Use of Vitamin D and Immunity: *Why supplementation are needed?*

Attilio Boner
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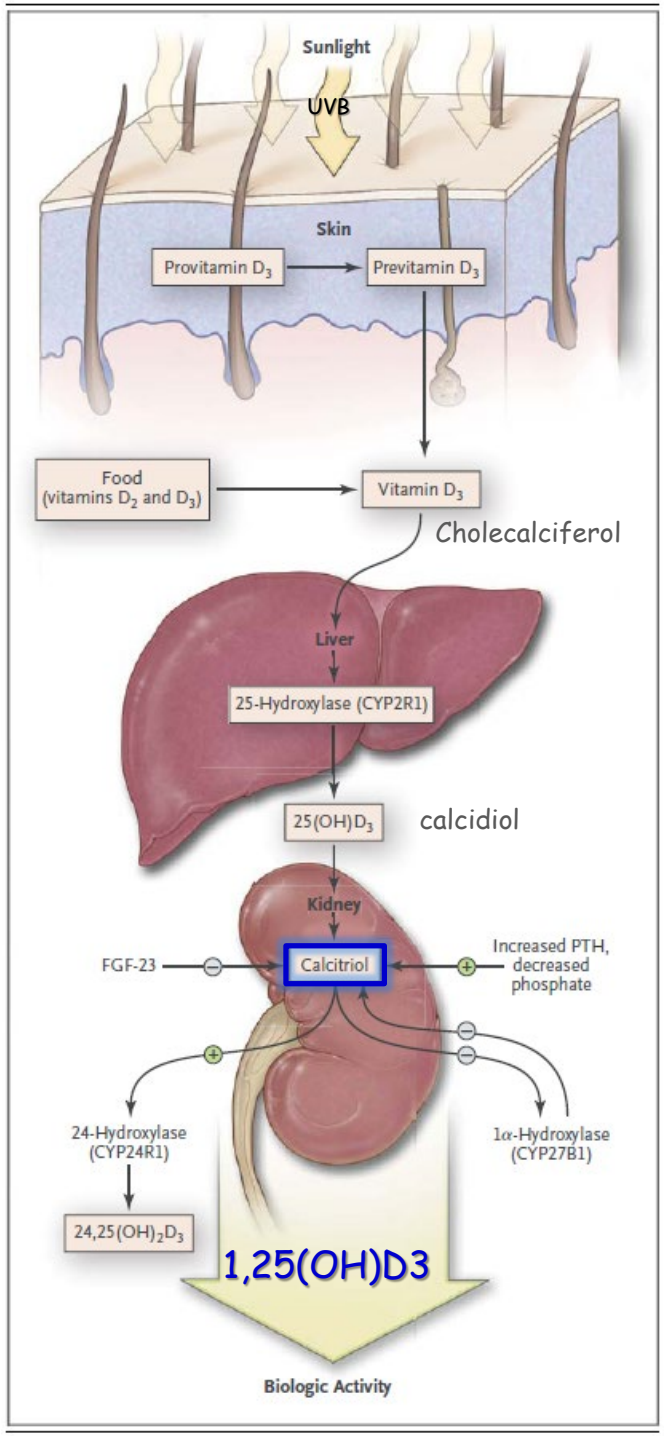
- ✓ **Introduction**
- ✓ Immunomodulation
- ✓ Fetal development
- ✓ Infections
- ✓ Prevention and modification of asthma & COPD
- ✓ Prevention and modification of allergic rhinitis
- ✓ Prevention and modification of atopic dermatitis
- ✓ Prevention and modification of food allergy anaphylaxis, urticaria
- ✓ Autoimmunity
- ✓ Other Diseases
- ✓ Conclusions

Synthesis and Metabolism of Vitamin D.

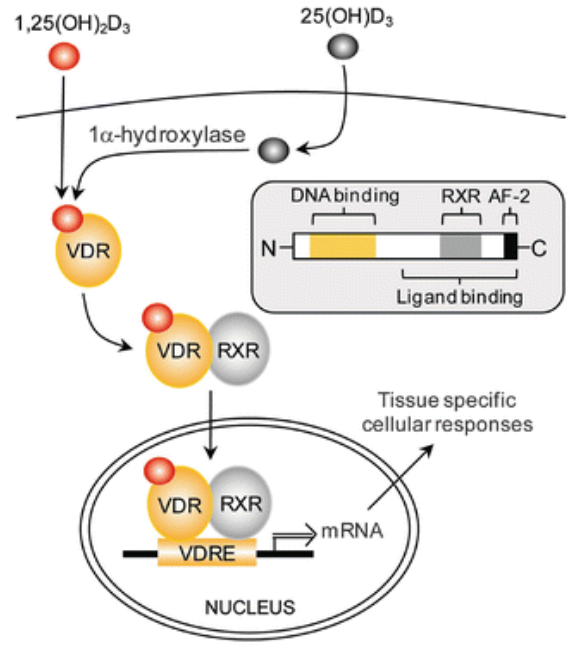
Rosen CJ. NEJM 2011;364:248

Vitamin D is initially generated in the skin from the nonenzymatic conversion of provitamin D3 to previtamin D3.
Dietary intake of vitamin D is usually relatively limited, since few foods, with the exception of certain kinds of fish, contain sizable amounts; supplements are commonly used.
Vitamin D **(Cholecalciferol)** is either stored in adipose tissue or converted in the liver by the enzyme 25-hydroxylase to 25-hydroxyvitamin D3 (25[OH]D3) or **calcidiol**, the form that circulates in the highest concentration and reflects solar and dietary exposure.

It is converted to the active metabolite, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), or **calcitriol**, in the kidney, although other tissues have 1α-hydroxylase (CYP27B1) enzymatic activity. The synthesis of calcitriol is enhanced (+) by increasing levels of parathyroid hormone (PTH), which rise in response to lower levels of serum calcium. Reduced levels of serum phosphate can also increase (+) the production of calcitriol.
Its synthesis is suppressed (–) by the production of fibroblast growth factor 23 (FGF-23), which is secreted by osteocytes in the bone matrix.
Calcitriol (1,25-dihydroxyvitamin D) inhibits the activity of 1α-hydroxylase (CYP27B1) and stimulates the activity of 24-hydroxylase (CYP24R1), an enzyme that promotes production of $24,25(OH)_2D3$, a vitamin D product that is not biologically active.
In CYP2R1, CYP27B1, and CYP24R1, CYP denotes cytochrome P.

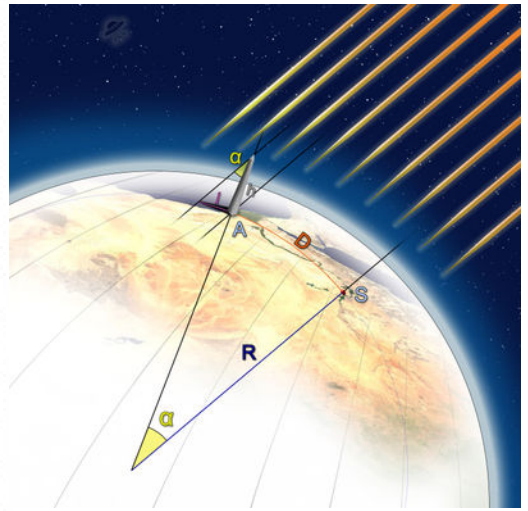


Vitamin D Receptors (VDR) are present in different tissues



bone
skin
intestine
kidneys
brain
eye
heart
immune cells
muscle
pancreatic islets
adipose tissue
thyroid
parathyroid
adrenal glands
placenta
?????

courtesy of Prof. Michele Miraglia del Giudice



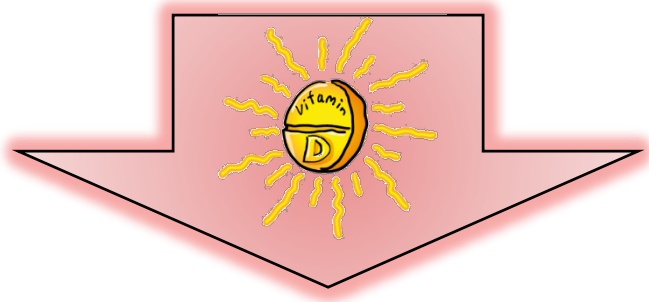
persons living **above 35° latitude** cannot produce adequate previtamin D_3 during **winter**.

My shadow at 12 a.m.

on February 5th

in Verona,

Latitude 45° N



No vitamin D production

by sun exposure !

25-hydroxyvitamin D serum level in children of different ethnicity living in Italy.

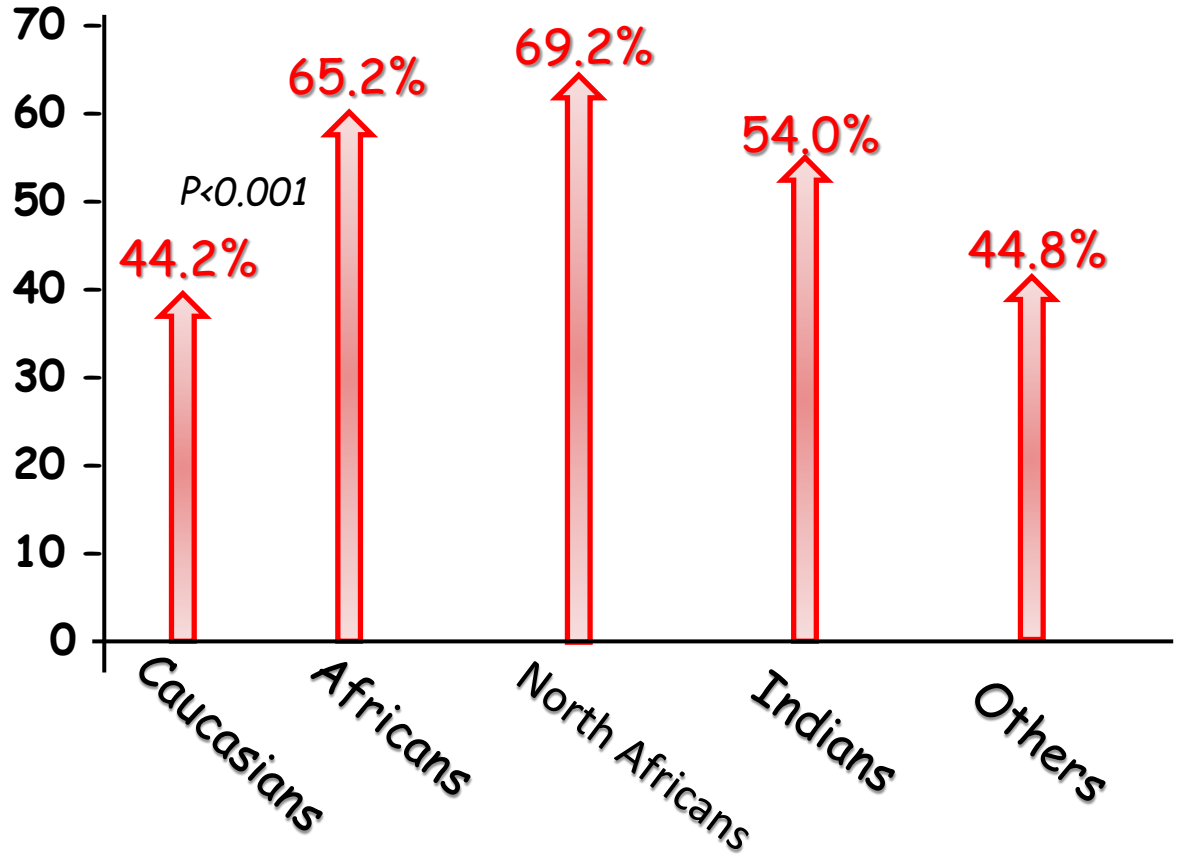
Franchi B , and Boner AL. Eur J Pediatr. 2015;174(6):749-57.

✓1374 pediatric subjects of different ethnicity

✓prevalence of 25(OH)D deficiency (≤ 20 ng/ml) and insufficiency (21–29 ng/ml)

	Severe deficiency	Deficiency	Insufficiency	Sufficiency
25(OH)D	< 10 ng/ml (< 25 nmol/l)	< 20 ng/ml (< 50 nmol/l)	20–29 ng/ml (50–74 nmol/l)	≥ 30 ng/ml (≥ 75 nmol/l)
Conversion factor: ng/ml = nmol/l*0.401; nmol/l = ng/ml*2.496				

prevalence of 25(OH)D ≤20 ng/ml (deficiency)



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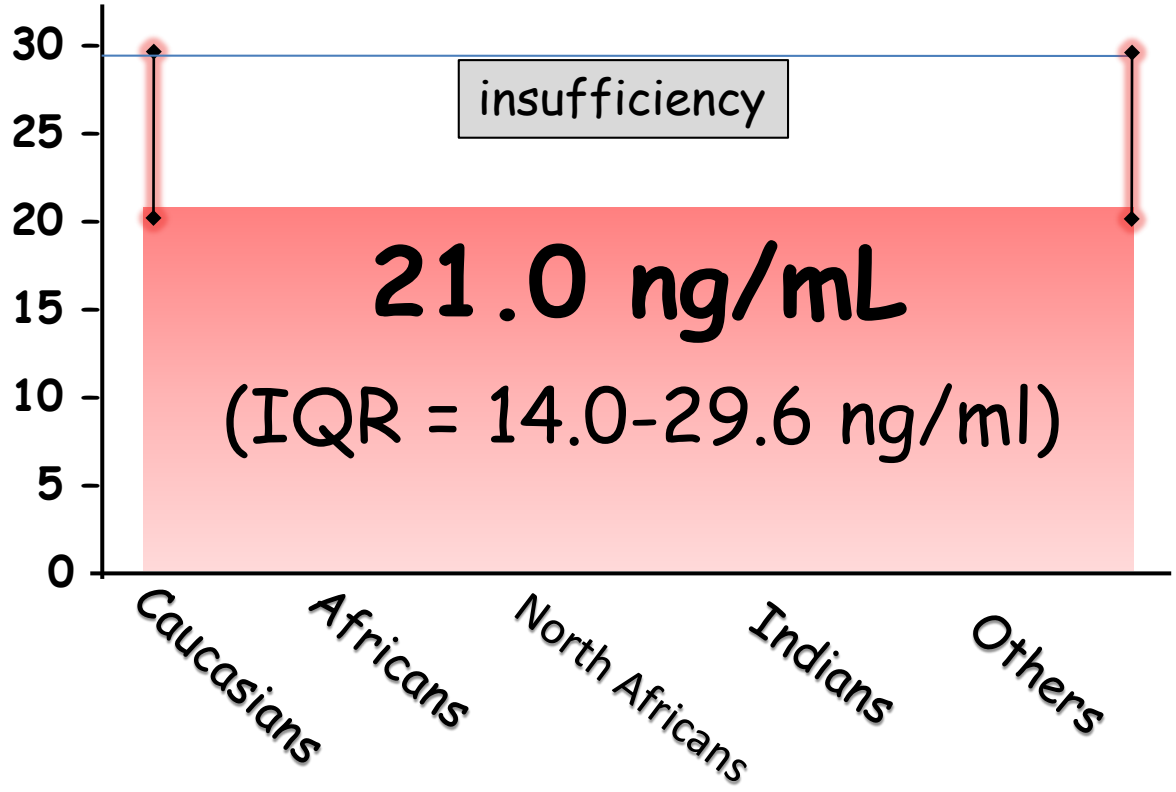
Median 25(OH)D concentration for the entire cohort



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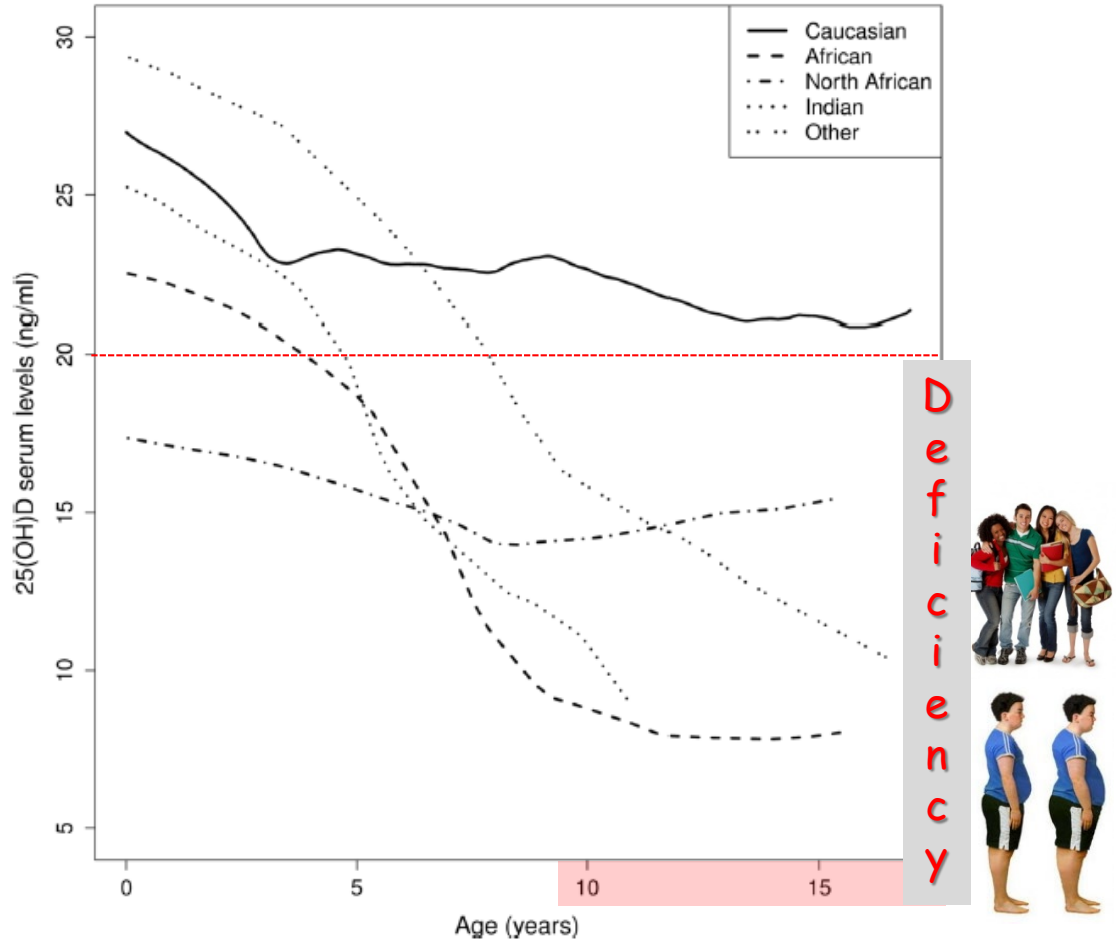
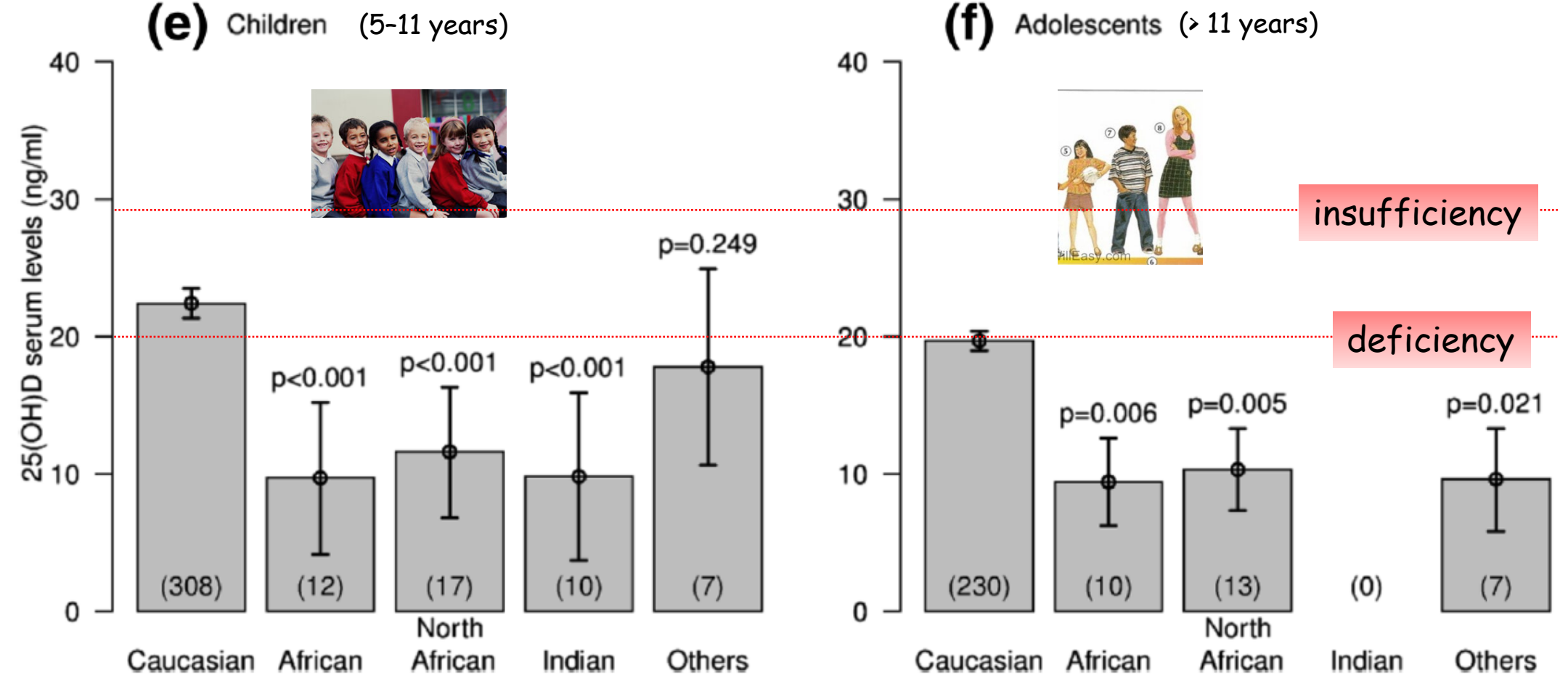
Mean serum levels of 25(OH)D as a function of age and by ethnicity



25-hydroxyvitamin D serum level in children of different ethnicity living in Italy.

