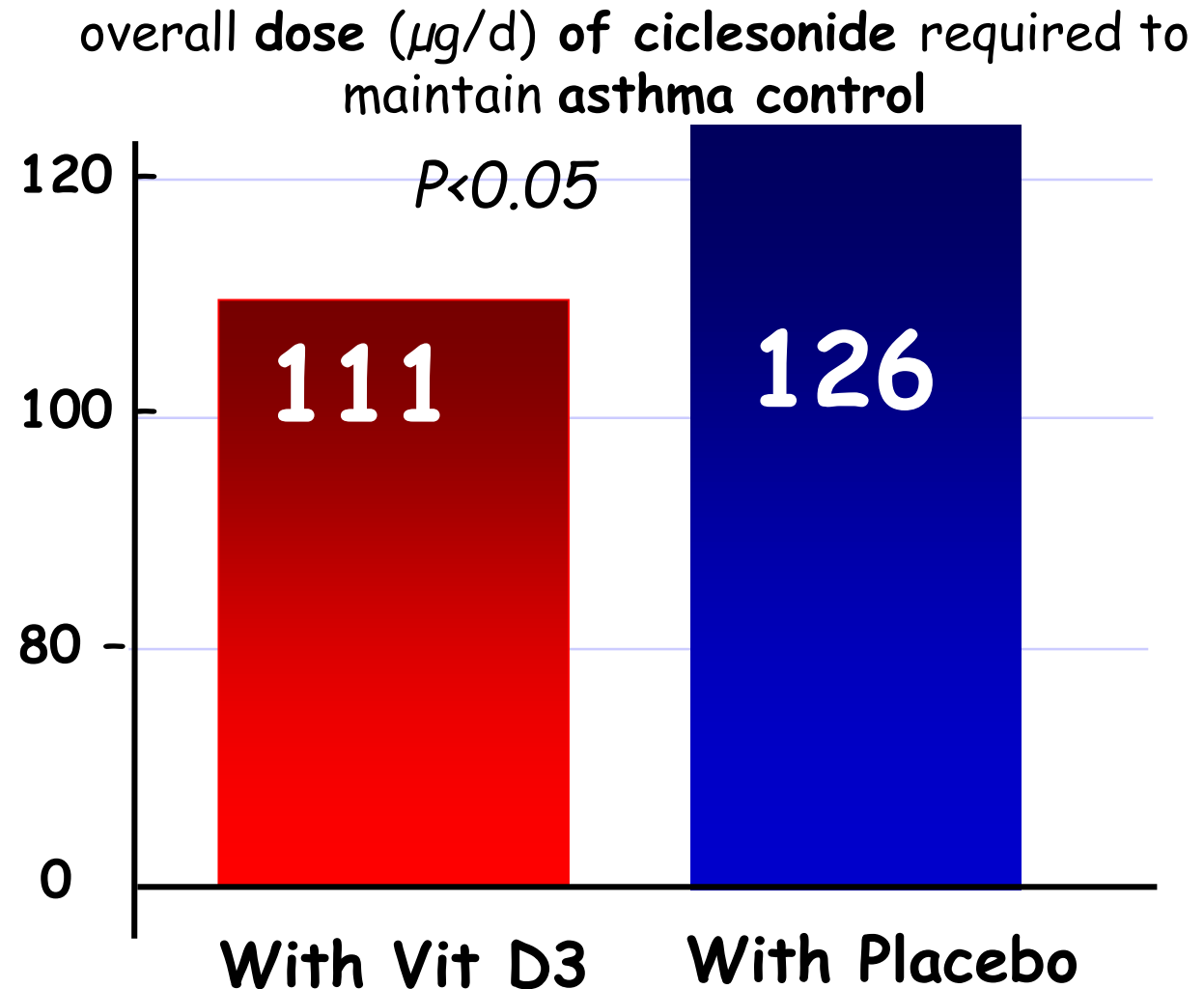
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Castro, JAMA 2014;311:2083

The VIDA (Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma) randomized, double-blind, parallel, placebo-controlled

Adult patients with asthma and a

Oral vitamin D3 (20,000 IU once, then 6000 IU 3 times/week) or placebo for 8 weeks) or placebo. Inhaled ciclesonide