Franchi B , and Boner AL. Eur J Pediatr. 2015;174(6):749-57.

Bar plot of adjusted median 25(OH)D levels (with 95 % confidence intervals) by ethnicity



Regular breakfast consumption is associated with higher blood vitamin status in adolescents: the HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) Study.

Mielgo-Ayuso J, Public Health Nutr. 2017. Jun;20(8):1393-1404.

✓1058 (52·8 % females) European adolescents (aged 12·5-17·5 years) from ten cities.

- Lower vitamin D, vitamin C, and folate concentrations were observed in male and female breakfast skippers than in consumers *(P<0·05)*.

- Female breakfast consumers presented higher holo-transcobalamin and lower total homocysteine *(P<0·05)*, while males had higher cobalamin (B12) concentrations, compared with skippers *(P<0·05)*.

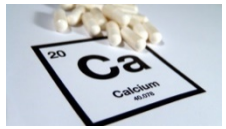
- Female consumers had higher intakes of vitamin B6 and vitamin E than occasional consumers *(P<0·05)*.

Approximately one-quarter of circulating cobalamin (vitamin B-12) binds to transcobalamin (holoTC) and is thereby available for the cells of the body. For this reason, holoTC is also referred to as active vitamin B-12.

The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know.

Ross AC, J Clin Endocrinol Metab. 2011;96:53-8.

TABLE 1. Calcium and vitamin D dietary reference intakes by life stage and for bone health



Life-stage group (age and gender)	Calcium RDA (mg/d) (intake that covers needs of ≥97.5% of population)	Calcium UL (mg/d)[a]	Vitamin D RDA (IU/d) (intake that covers needs of ≥97.5% of population)	Vitamin D Serum 25OHD level (ng/ml) (corresponding to the RDA)[b]	Vitamin D UL (IU/d)[a]
1–3 yr (M+F)	700	2500	600	20	2500
4–8 yr (M+F)	1000	2500	600	20	3000
9–13 yr (M+F)	1300	3000	600	20	4000
14–18 yr (M+F)	1300	3000	600	20	4000
19–30 yr (M+F)	1000	2500	600	20	4000
31–50 yr (M+F)	1000	2500	600	20	4000
51–70 yr (M)	1000	2000	600	20	4000
51–70 yr (F)	1200	2000	600	20	4000
71+ yr (M+F)	1200	2000	800	20	4000
Pregnant or lactating (F)					
14–18 yr	1300	3000	600	20	4000
19–50 yr	1000	2500	600	20	4000
Infants					
0–6 months (M+F)	200[c]	1000	400[c]	20	1000
6–12 months (M+F)	260[c]	1500	400[c]	20	1500

100 IU=2.5μg

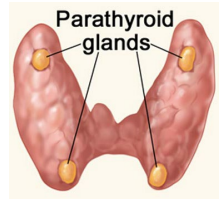
RDA = Recommended Dietary Allowance; UL= tolerable upper intake level; c= not well defined

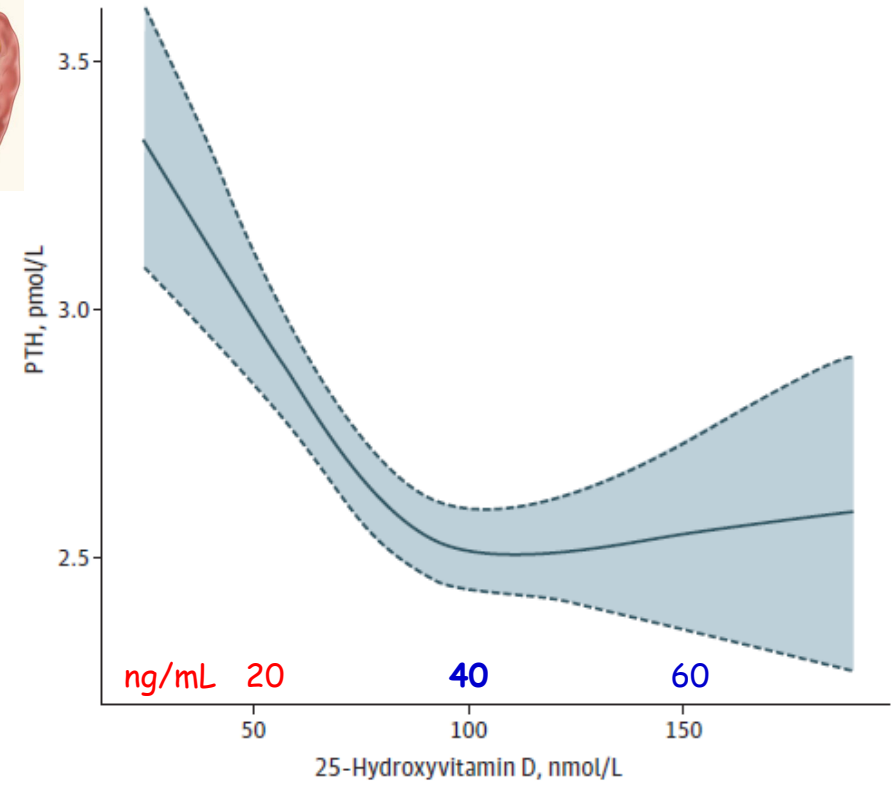
Parathyroid Hormone as Functional Indicator of Vitamin D Sufficiency in Children

Maguire JL, JAMA Ped 2014;168;383-384

- ✓ 1370 healty children
  1 to 6 years of age
- ✓ Healt maintenance physician's visit in Toronto, Ontario, Canada
- ✓ Nonfasting total 25-hydroxyvitamin D
- ✓ Nonfasting PTH

Plot of the Regression Model for 25-Hydroxyvitamin D and Parathyroid Hormone (PTH)





Shaded areas inside the dashed lines represent 95% confidence intervals.

Parathyroid Hormone as Functional Indicator of Vitamin D Sufficiency in Children

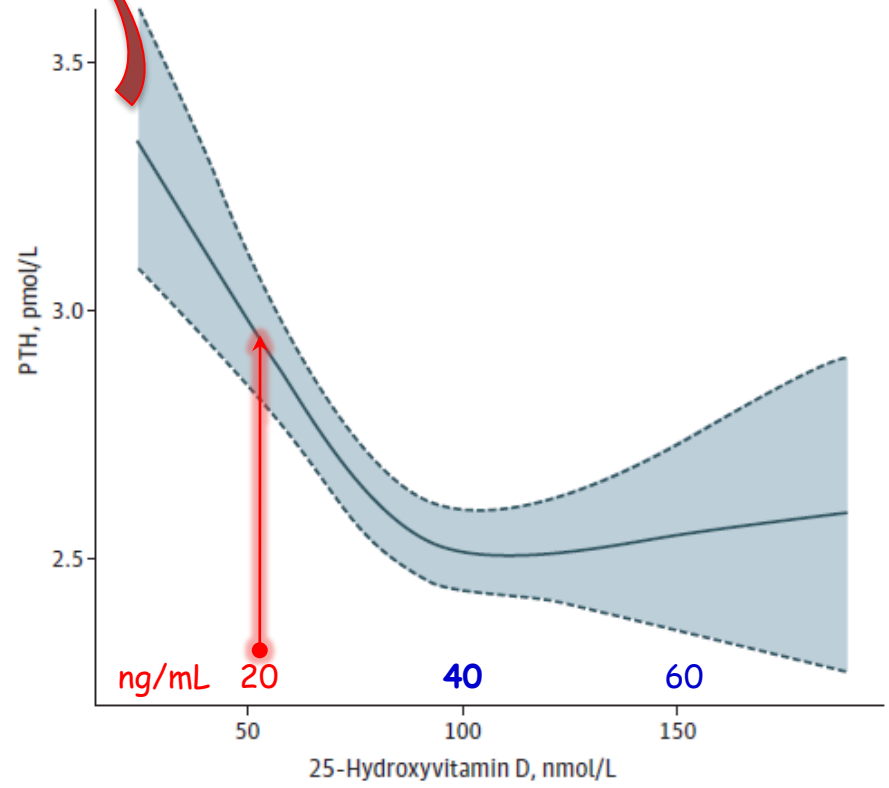
Maguire JL, JAMA Ped 2014;168;383-384

PTH elevation may promote:

1) cardiovascular disease through diminished cardiac contractility, enhanced coronary risk, and cardiac valvular and vascular calcification.
2) metabolic syndrome and hyperlipidemia, decreased insulin sensitivity, and, perhaps, decreased insulin secretion.
3) neuroendocrine activation,
4) increased sympathetic activity,
5) endothelial stress.

Gröber U, Dermatoendocrinol. 2013;5:331-47

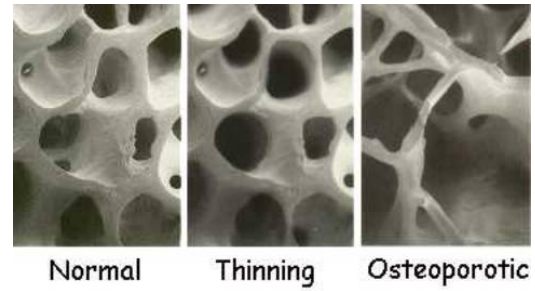
Plot of the Regression Model for 25-Hydroxyvitamin D and Parathyroid Hormone (PTH)



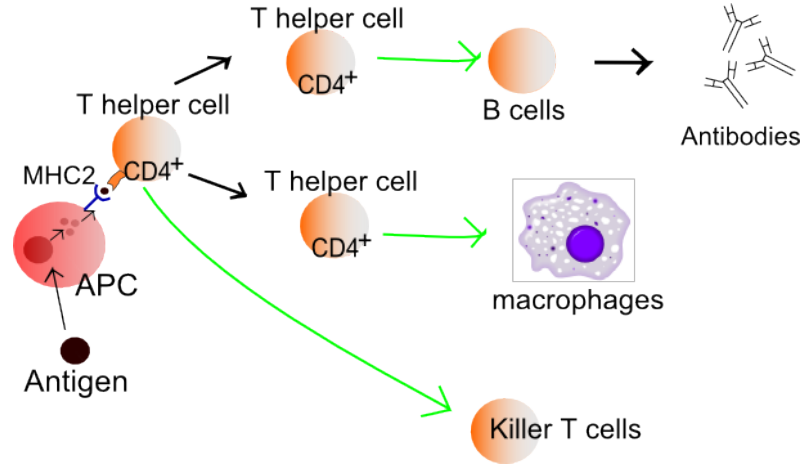
Shaded areas inside the dashed lines represent 95% confidence intervals.

Vitamin D levels optimal for overall health.

- The lower defined **threshold value for bone health (25OHD ≥ 20 ng/mL [50 nmol/L])**,
Holick MF, J Clin Endocrinol Metab 2011;96:1911-30
Rosen CJ, J Clin Endocrinol Metab 2012;97:1146-52.



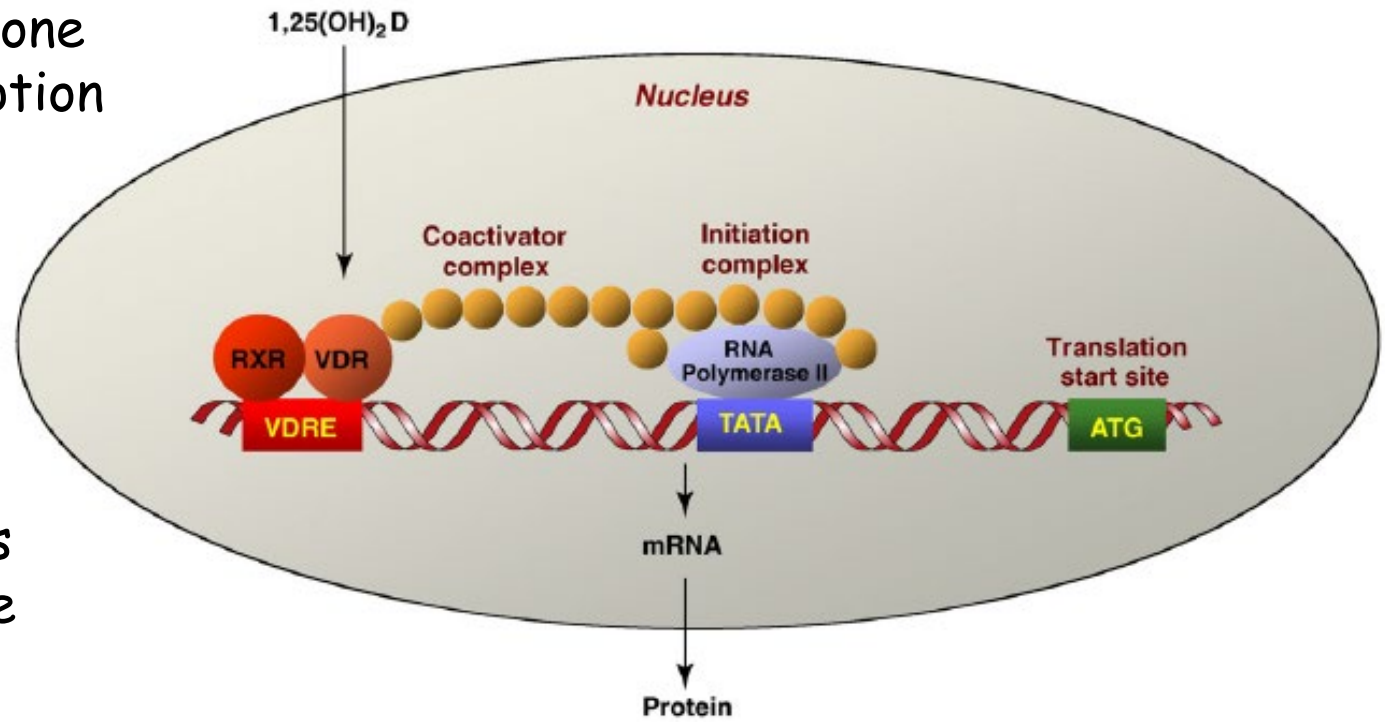
- Serum level of 25OHD **30–40 ng/mL (75–100 nmol/L)** has been suggested **as a lower threshold** of an optimal serum level **for the immune effects** of vitamin D.
Vieth R, Am J Clin Nut 2007;85:649-50.
Bischoff-Ferrari HA, Am J Clin Nut 2006; 84:18-28.



- **More** than **one-third of the population worldwide** may have levels of vitamin D **<20 ng/mL (50 nmol/L)**. *Hilger J. British J Nut 2014;111:23-45.*

The mechanism of action of 1,25(OH)2D.

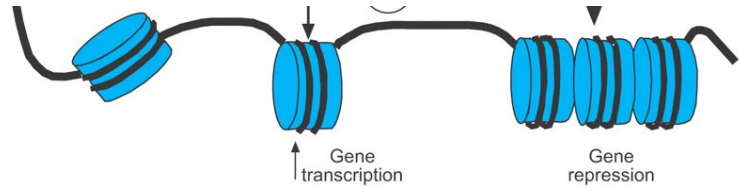
•1,25(OH)2D is a sterol hormone and is a ligand for a transcription factor, which in the case of 1,25(OH)2D is the vitamin D receptor (VDR).



•When 1,25(OH)2D binds to VDR it is transported into the nucleus where it partners with another nuclear hormone receptor, most often the retinoid X receptor (RXR).

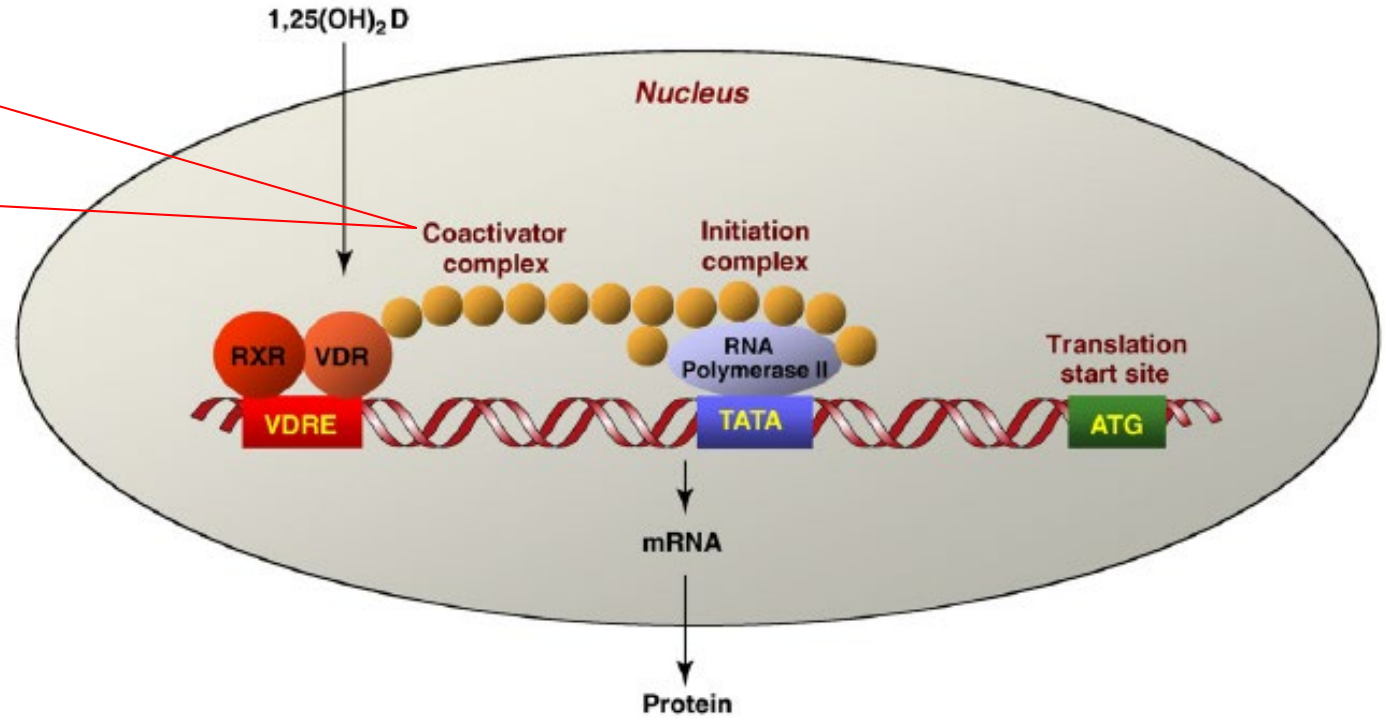
•These heterodimers bind to regions of the genes they regulate at specified sequences called vitamin D response elements (VDREs).

•Binding to the VDREs can facilitate the expression of the targeted gene (coactivators) or inhibitits expression (cosuppressors).



The mechanism of action of 1,25(OH)2D.

Different tissues have varying levels of these coregulators, providing some degree of tissue specificity for vitamin D action.



Thus, an appreciation of the ability of individual tissues to produce their own 1,25(OH)2D3 in a tissue specific manner and to respond to 1,25(OH)2D3, again in a tissue specific manner, provides the basis for the concept that vitamin D regulates many functions in many tissues, and does so selectively.

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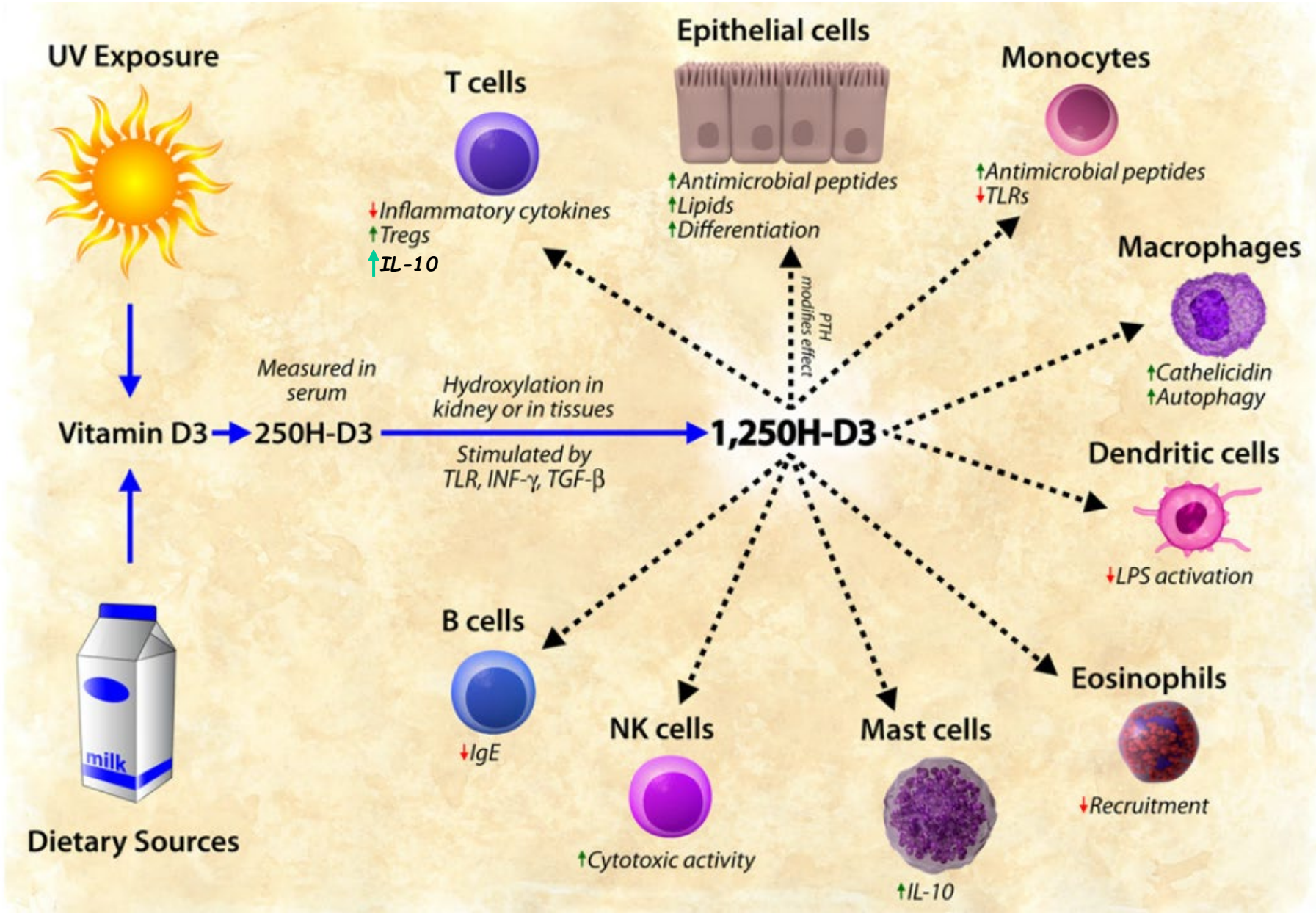
Overview of vitamin D and its interactions with cells of the immune system. *Muehleisen B, JACI 2013;131:324-9.*



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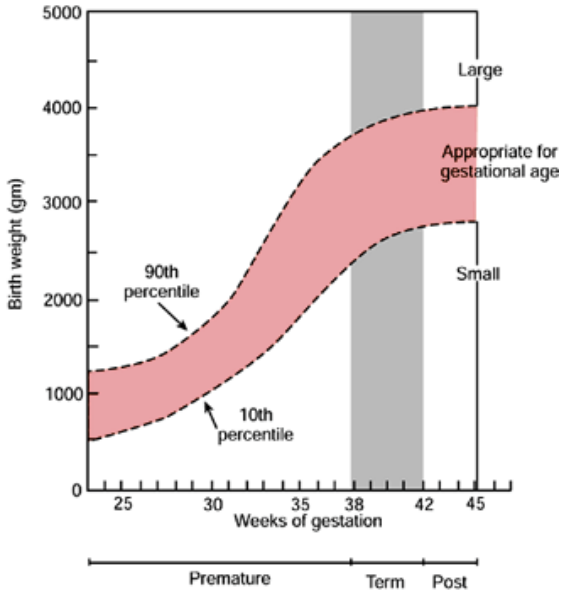
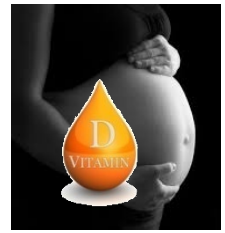
Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis.

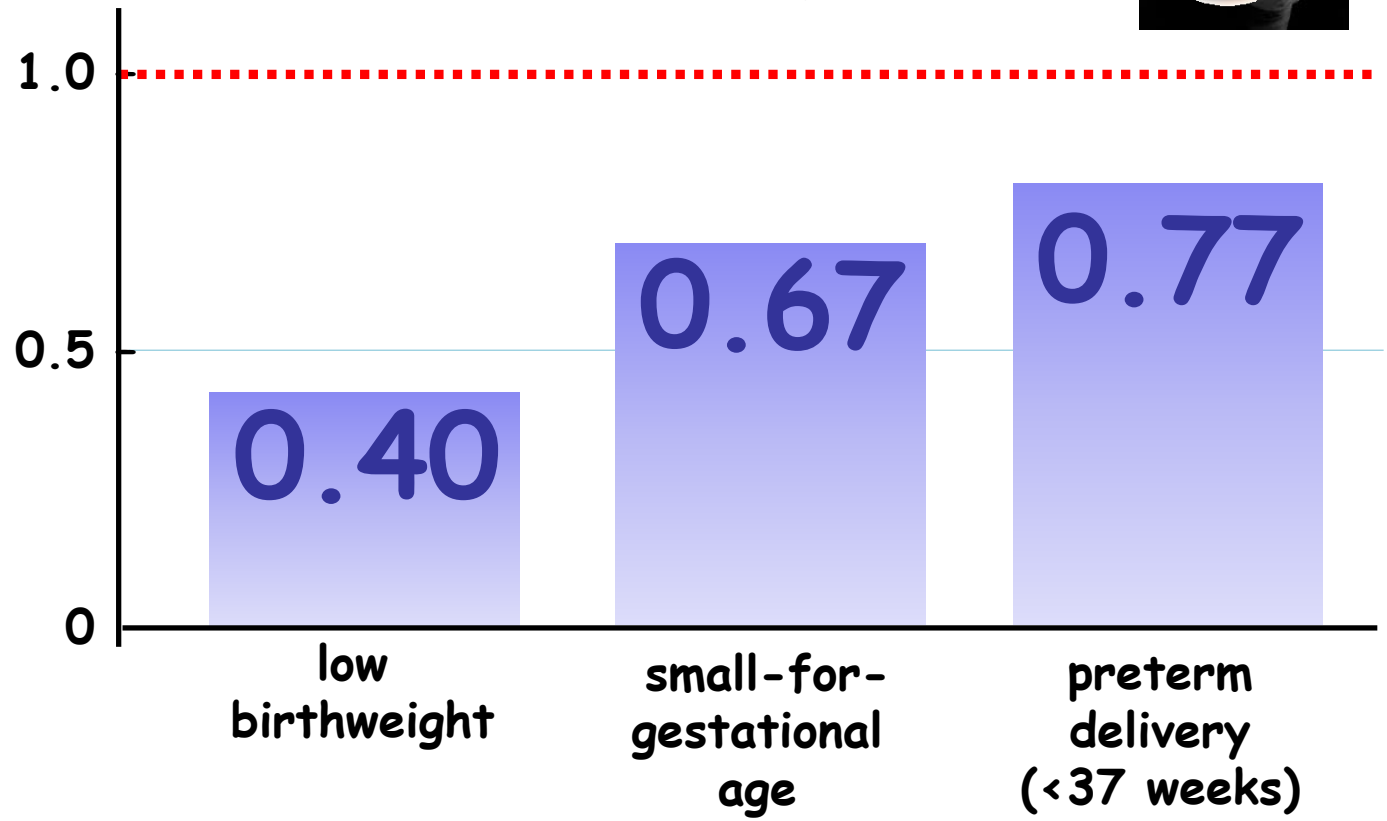
Thorne-Lyman A, Paediatr Perinat Epidemiol 2012;26(Suppl 1):75-90.

- ✓5 randomised trials
- ✓25-OH-vitamin D supplementation, intake or status during pregnancy
- ✓perinatal and infant health outcomes.





In vitamin D supplemented mother RR for



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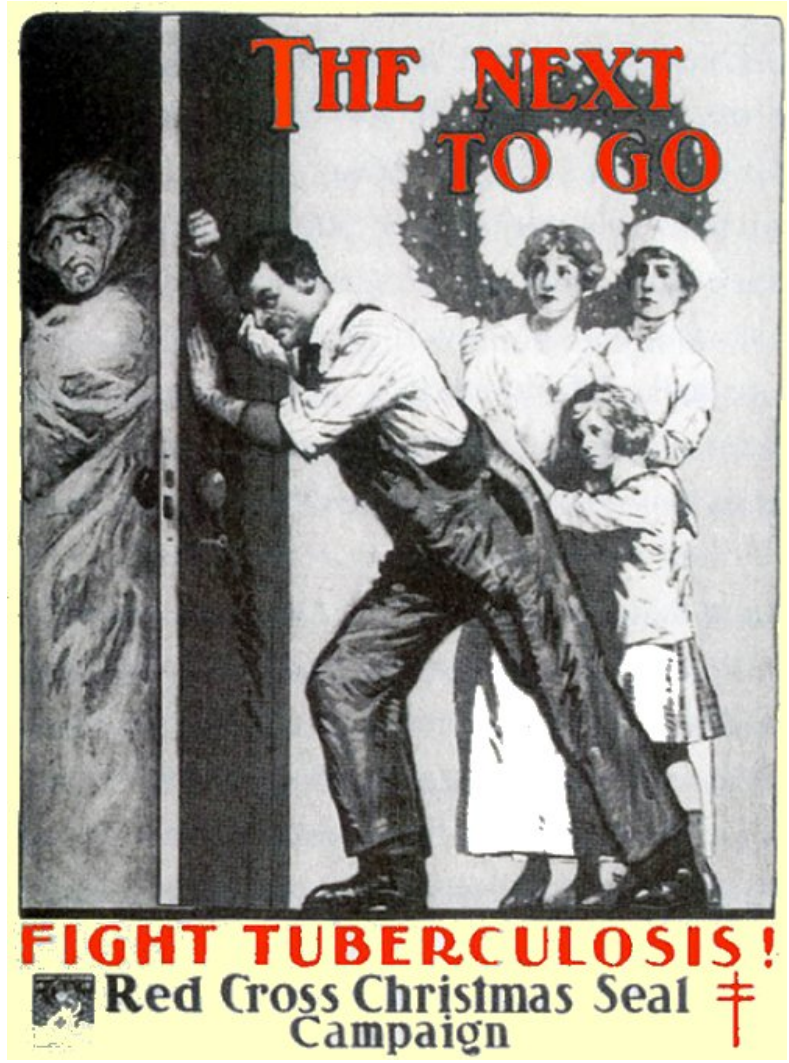
Regulation of immune function: Innate Immunity

✓It has long been appreciated that vitamin D deficiency is associated with increased susceptibility to tuberculosis.
Ustianowski, A. J. Infect. 2005;50:432–437

✓Sunlight was the prescribed therapy before antituberculosis drugs became available.

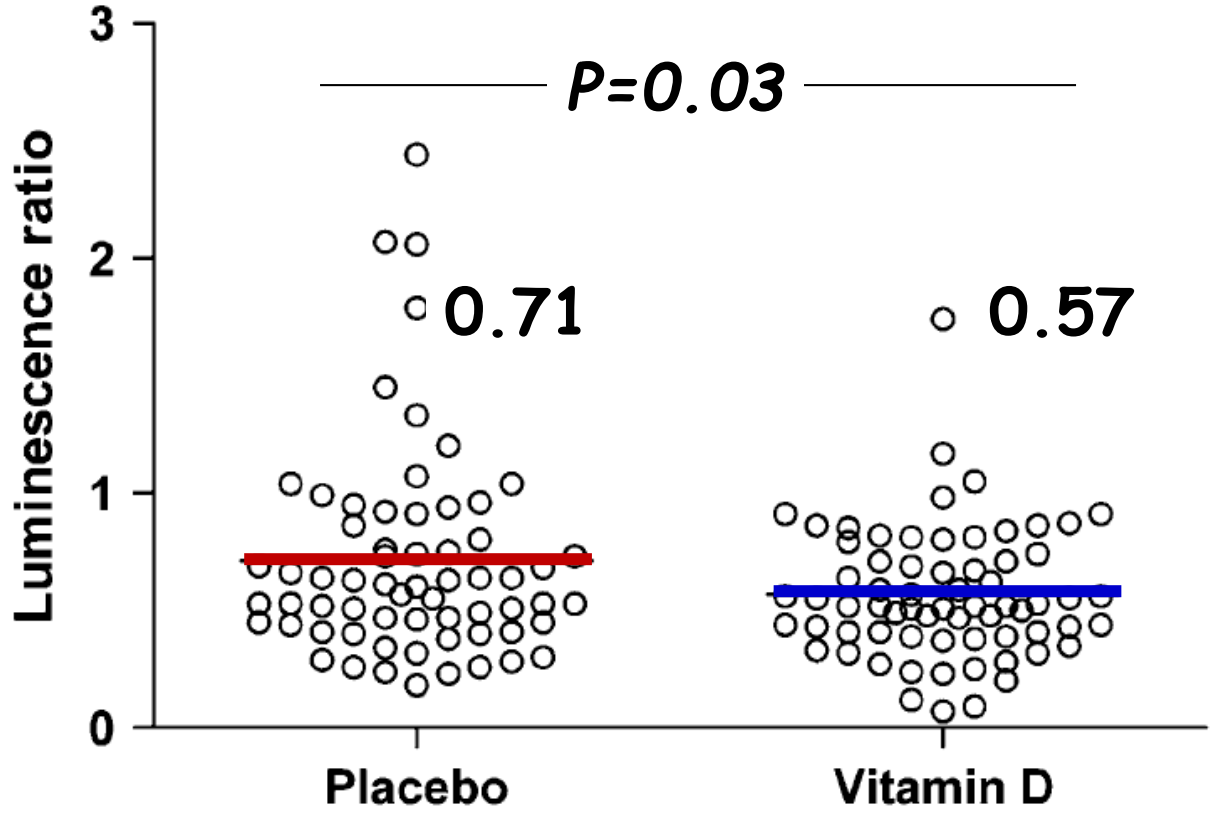
✓Both macrophages and bronchial epithelia produce 1,25(OH)2D and **cathelicidin**, enabling them to **resist** infection by **Mycobacterium tuberculosis**.
Gombart, A.F. FASEB J.2005;19:1067–1077
Wang, T.T. J. Immunol. 2004;173:2909–2912



A single dose of vitamin D enhances immunity to mycobacteria. *Martineau AR, AJRCCM. 2007;176(2):208-13.*

- ✓ Vitamin D was used to treat tuberculosis (TB) in the preantibiotic era.
- ✓ 192 healthy adult TB contacts in London randomized to receive a single oral dose of 2.5 mg ergocalciferol (120.000 UI) or placebo and followed up at 6 weeks.
- ✓ Ability of whole blood to restrict luminescence, and thus growth, of mycobacteria *in vitro*.

Ability of whole blood to restrict luminescence, and thus growth, of recombinant reporter mycobacteria in vitro; the readout is expressed as a luminescence ratio (luminescence postinfection/baseline luminescence).

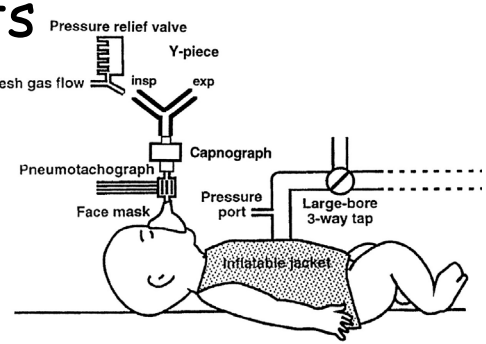


Low cord-serum 25-hydroxyvitamin D levels are associated with poor lung function performance and increased respiratory infection in infancy.

Lai SH. PLoS One. 2017;12(3):e0173268.

✓122 mother-infant pairs

✓lung function testing at 6 months of age in 71 infants



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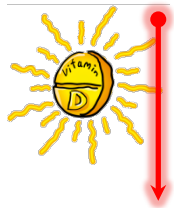
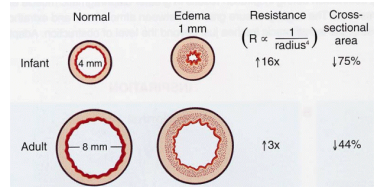
Infants with lower cord serum 25(OH)D levels (< 13.7 ng/ml) had:



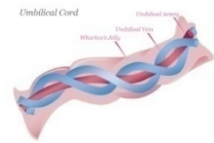


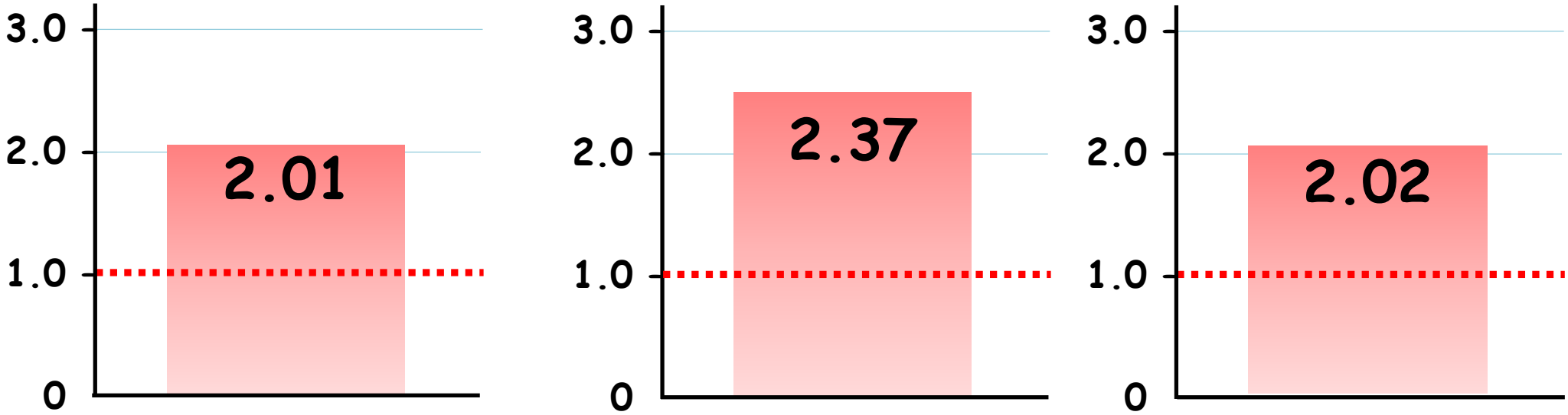
1) higher resistance of respiratory system ($p < 0.01$) and
2) higher risk of a respiratory tract infection (OR=7.6) before the age of 6 months ($p < 0.01$).

Interaction between 25-hydroxyvitamin D and variants at 17q12-21 on respiratory infections

Sheen YH, Pediatr Pulmonol 2016;51:958-967

✓ Relationship between cord-blood 25(OH)D levels of 473 newborn and within the first year of life, predicted probability of:

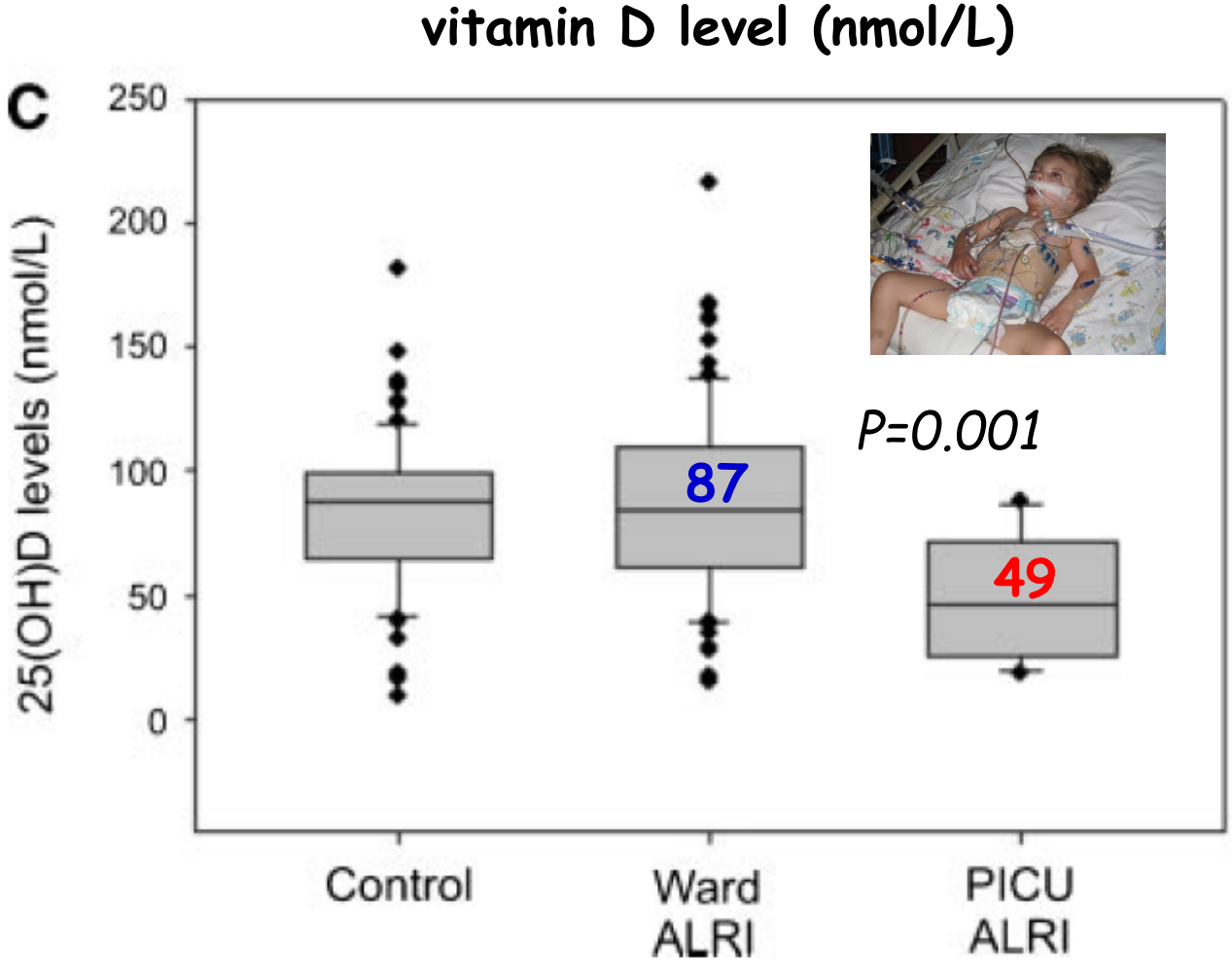




In infants with cord-blood vitamin D <20.0 ng/mL compared to infants with CB 25(OH)D ≥ 20.0 ng/mL

Vitamin D deficiency in young children with severe acute lower respiratory infection *McNally, Ped Pul 2009;44:981*

- ✓ Serum 25 hydroxyvitamin D [25(OH)D] levels.
- ✓ Young children with bronchiolitis (n = 55) or pneumonia (n = 50). (ALRI)
- ✓ Subjects without respiratory symptoms (n = 92).