Primary outcome: time to first asthma treatment failure

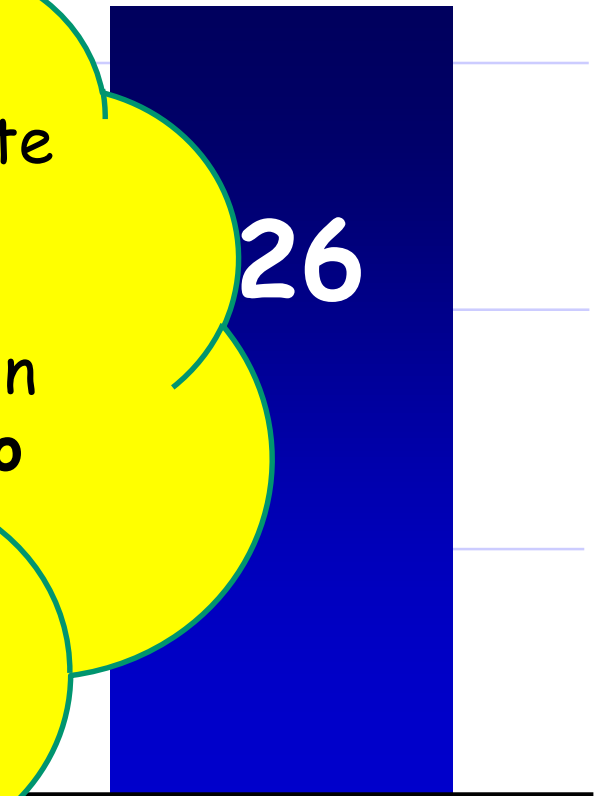
overall dose ($\mu\text{g}/\text{d}$) of ciclesonide required to maintain asthma control

Vitamin D3 did not reduce the rate of first treatment failure or exacerbation in adults with persistent asthma and vitamin D insufficiency. These findings do not support a strategy of therapeutic vitamin D3 supplementation in patients with symptomatic asthma

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With Vit D3

With Placebo



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Therapeutic Effects of Vitamin D in Asthma and Allergy

Cecilia Benetti^{1,#}, Pasquale Comberati^{1,#}, Carlo Capristo², Attilio L. Boner¹ and Diego G. Peroni^{3,*}

Author	Study type	Sample size	Intervention	Duration	Results
Sidbury <i>et al.</i> , 2008 [77]	Double-blind PC RCT	11 children (2-13 years) with mild AD (rated by EASI score)	1000 IU/day oral VD2 vs placebo Patients were allowed to continue previous topical therapies as needed, but not to begin new treatment.	1 month	Decreased severity of AD in the VD group rated by the IGA score ($P = 0.04$)
Javanbakht <i>et al.</i> , 2011 [79]	Double-blind PC RCT	45 patients with AD (rated by SCORAD index)	Group P (n = 11): oral VD and oral VE placebos; Group D (n = 12): 1600 IU/day oral VD plus VE placebo; Group E (n = 11): 600 IU/day oral VE plus VD placebo; Group DE (n = 11): 1600 IU/ day oral VD plus 600 IU/day oral VE	2 months	Group D showed significant increase in serum VD levels ($P < 0.001$) and decrease in severity of AD from baseline by 34.8% as rated by SCORAD ($P = 0.004$). This group showed a larger decrease in SCORAD index than the placebo group (28.9%), but this difference was not statistical significant.
Amestejani <i>et al.</i> , 2012 [80]	Double-blind PC RCT	60 patients with mild to severe AD (rated by SCORAD index)	1600 IU/day oral VD3 vs placebo	2 months	Decreased severity of AD in the VD group as rated by SCORAD index ($P < 0.05$)
Camargo <i>et al.</i> , 2014 [78]	Double-blind PC RCT	107 children (2 - 17 years) with mild to severe AD (rated by EASI score)	1000 IU/day oral VD3 vs placebo Patients were allowed to continue previous topical therapies as needed, but not to begin new treatment	1 month	Decreased severity of AD in the VD group rated by the EASI score (mean change - 6.5 (SD 8.8) for VD vs - 3.3 (SD 7.6) for placebo, $P = 0.04$)
Hata <i>et al.</i> , 2014 [81]	Double-blind PC RCT	76 adults: 30 with moderate to severe AD (rated by Rajka-Langeland score); 30 non-atopic controls; 16 with psoriasis	4000 IU/day oral VD3 vs placebo	21 days	Significant increase in mean serum 25OHD level in the VD group No significant change in skin cathelicidin, HBD-3, IL-13 and EASI score.