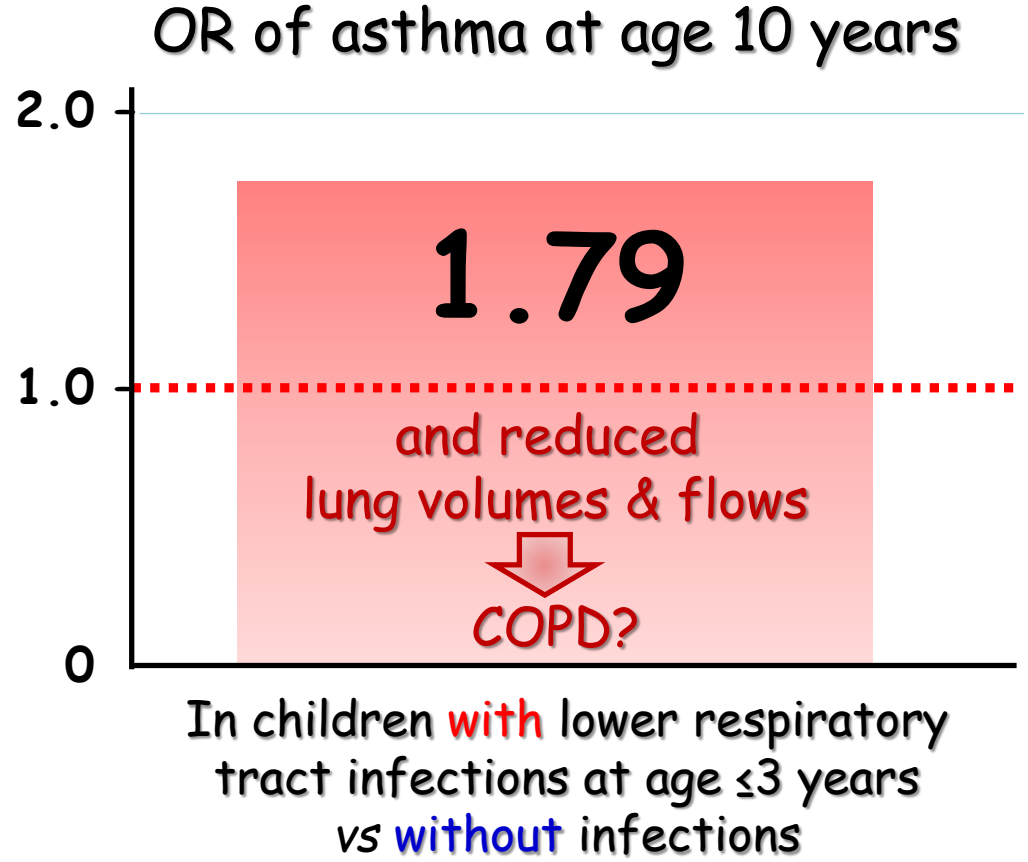
A population-based prospective cohort study examining the influence of early-life respiratory tract infections on school-age lung function and asthma.

van Meel ER, Thorax. 2018 Feb;73(2):167-173.

✓a population-based prospective cohort study of 5197 children born between April 2002 and January 2006

✓Information on physician-attended upper and lower respiratory tract infections at age ≤ 3 and >3–6 years obtained by annual questionnaires.

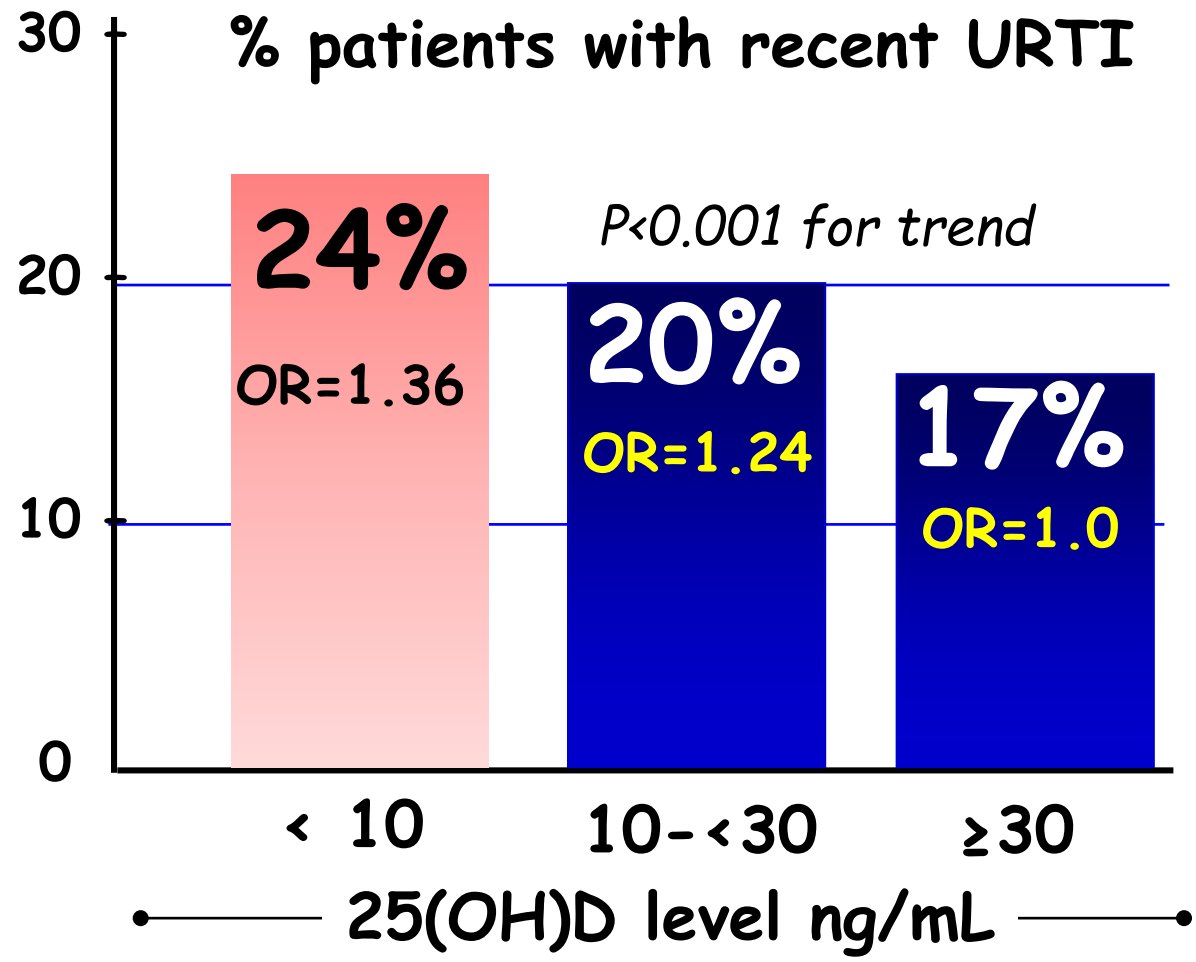
✓Spirometry and physician-diagnosed asthma assessed at age 10 years.



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;169:384-90.*

- ✓ 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.

	Severe deficiency	Deficiency	Insufficiency	Sufficiency
25(OH)D	< 10 ng/ml (< 25 nmol/l)	< 20 ng/ml (< 50 nmol/l)	20–29 ng/ml (50–74 nmol/l)	≥ 30 ng/ml (≥ 75 nmol/l)
Conversion factor: ng/ml = nmol/l*0.401; nmol/l = ng/ml*2.496				



Children with lower respiratory tract infections and serum 25-hydroxyvitamin D_3 levels: A case-control study

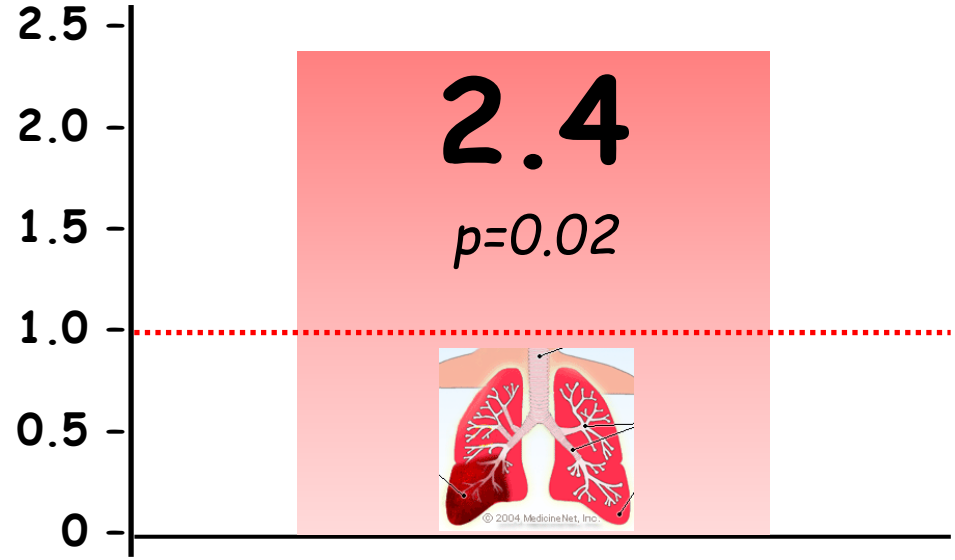
López AV, Pediatr Pulmonol 2016;51:1080-1087

- ✓ A case-control study of 70 children ages 3–60 months from the Guatemala City metropolitan area, hospitalized with community-acquired pneumonia.

- ✓ 113 controls from the well-baby/care immunization clinics.

OR

for vitamin D <20 ng/ml



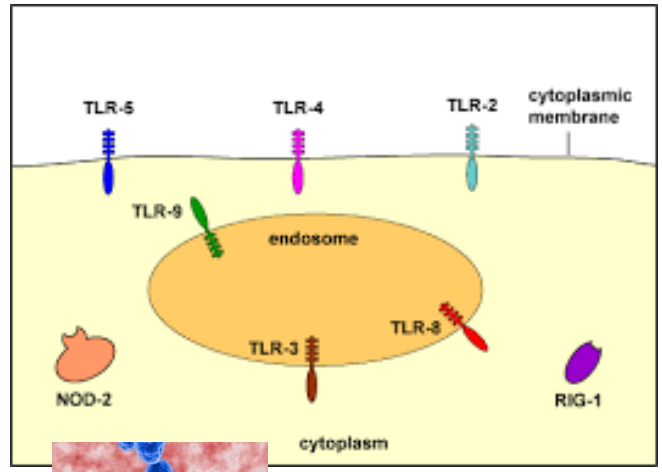
In cases
***vs* controls**

Vitamin D Promotes Pneumococcal Killing and Modulates Inflammatory Responses in Primary Human Neutrophils.

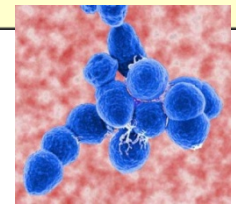
Subramanian K, J Innate Immun. 2017;9(4):375-386

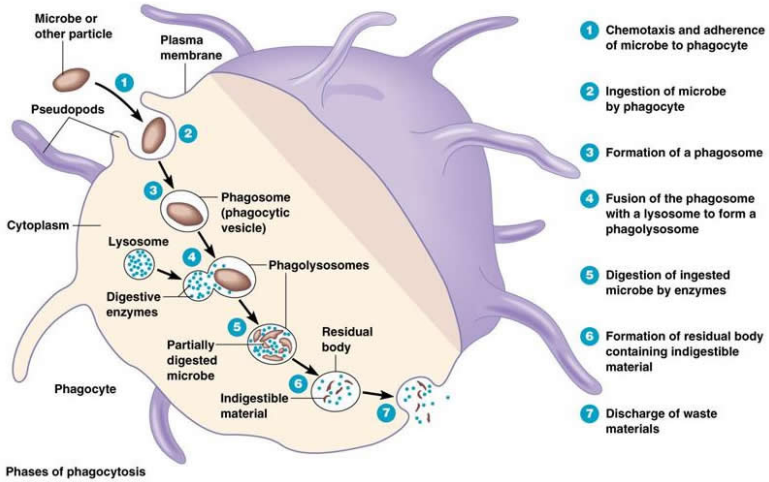
vitamin D

- upregulated pattern recognition receptors, TLR2, and NOD2,
- induced the antimicrobial human neutrophil peptides (HNP1-3) and LL-37,



increased killing of pneumococci

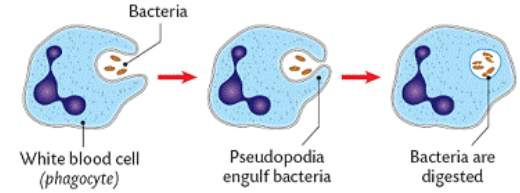




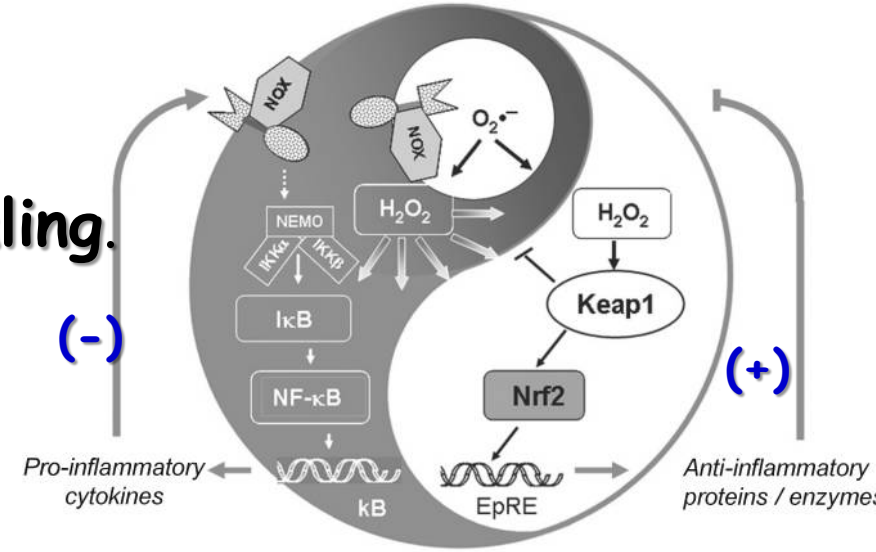
- Vitamin D supplementation of serum from patients with bacterial respiratory tract infections enhanced neutrophil killing.

Vitamin D Promotes Pneumococcal Killing and Modulates Inflammatory Responses in Primary Human Neutrophils.

Subramanian K, J Innate Immun. 2017;9(4):375-386

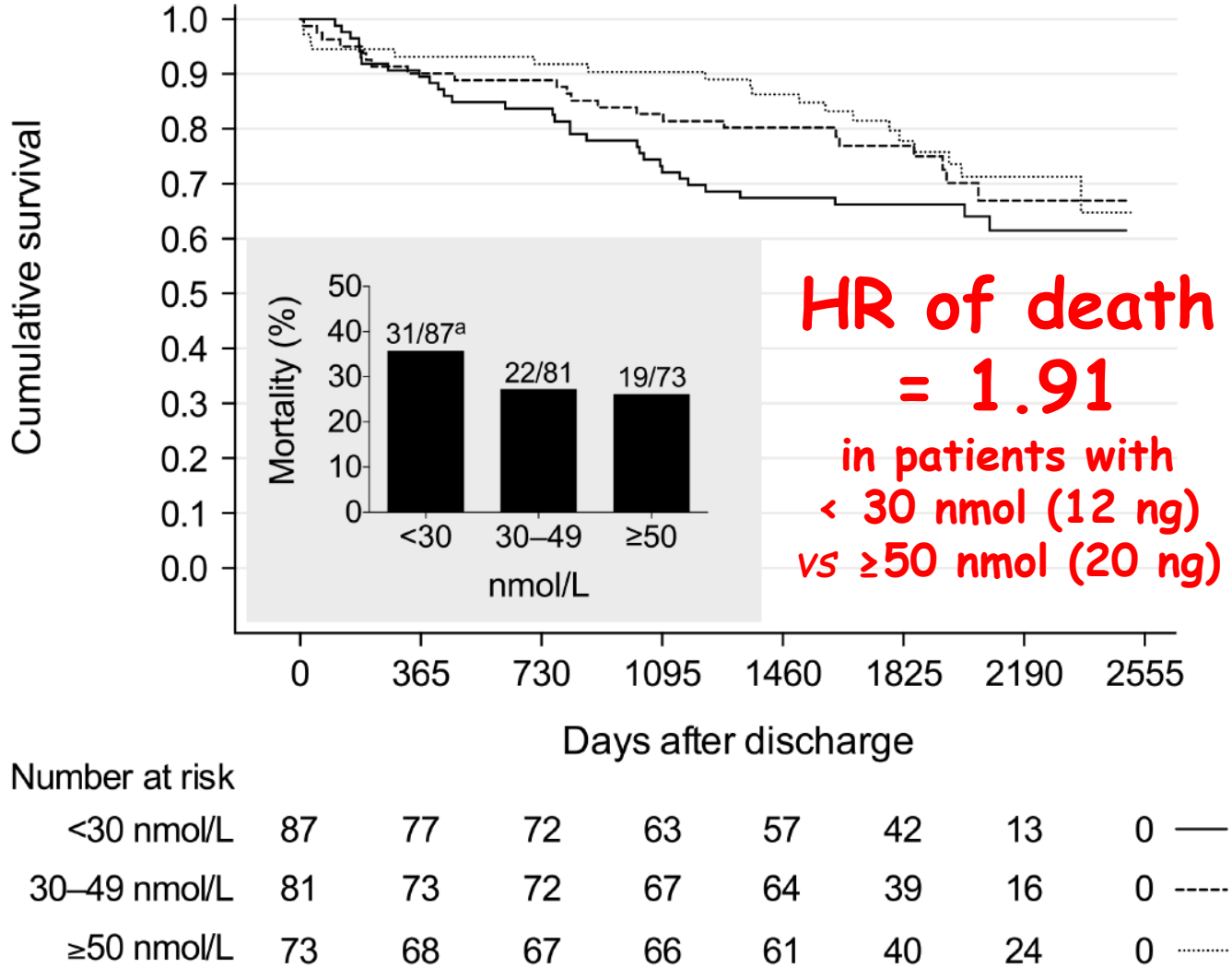


- Moreover, **vitamin D lowered inflammatory cytokine production by** infected neutrophils via IL-4 production and the induction of suppressor of cytokine signaling (SOCS) proteins SOCS-1 and SOCS-3, leading to the **suppression of NF-κB signaling**.



- Thus, vitamin D enhances neutrophil killing of S. pneumoniae while dampening excessive inflammatory responses and apoptosis, suggesting that vitamin D could be used alongside antibiotics when treating pneumococcal infections.

Vitamin D Status and Long-Term Mortality in Community-Acquired Pneumonia: Secondary Data Analysis from a Prospective Cohort. *Holter JC, PLoS One. 2016;11(7):e0158536.*



HR of death = 1.91

in patients with < 30 nmol (12 ng) *vs* ≥50 nmol (20 ng)

Kaplan-Meier plot of long-term survival for 241 patients (median age was 66 years) discharged from hospital after treatment of community-acquired pneumonia, stratified by serum 25-(OH)D levels measured at hospital admission and the corresponding mortality rates at the end of the follow-up period

Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis

Chalmers JD, Thorax 2013;68:39-47.

- ✓ 402 stable patients with **bronchiectasis** classified as vitamin-D **deficient** (serum 25-hydroxyvitamin-D < 25 nmol/l), **insufficient** (25 nmol/l-74 nmol/l).

	Severe deficiency	Deficiency	Insufficiency	Sufficiency
25(OH)D	< 10 ng/ml (< 25 nmol/l)	< 20 ng/ml (< 50 nmol/l)	20–29 ng/ml (50–74 nmol/l)	≥ 30 ng/ml (≥ 75 nmol/l)
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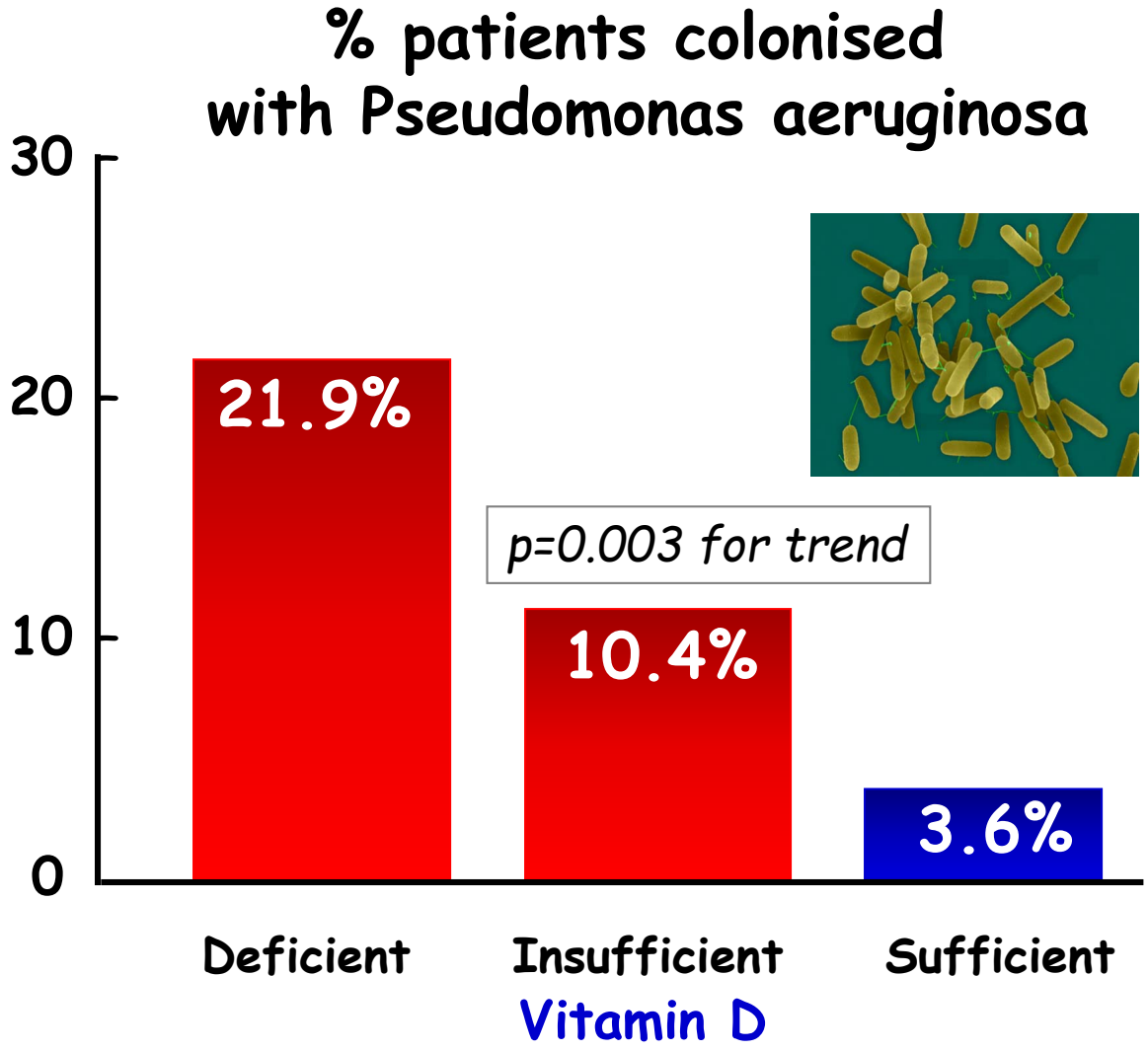
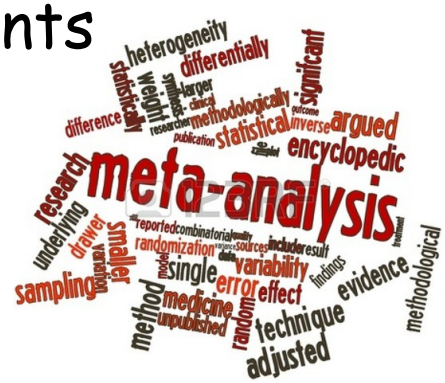
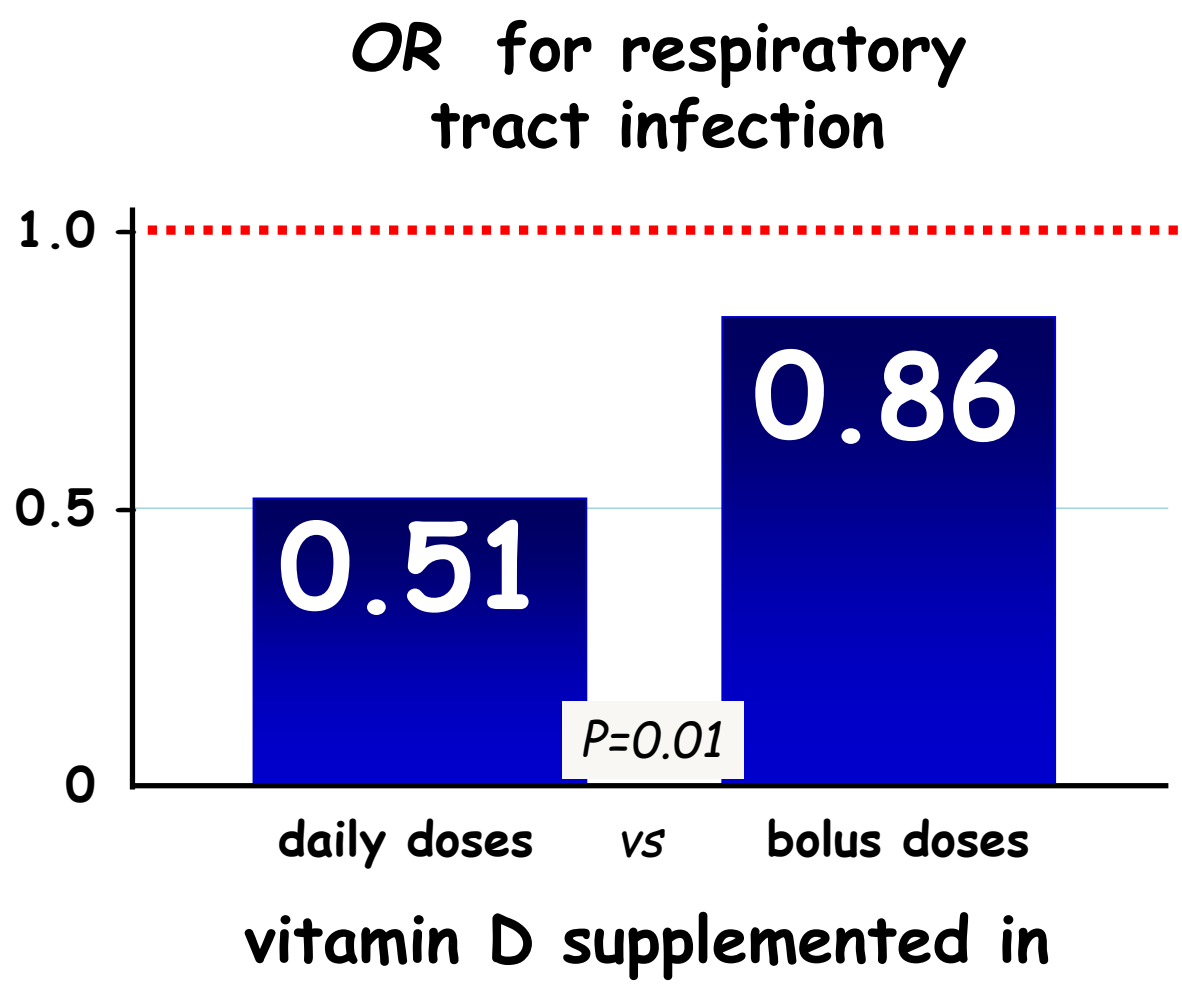


Vitamin D and respiratory tract infections: A systematic review and meta-analysis of randomized controlled trials.

Bergman P, PLoS One 2013;8:e65835

- ✓meta-analysis of 11 placebo-controlled studies
- ✓5660 patients included

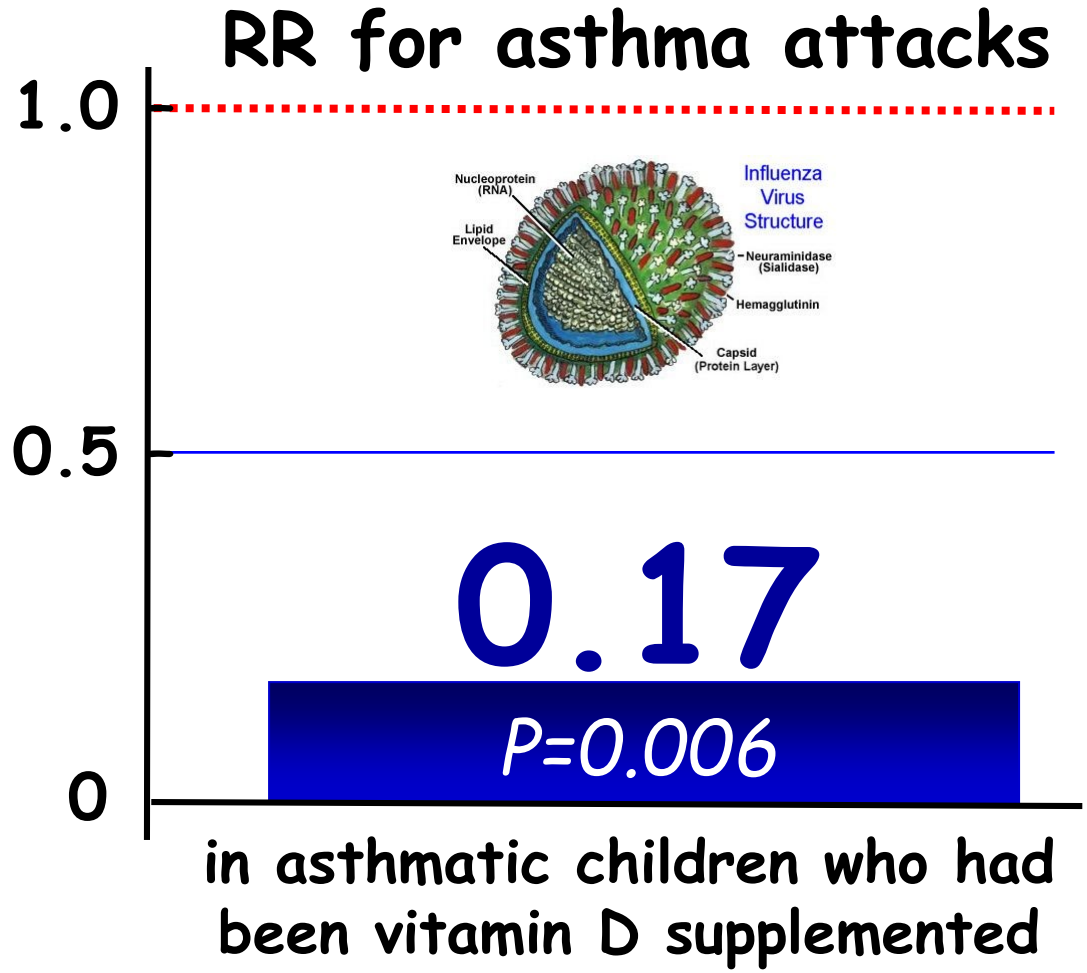




Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren.

Urashima M, Am J Clin Nutr 2010;91:1255–1260.

- ✓Vitamin D(3) supplements (1200 IU/d) (n= 167) or placebo (n= 167) in schoolchildren
- ✓From December 2008 through March 2009
- ✓incidence of influenza A, diagnosed with influenza antigen testing with a nasopharyngeal swab specimen.



Use of Vitamin D and Immunity: *Why supplementation are needed?*

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

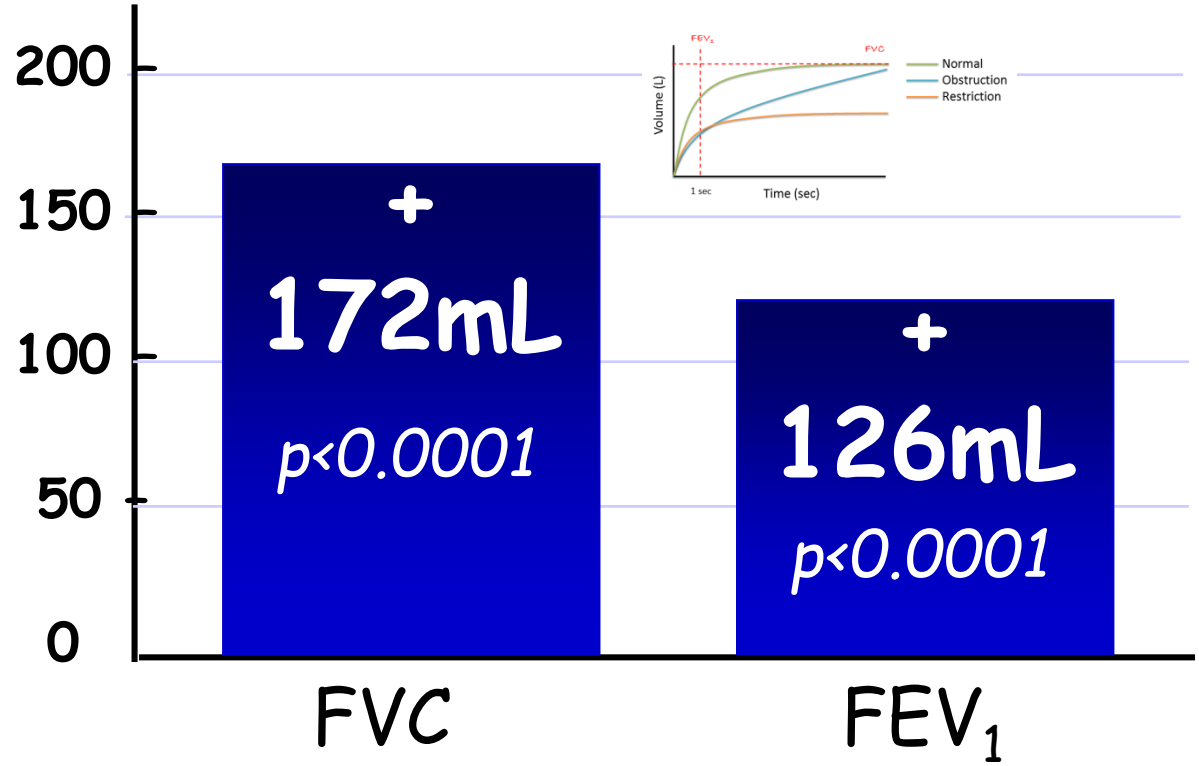
- ✓ Introduction
- ✓ Immunomodulation
- ✓ Fetal development
- ✓ Infections
- ✓ **Prevention and modification of asthma & COPD**
- ✓ Prevention and modification of allergic rhinitis
- ✓ Prevention and modification of atopic dermatitis
- ✓ Prevention and modification of food allergy anaphylaxis, urticaria
- ✓ Autoimmunity
- ✓ Other Diseases
- ✓ Conclusions

Relationship between serum 25-hydroxyvitamin D and pulmonary function in the Third National Health and Nutrition Examination Survey.

Black PN, Chest 2005;128:3792–3798.

- ✓a cross-sectional survey of 14,091 people > 20 years of age,
- ✓spirometry, and serum 25-hydroxy vitamin D levels

Mean increase for the highest quintile of serum 25-hydroxy vitamin D level (>85.7 nmol/L – 34 ng/mL) compared with the lowest quintile (<40.4 nmol/L - 16 ng/mL).



Vitamin D over the first decade and susceptibility to childhood allergy and asthma

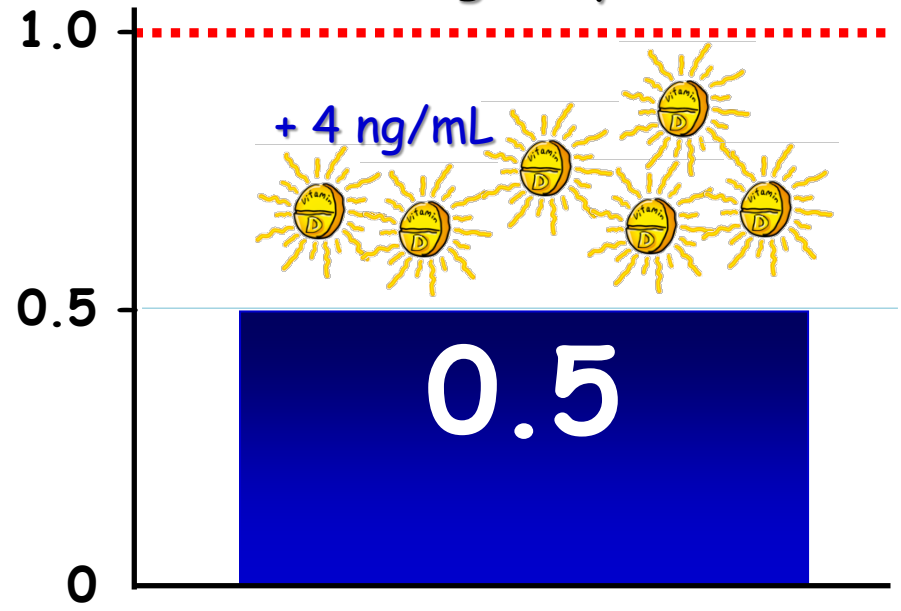
Hollams EM, J Allergy Clin Immunol 2017;139:472-81

✓A high-risk birth cohort.

✓Plasma 25(OH)D concentrations at birth and at the ages of 0.5, 1, 2, 3, 4, 5, 10 years

✓8 years follow – up.

OR for sensitization at age 2 yrs



with every 10 nmol/L increase in 25(OH) D concentration

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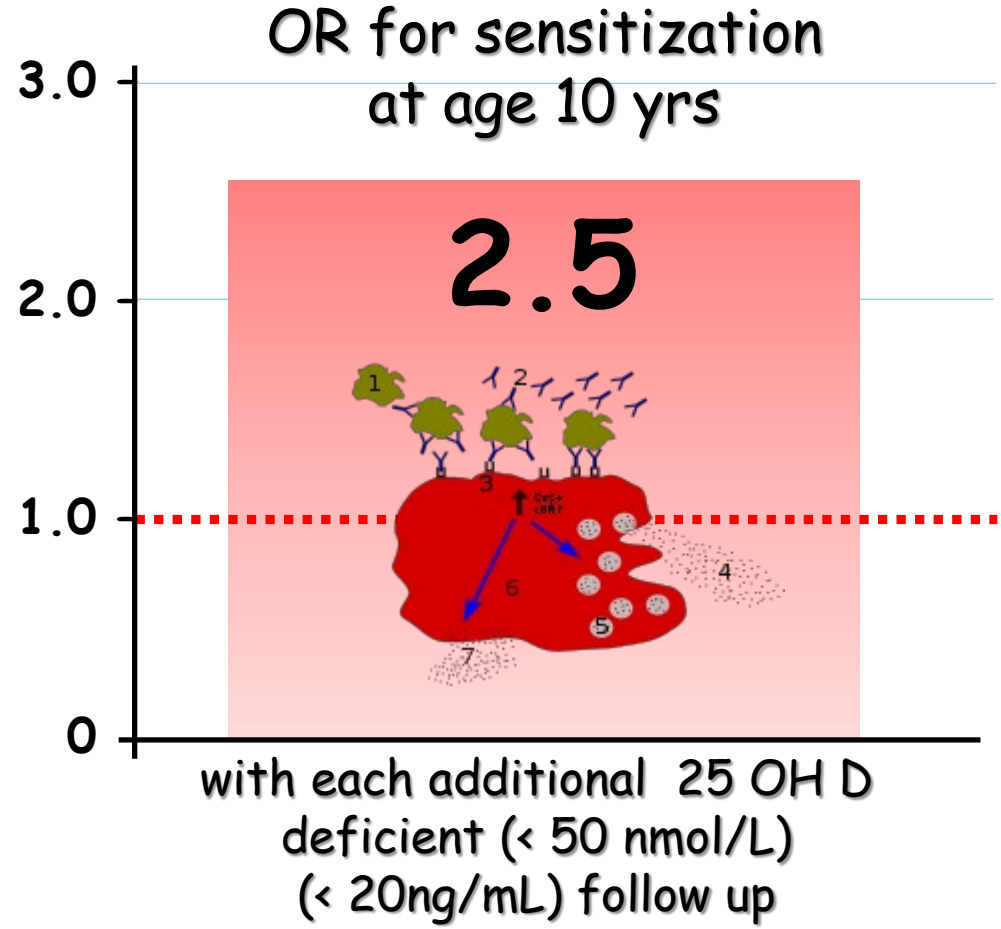

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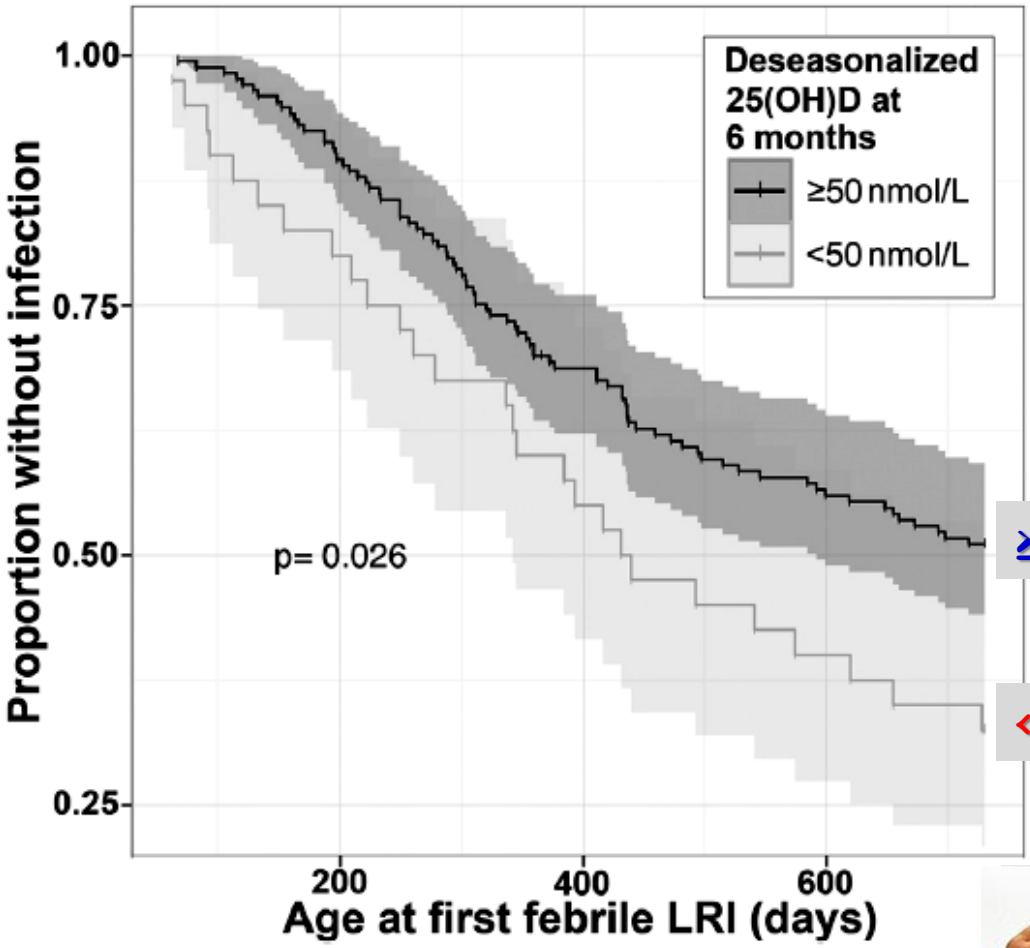


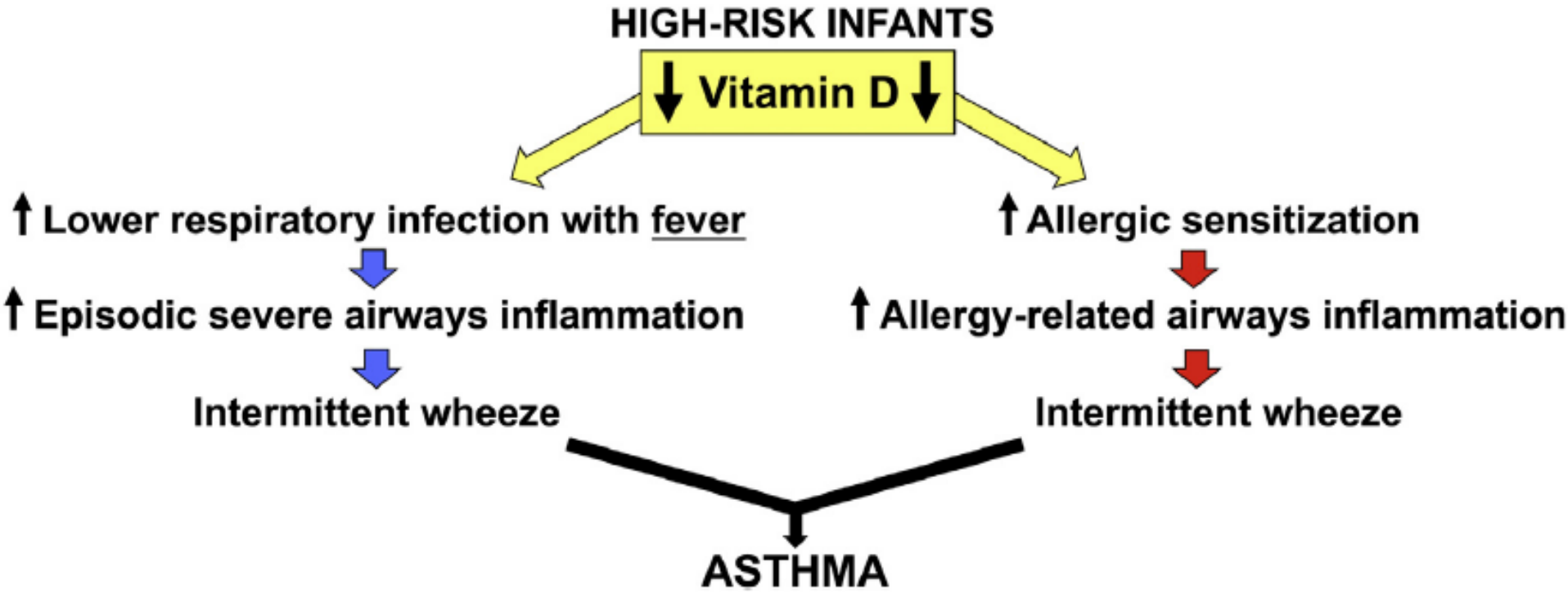
≥ 20ng/mL

< 20ng/mL

25 (OH) D deficiency at 6 months is associated with younger age at first febrile LRI.