Therapeutic Effects of Vitamin D in Asthma and Allergy

Cecilia Benetti^{1,#}, Pasquale Comberati^{1,#}, Carlo Capristo², Attilio L. Boner¹ and Diego G. Peroni^{3,*}

Author	Study type	Sample size	Intervention	Duration	Results
Majak <i>et al.</i> , 2011 [55]	Double-blind PC RCT	48 asthmatic children (5-18 years)	500 IU/day oral VD3 vs placebo, in addition to asthma control therapy (inhaled budesonide)	6 months	Reduced risk of asthma exacerbation triggered by acute respiratory tract infection in the VD group
Yadav <i>et al.</i> , 2014 [56]	Double-blind PC RCT	82 asthmatic children (5-11 years)	60.000 IU/month oral VD3 vs placebo, in addition to standard steroid-based therapy	6 months	Reduced number of asthma exacerbation ($P = 0.011$), emergency visits ($P = 0.015$) and decreased steroid dosage ($P = 0.013$) in the VD group
Castro <i>et al.</i> , 2014 [57]	Double-blind PC RCT	408 asthmatic adults (≥ 18 years)	100.000 IU bolus plus 4.000 IU/day oral VD3 vs placebo, in addition to asthma controllers (inhaled ciclesonide)	28 weeks	VD did not reduce the rate of first treatment failure (primary outcome, defined as combination of decline in lung function parameters and increase in use of β_2 -agonists, systemic corticosteroids and health care). VD slightly reduced the dose of inhaled corticosteroid required to maintain asthma control (difference of 14.9 $\mu\text{g}/\text{d}$).
Arshi <i>et al.</i> , 2014 [58]	PC RCT	130 asthmatic children and adults (10-50 years)	Asthma medications (budesonide or budesonide plus formoterol in a dry powder inhaler) with and without addition of 100.000 IU bolus (IM) plus 50.000 IU/week oral VD3	24 weeks	24 weeks after the intervention FEV1 improved by about 20% in the VD group compared to about 7% among those who only used the inhaler ($P < 0.001$).
Bar Yoseph <i>et al.</i> , 2014 [59]	Double-blind PC RCT	39 children (6-18 years) with mild non-treated asthma	14.000 IU/week oral VD vs placebo	6 weeks	No differences in relation to airway hyperreactivity parameters (i.e. FeNO and PC20-FEV1) and airways inflammation markers (i.e. exhaled breath condensate cytokines IL4, IL5, IL10, IL17, and γ -interferon) among the two groups.
Nanzer <i>et al.</i> , 2014 [64]	Double-blind PC RCT	24 adults (≥ 18 years) with steroid-resistant asthma	0.25 μg calcitriol twice daily vs placebo, in addition to oral prednisolone (during the last 2 weeks)	4 weeks	Modest but significant improvement in absolute and predicted FEV1 in the calcitriol group ($P = 0.03$).



How much sun is enough?

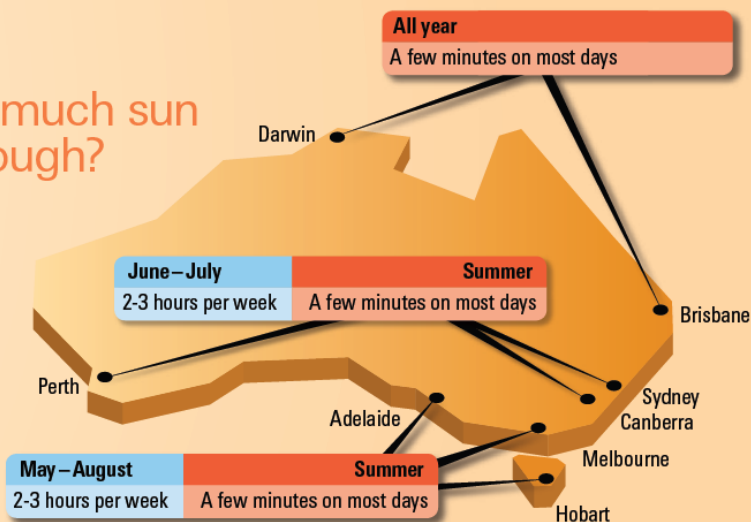
GETTING THE BALANCE RIGHT
VITAMIN D AND SUN PROTECTION

However, certain sections of the population are more likely to be at risk of vitamin D deficiency. These include:

- Naturally dark skinned people – who need more UV exposure to produce adequate levels of vitamin D as the pigment in their skin reduces UV penetration
- People who cover their skin for religious or cultural reasons
- The elderly and people who are housebound or in institutional care
- Babies and infants of vitamin D deficient mothers, especially babies who are exclusively or partially breastfed
- Patients with osteoporosis.