Vitamin D over the first decade and susceptibility to childhood allergy and asthma

Hollams EM, J Allergy Clin Immunol 2017;139:472-81

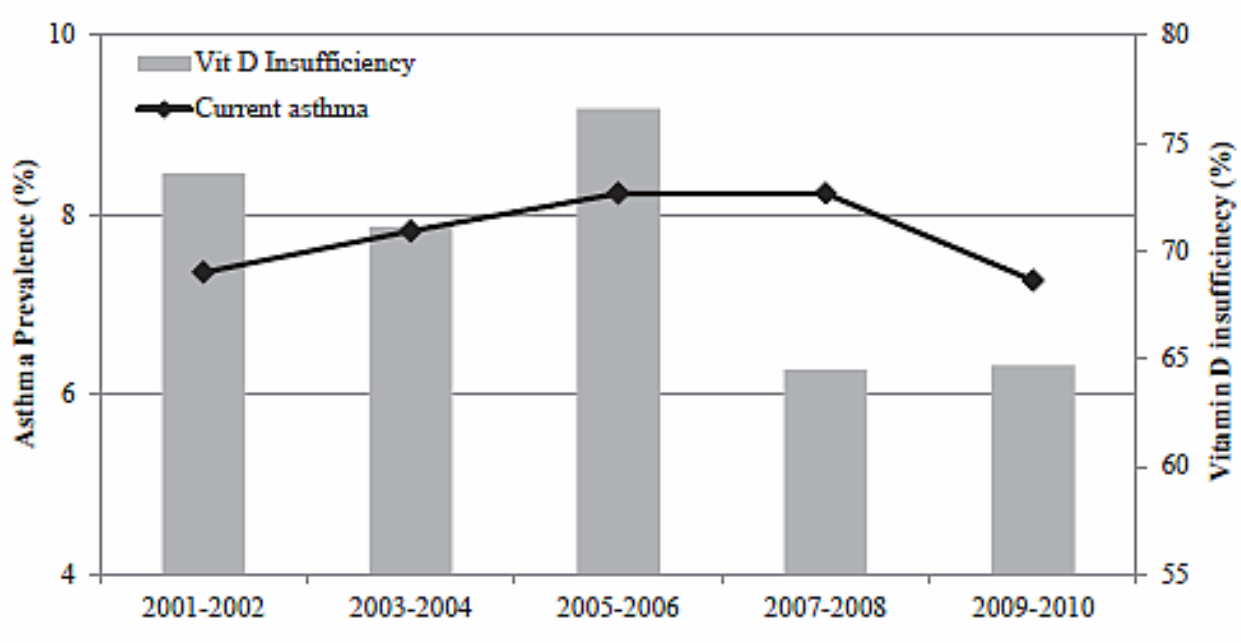


Vitamin D Insufficiency and Asthma in a US Nationwide Study

Han YY, JACI Pract 2017; 5:790-796

- Vitamin D insufficiency prevalence was 72% to 76% from 2001 to 2006, and then decreased from 2007 to 2010 (64%-65%); interestingly,
- asthma prevalence decreased for the first time from the period 2007 to 2008 (8.2%) to the period 2009 to 2010 (7.4%)

Prevalence of current asthma and vitamin D insufficiency (25[OH]D <30 ng/mL) by NHANES study waves (2001-2002 to 2009-2010), in all participants



Vitamin D Levels, Asthma, and Lung Function: Time to Act on Deficiency?

Litonjua AA, JACI Pract 2017; 5:797-798 Editorial

- Vitamin D insufficiency (25 hydroxyvitamin D [25OHD] levels of <30 ng/mL) and deficiency (25OHD levels of <20 ng/mL) are prevalent around the world, even in some countries situated near the equator.

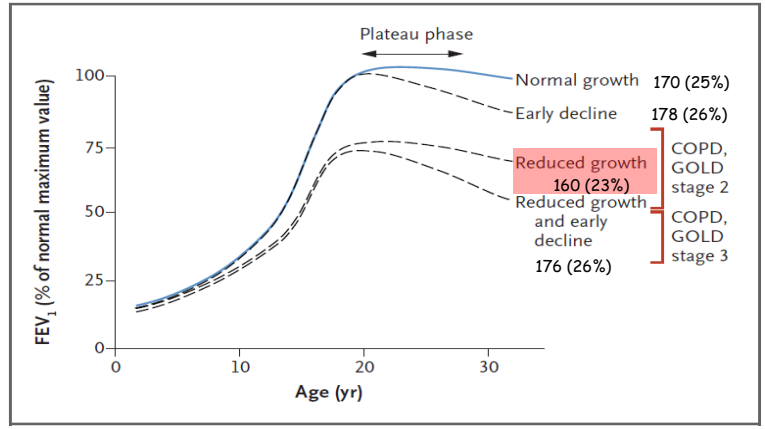
- Deficiency is also prevalent in developed countries such as the United States, despite vitamin D fortification of certain foods, suggesting that the amount of vitamin D from the food supply is insufficient to maintain adequate 25OHD levels in all individuals.

- The recognition that vitamin D deficiency is widespread led to the hypothesis that it contributed to the asthma epidemic.

Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma

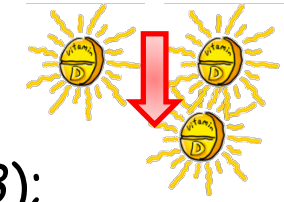
McGeachie MJ, N Engl J Med 2016;374:1842-1852

✓684 patients with persistent childhood asthma



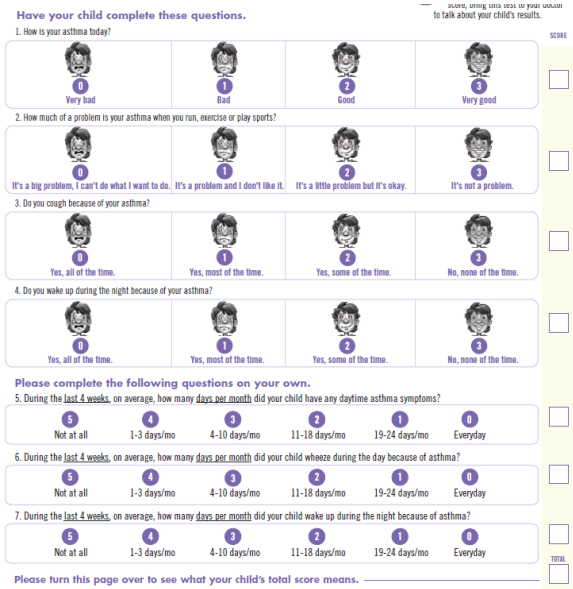
❑**Participants with the reduced-growth pattern**, as compared with those who had normal growth, had:

- **lower FEV_1 values at enrollment** (OR, 0.86 per 1% change in the pred. value; *P<0.001*),
- **a lower bronchodilator response** (OR, 0.91 per 1% change; *P<0.001*), and
- **greater airway hyperresponsiveness** (OR, 0.61 per unit change in log-transformed milligrams per milliliter; *P<0.001*);
- were more likely to be **male** (OR, 8.18; *P<0.001*);
- were **younger at enrollment** (OR, 0.55 per year of age; *P<0.001*);
- had a **lower level of parental education** (OR for at least a college degree vs. a lower level, 0.33; *P = 0.002*);
- were more likely to have **vitamin D insufficiency** (OR, 2.15; *P = 0.03*);
- received **more courses of prednisone per year during the trial** (OR, 4.12 for each additional course; *P = 0.03*).



Vitamin D Serum Levels and Markers of Asthma Control in Italian Children *Chinellato I, Boner AL. J Pediatr 2011;158:437*

- ✓75 asthmatic children
- ✓25-hydroxyvitamin D
- ✓Spirometry
- ✓asthma control, according to GINA guidelines and with Childhood Asthma Control Test


Have your child complete these questions.

1. How is your asthma today?
0 Very bad · 1 Bad · 2 Good · 3 Very good

2. How much of a problem is your asthma when you run, exercise or play sports?
0 It's a big problem, I can't do what I want to do. · 1 It's a problem and I don't like it. · 2 It's a little problem but it's okay. · 3 It's not a problem.

3. Do you cough because of your asthma?
0 Yes, all of the time. · 1 Yes, most of the time. · 2 Yes, some of the time. · 3 No, none of the time.

4. Do you wake up during the night because of your asthma?
0 Yes, all of the time. · 1 Yes, most of the time. · 2 Yes, some of the time. · 3 No, none of the time.

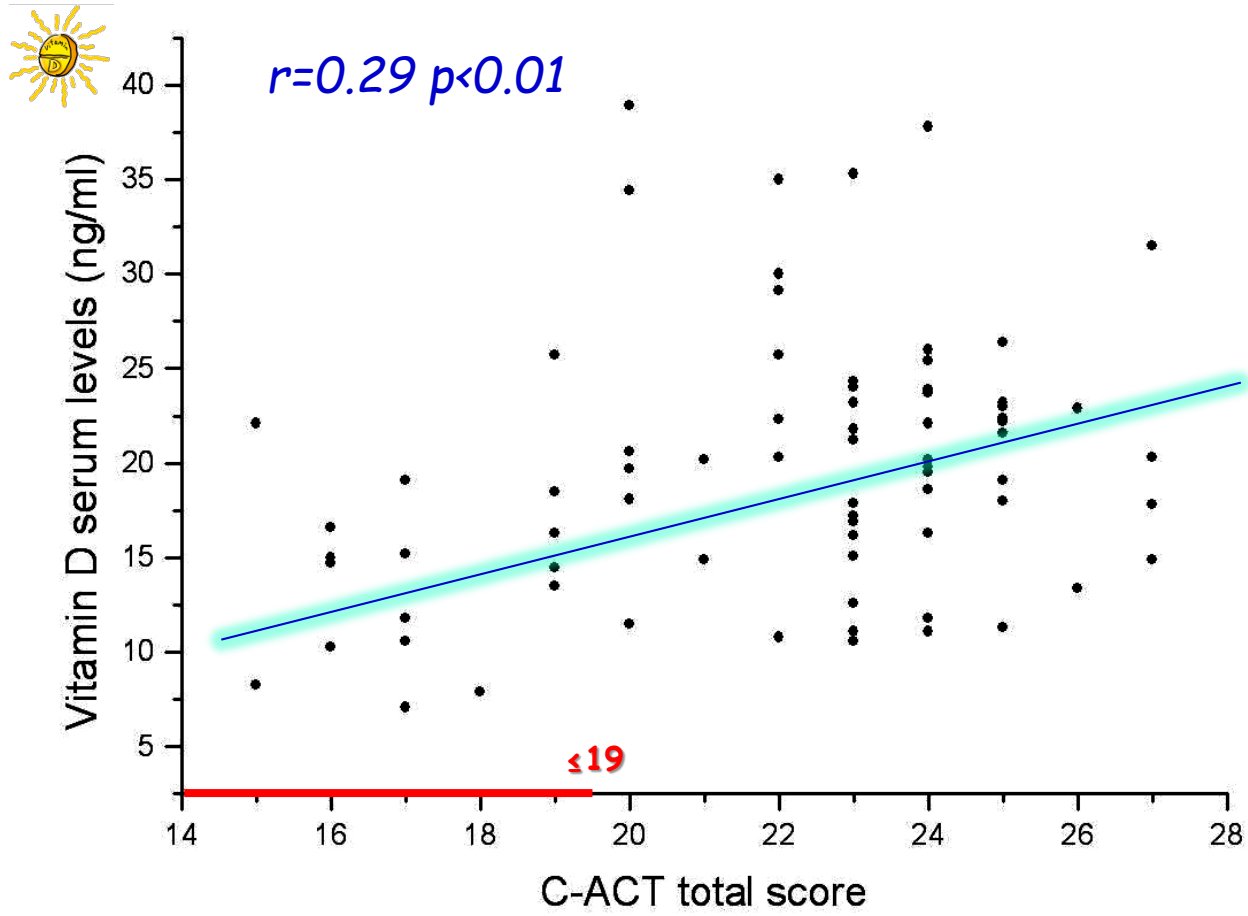
Please complete the following questions on your own.

5. During the last 4 weeks, on average, how many days per month did your child have any daytime asthma symptoms?
5 Not at all · 4 1-3 days/mo · 3 4-10 days/mo · 2 11-18 days/mo · 1 19-24 days/mo · 0 Everyday

6. During the last 4 weeks, on average, how many days per month did your child wheeze during the day because of asthma?
5 Not at all · 4 1-3 days/mo · 3 4-10 days/mo · 2 11-18 days/mo · 1 19-24 days/mo · 0 Everyday

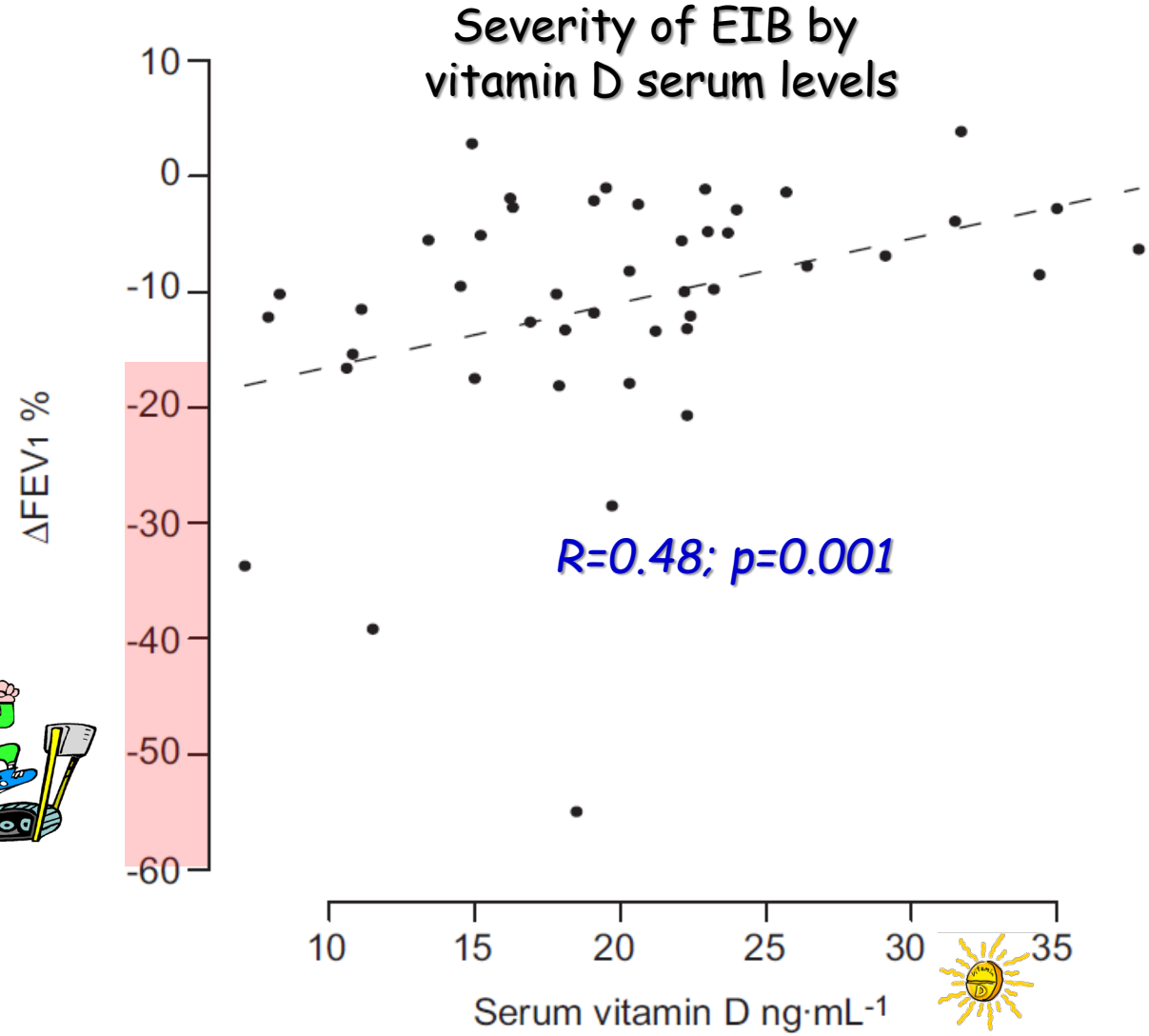
7. During the last 4 weeks, on average, how many days per month did your child wake up during the night because of asthma?
5 Not at all · 4 1-3 days/mo · 3 4-10 days/mo · 2 11-18 days/mo · 1 19-24 days/mo · 0 Everyday

Please turn this page over to see what your child's total score means.



Vitamin D Serum Levels and Lung Function and Exercise Induced Bronchoconstriction in Children with Intermittent Asthma. *Chinellato I, ERJ 2011;37:1366*

- ✓45 children with intermittent asthma
- ✓25-hydroxyvitamin D baseline FVC, FEV_1
- ✓ΔFEV_1 after a standardized exercise challenge



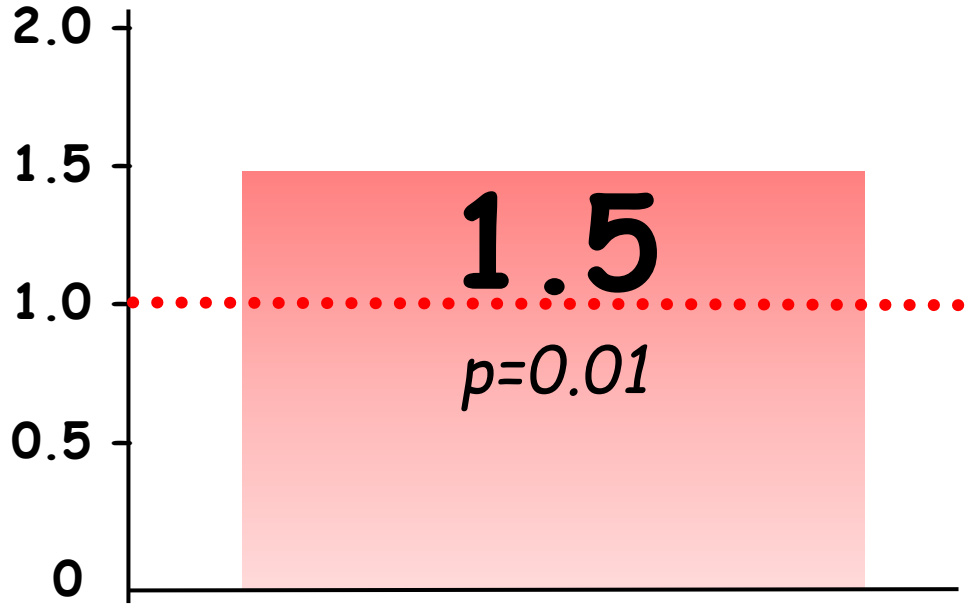
Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study

Brehm JM, JACI 2010;126:52-58

- ✓ 25-hydroxyvitamin D levels in sera in a retrospective **longitudinal study**.
- ✓ Follow-up: 4 years

- ✓ 1024 children with mild-to-moderate persistent asthma at the time of enrollment in **CAMP** study.

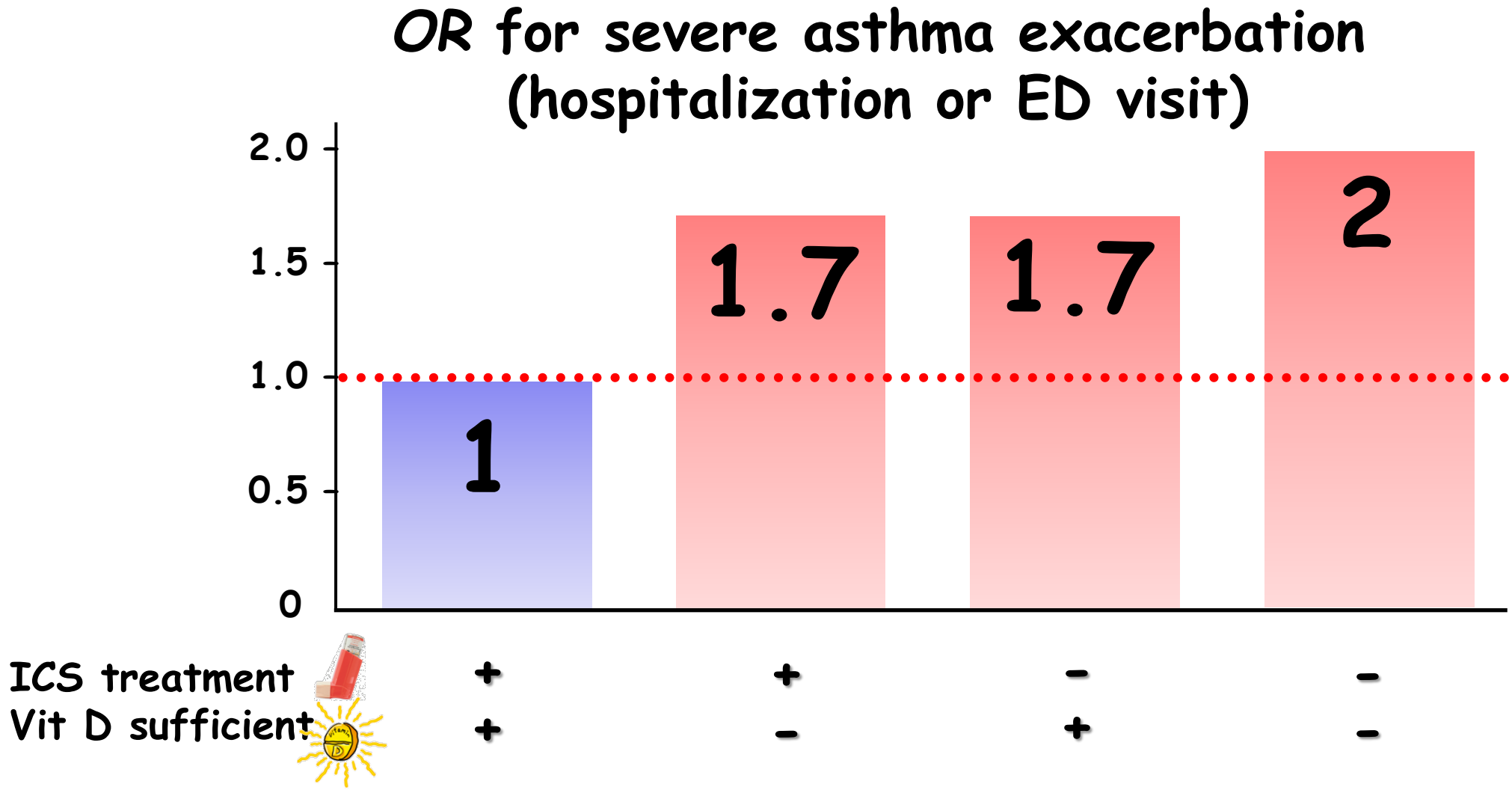
OR for any hospitalization or ED visit in the 4 years follow-up



in Vit D insufficiency (<30 ng/mL) at baseline

Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study

Brehm JACI 2010;126:52



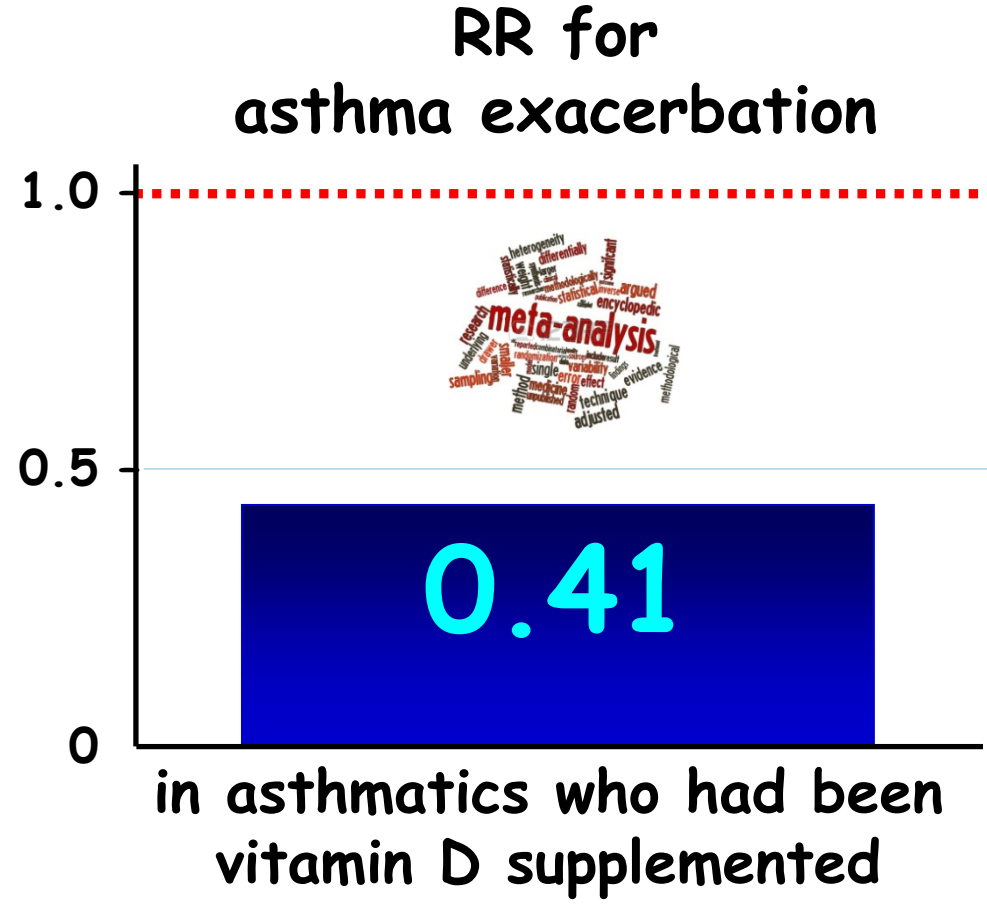
Efficacy of high-dose vitamin D in pediatric asthma: a systematic review and meta-analysis.

Pojsupap S, J Asthma. 2015;52(4):382-90.

✓5 studies that met study eligibility and assessed final data synthesis.

✓The median trial size was 48 participants (range 17-430)

✓The average daily dose of cholecalciferol ranged from 500 to 2000 IU/day.

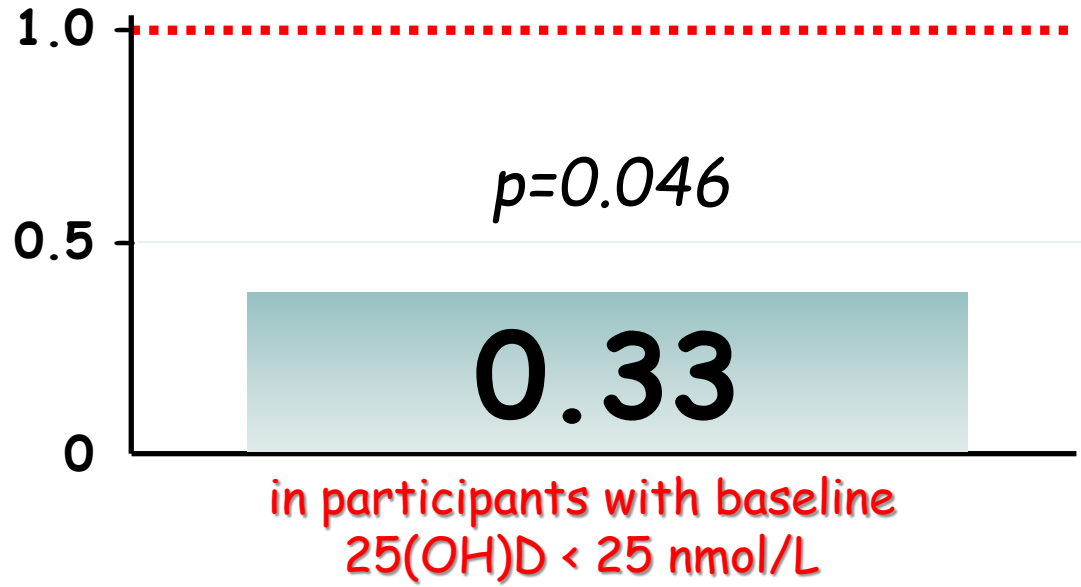


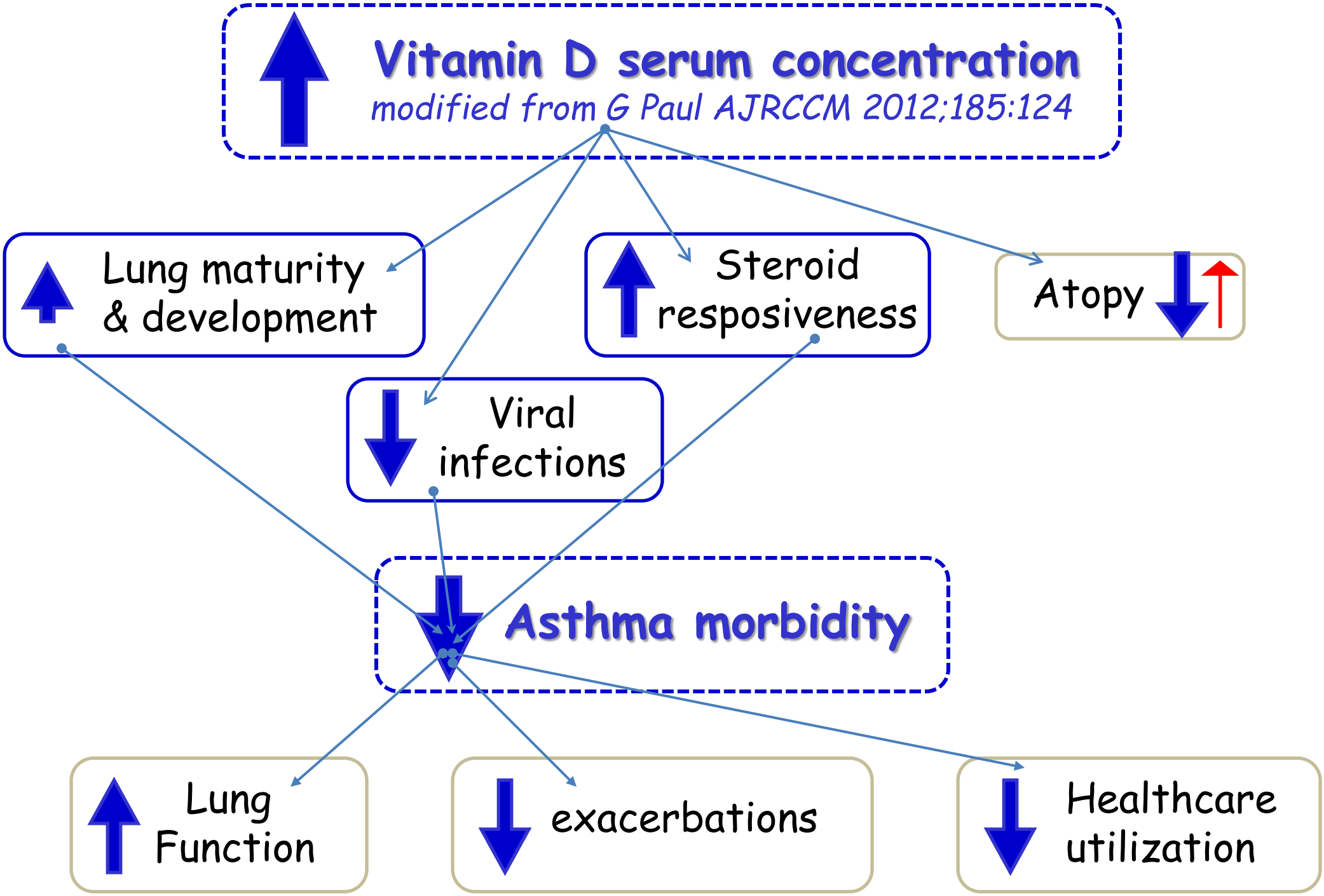
Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data.

Jolliffe DA, Lancet Respir Med. 2017 Nov;5(11):881-890.

- ✓8 randomised controlled trials
- ✓1078 participants
- ✓adjusted incidence rate ratio [aIRR]

In Vitamin D supplemented patients Incidence Rate Ratio of asthma exacerbation requiring treatment with systemic corticosteroids




Vitamin D serum concentration
modified from G Paul AJRCCM 2012;185:124
Lung maturity & development
Steroid resposiveness
Atopy
Viral infections
Asthma morbidity
Lung Function
exacerbations
Healthcare utilization

Use of Vitamin D and Immunity: *Why supplementation are needed?*

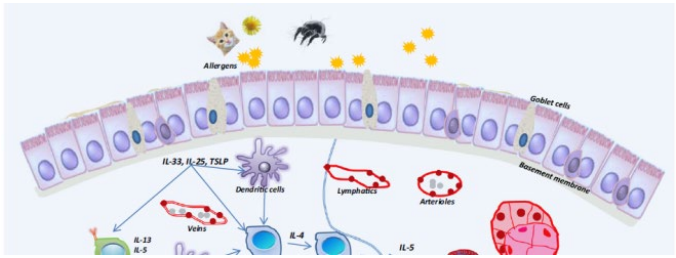
Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

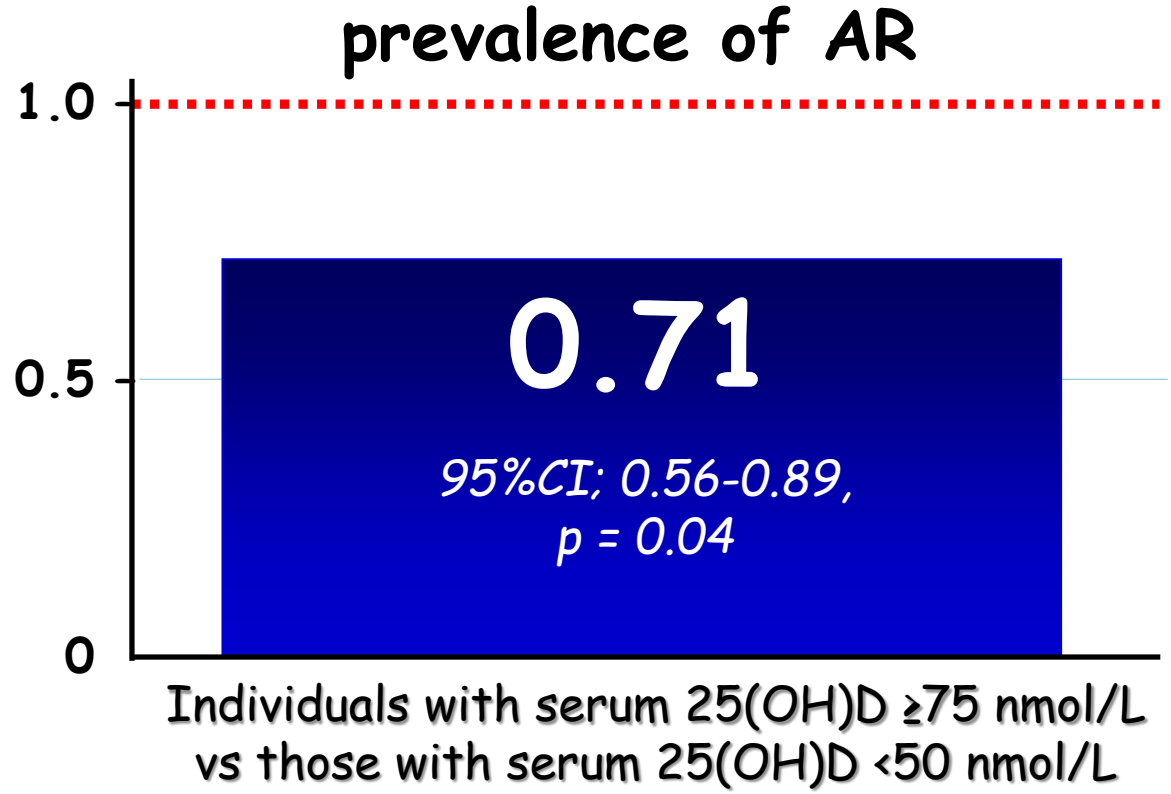
- ✓ Introduction
- ✓ Immunomodulation
- ✓ Fetal development
- ✓ Infections
- ✓ Prevention and modification of asthma & COPD
- ✓ **Prevention and modification of allergic rhinitis**
- ✓ Prevention and modification of atopic dermatitis
- ✓ Prevention and modification of food allergy anaphylaxis, urticaria
- ✓ Autoimmunity
- ✓ Other Diseases
- ✓ Conclusions

Vitamin D status, aeroallergen sensitization, and allergic rhinitis: A systematic review and meta-analysis.

Aryan Z. Int Rev Immunol. 2017;36(1):41-53.

✓21 observational studies



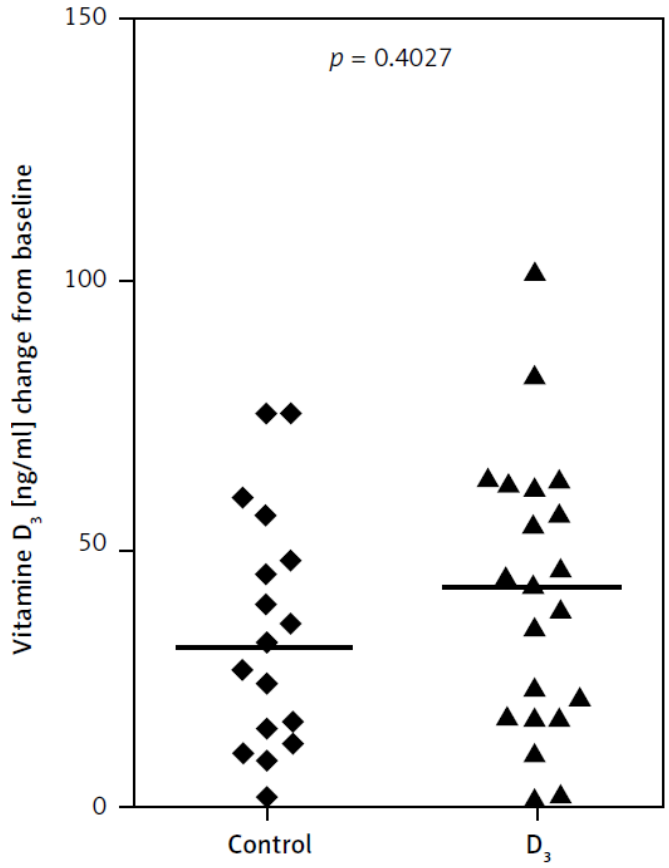


Clinical and immunological effects of vitamin D supplementation during the pollen season in children with allergic rhinitis.

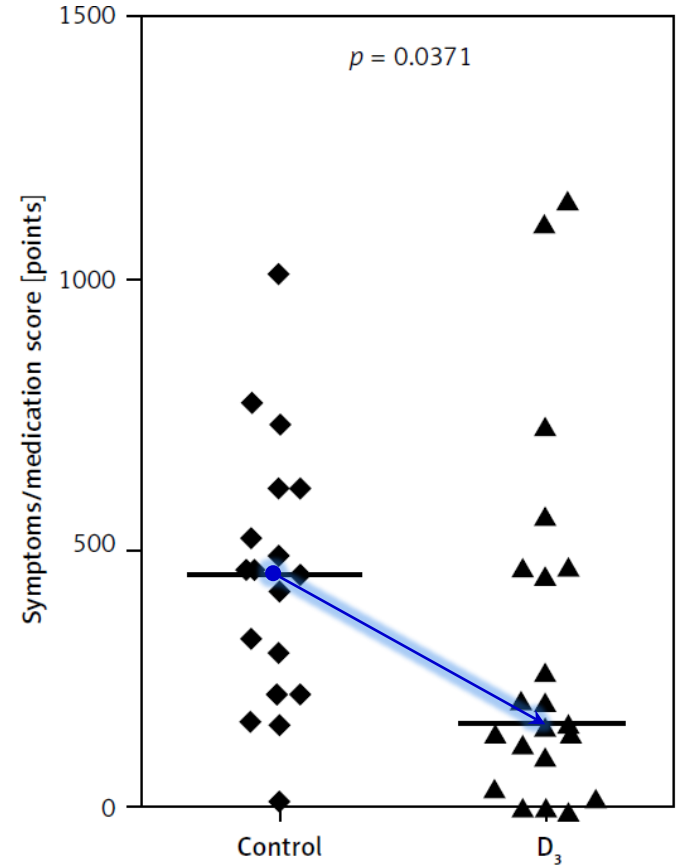
Jerzyńska J, Arch Med Sci. 2018 Jan;14(1):122-131.