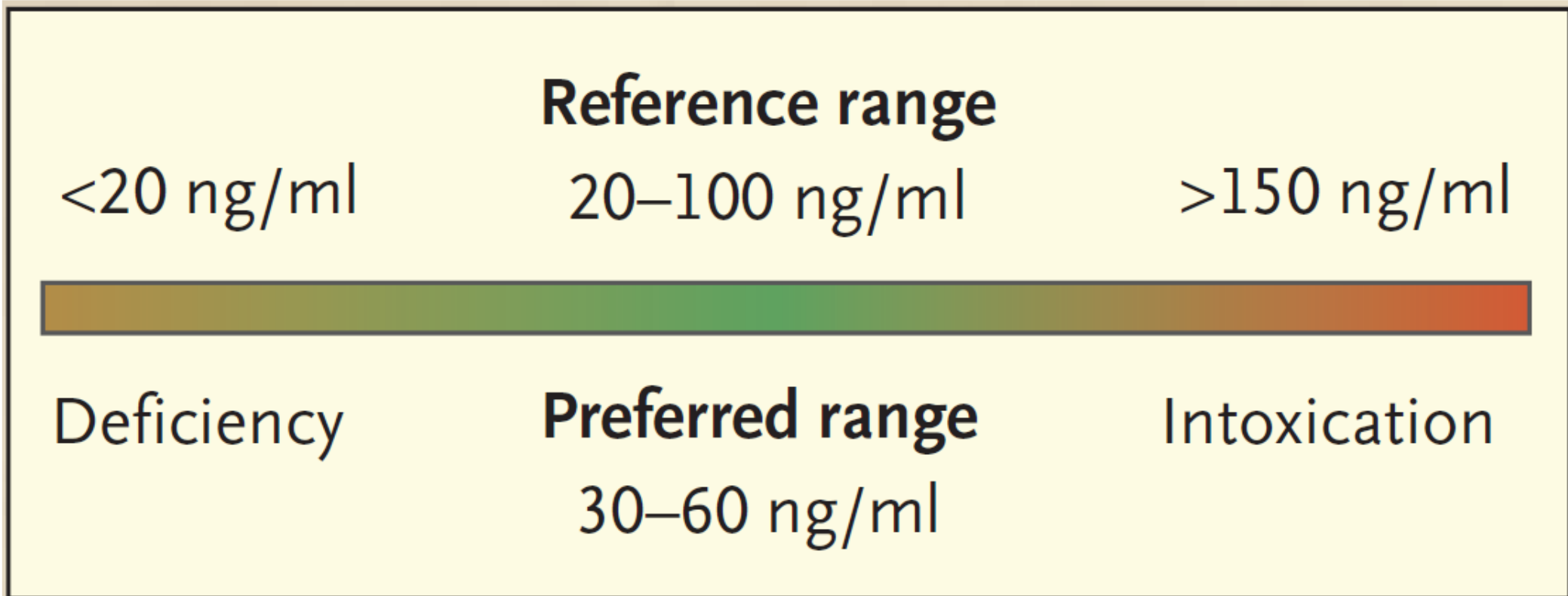
People in these groups should consult their doctor for advice on whether they need to take a vitamin D supplement.

How much sun is enough?



Vitamin D Deficiency

Holick NEJM 2007;357:266-81.



20 ng/mL = 50 nmol/L
30 ng/mL = 75 nmol/L
150 ng/mL = 374 nmol/L

To convert 25-OH vitamin D concentrations from ng/mL to nanomoles per liter, multiply by 2.496.

Vitamin D Treatment Strategies

Current recommendations for daily vitamin D supplementation:

- 200 IU for children and young adults,
- 400 IU for adults 51-70 years old, and
- 600 IU for adults older than 71 years of age



Are too low and do not maintain 25OHD at the desired level for many individuals.

Recently, the American Academy of Pediatrics recommended increasing the dose to **400 IU for children.**

Vitamin D and corticosteroids in asthma: synergy, interaction and potential therapeutic effects. *A Litonjua, Expt Rev Respir Med 7, 101, 2013*

“The mechanisms reviewed ... in addition to the results of the clinical studies, strengthen the notion of a synergy between corticosteroids and vitamin D, which may have particular relevance for asthma and allergies. Larger studies in humans will be needed to verify this synergy, and to determine its clinical use.”