- ✓38 children aged 5-12, with allergic rhinitis due to grass pollen sensitivity
- ✓pre-coseasonal vitamin D 1000 IU daily or placebo supplementation for 5 months

Relative changes in serum concentration of 25(OH)D between visit #1 and visit #2



Relative changes in symptoms medication scoree between visit #1 and visit #2



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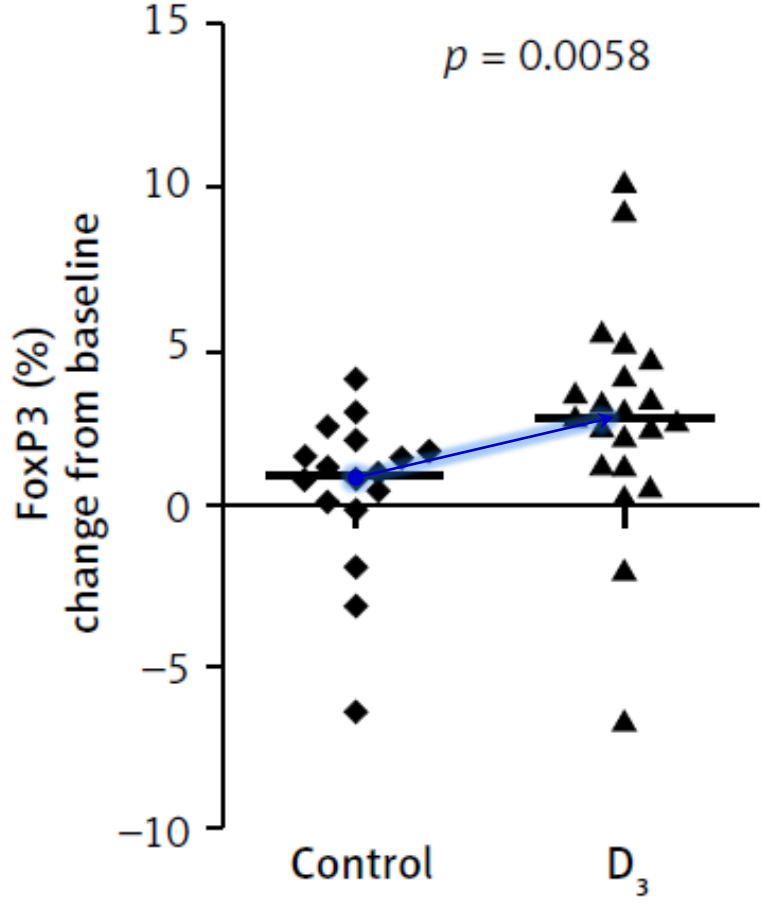
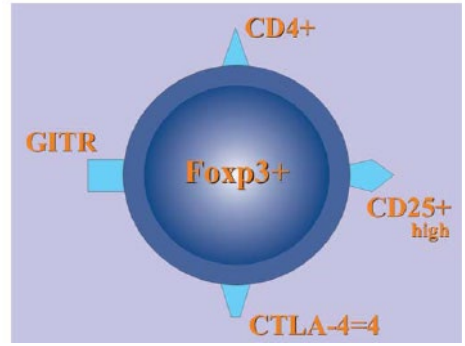
- ✓38 children aged 5-12, with allergic rhinitis due to grass pollen sensitivity
- ✓pre-coseasonal vitamin D 1000 IU daily or placebo supplementation for 5 months



A significantly increased percentage of CD4+CD25+Foxp3+ cells **(Treg)** was observed in the vitamin D treated group

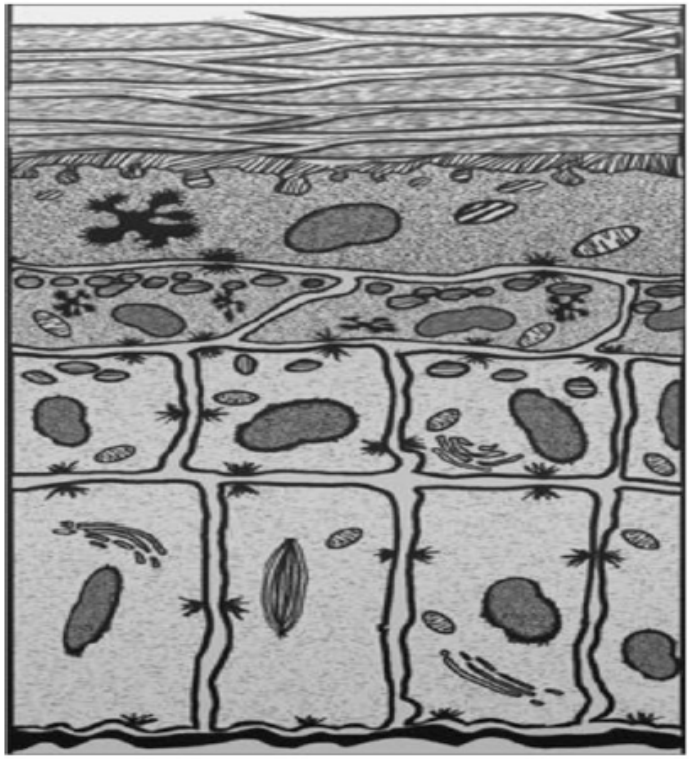


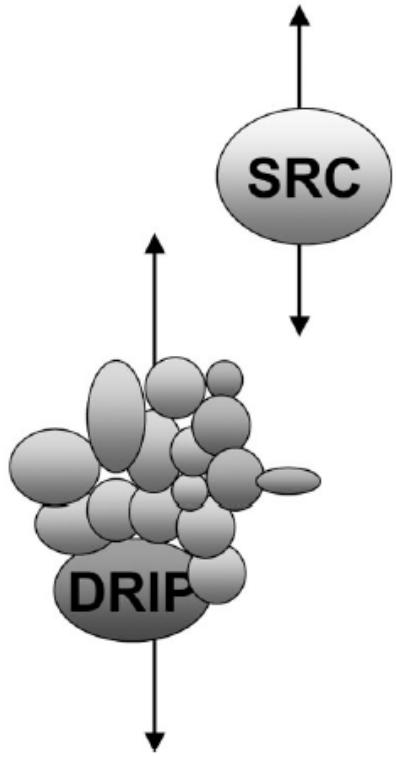
Use of Vitamin D and Immunity: *Why supplementation are needed?*

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Immunomodulation
- ✓ Fetal development
- ✓ Infections
- ✓ Prevention and modification of asthma & COPD
- ✓ Prevention and modification of allergic rhinitis
- ✓ **Prevention and modification of atopic dermatitis**
- ✓ Prevention and modification of food allergy anaphylaxis, urticaria
- ✓ Autoimmunity
- ✓ Other Diseases
- ✓ Conclusions

The different layers of the epidermis, and the functions within those layers regulated by VDR and its coactivators



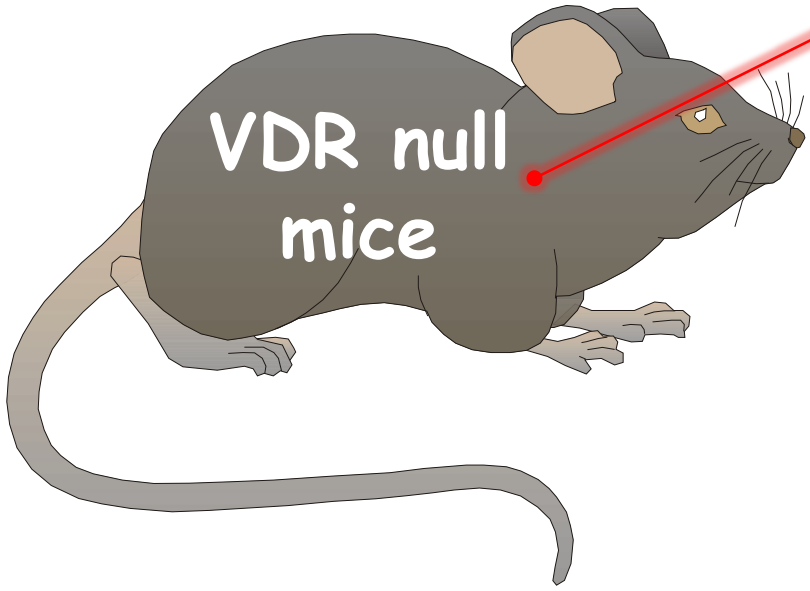


Coactivators	VDR Function	Target genes
SRC	Barrier formation	ABCA12, UGCG, ELOVL4
SRC	Innate Immunity	Cathelicidin, CD14
SRC	Epidermal Differentiation	K1, K10, FLG, LOR
DRIP	Hair Differentiation	Hair keratins
DRIP	Proliferation	Cyclin D1, Gli 1
DRIP	Wnt signaling	

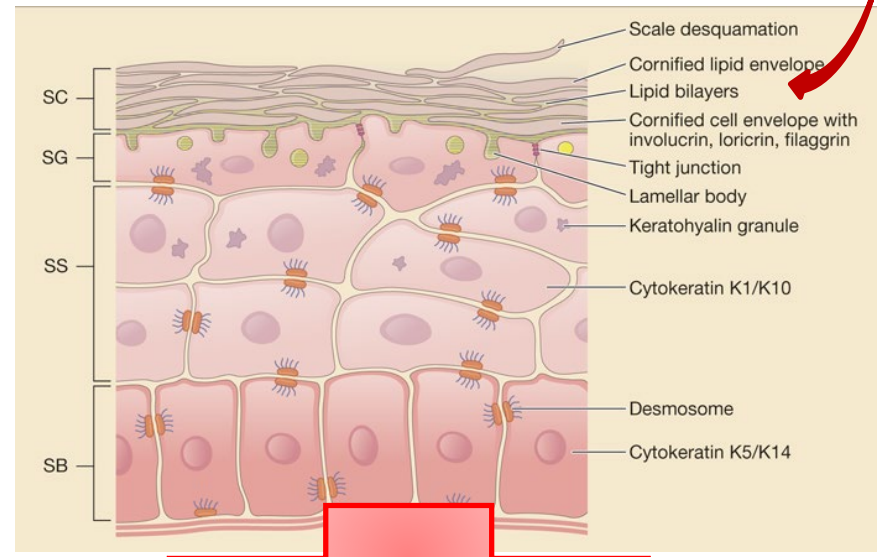
Bikle DD. ***Vitamin D metabolism and function in the skin.***
Mol Cell Endocrinol. 2011;347(1-2):80-9.

Vitamin D receptor and coactivators SRC2 and 3 regulate epidermis-specific sphingolipid production and permeability barrier formation.

Oda Y, J Invest Dermatol. 2009;129(6):1367-78.



altered epidermis-specific sphingolipid lipid production and composition *in vivo*.



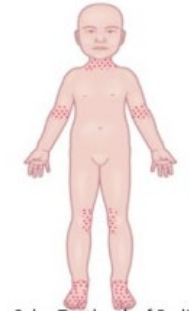
Reduced Skin Barrier Function

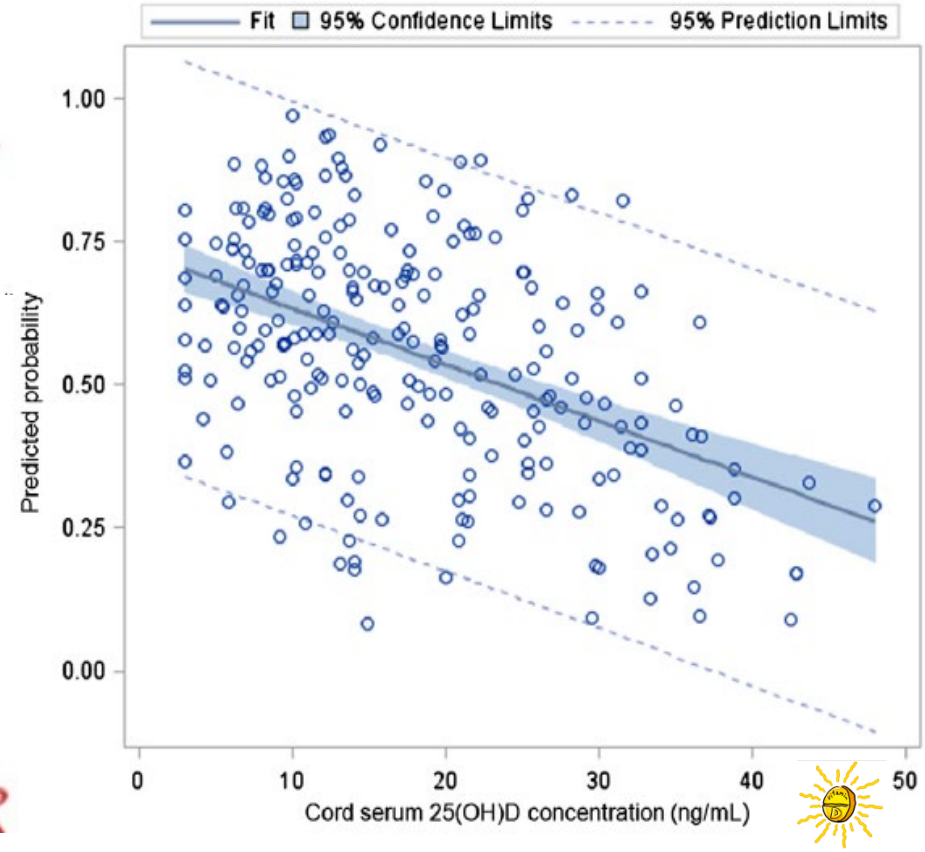
Cord serum 25-hydroxyvitamin D and risk of early childhood transient wheezing and atopic dermatitis

Baiz N, J Allergy Clin Immunol. 2014 Jan;133(1):147-53

- ✓ 239 newborns followed up until age 5 years
- ✓ cord serum 25(OH)D levels
- ✓ 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



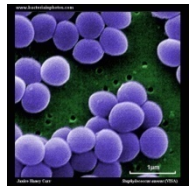


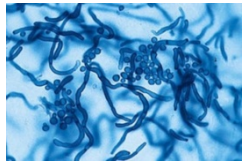
Cord Blood

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

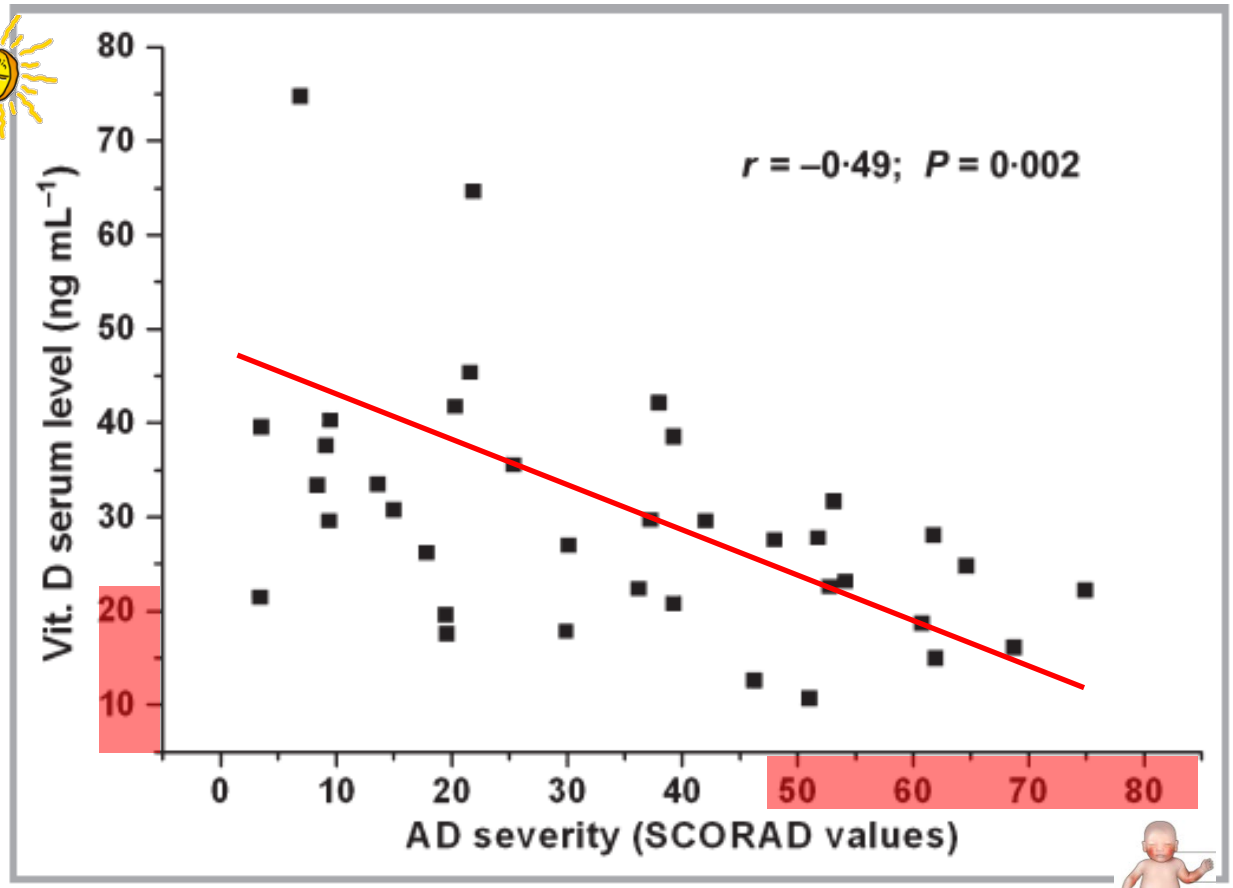
Peroni DG and Boner AL, Br J Dermatol. 2011;164:1078-82.

- ✓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 vitamin D levels and individual SCORAD values.

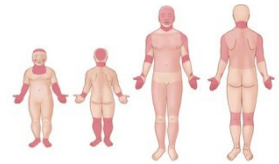


Lower vitamin D status is closely correlated with eczema of the head and neck.

Noh S, J Allergy Clin Immunol 2014;133:1767-69

The correlation study showed a statistically significant negative correlation between the 25(OH) Vitamin D concentration and eczema involvement of:

total area

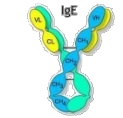


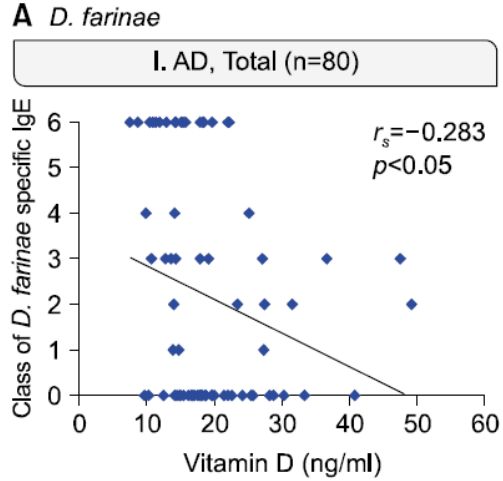
head and neck area

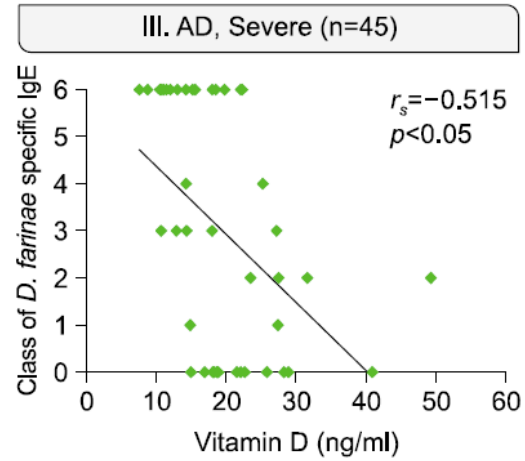
House Dust Mite Sensitization Is Inversely Associated with Plasma 25-Hydroxyvitamin D3 Levels in Patients with Severe Atopic Dermatitis.

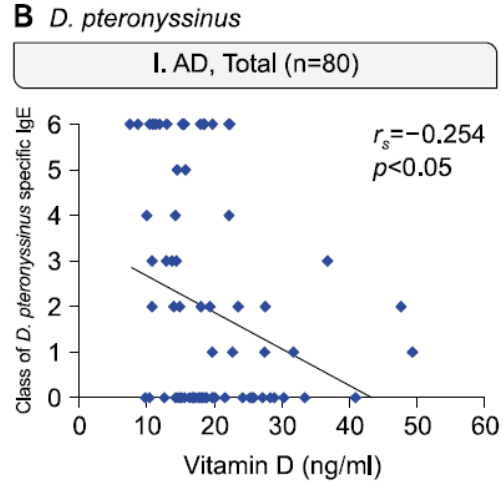
Jang YH, Ann Dermatol. 2017;29(4):400-406.

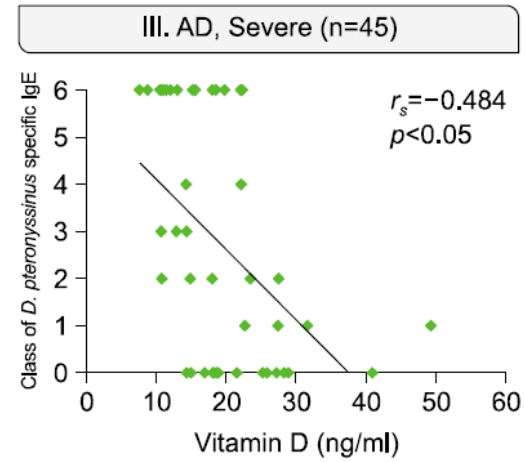
- ✓80 patients with AD
- ✓AD severity by Rajka and Langeland scores.
- ✓serum 25-hydroxyvitamin D3,
- ✓total IgE, sIgE against *Dermatophagoides farinae* and *D. pteronyssinuso* (class 0 to 6).











Vitamin D and antimicrobial peptide levels in patients with atopic dermatitis and atopic dermatitis complicated by eczema herpeticum: A pilot study.

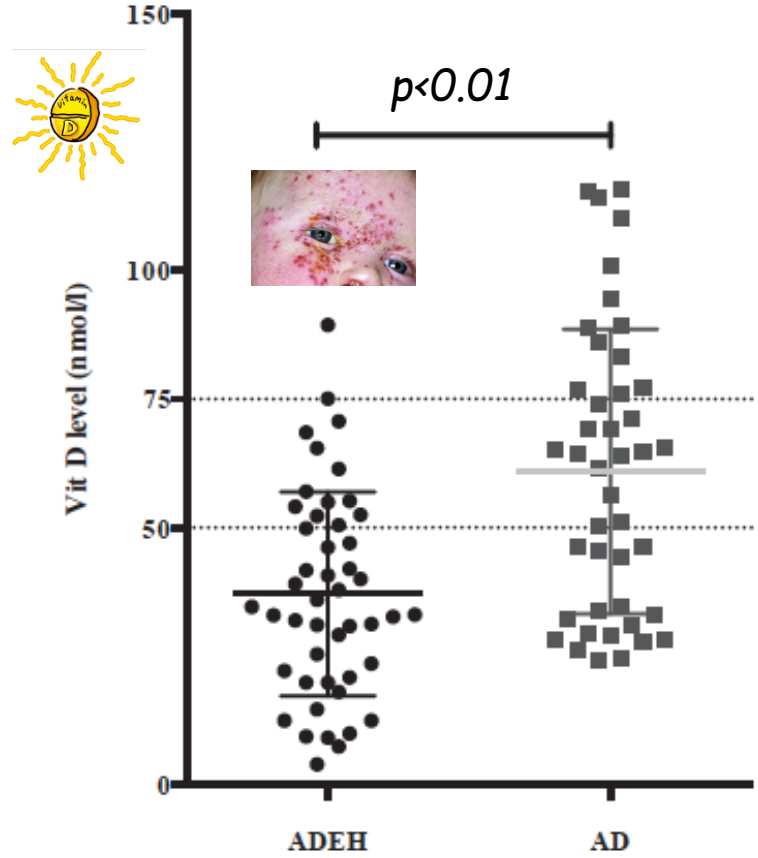
Albenali LH , JACI 2016;138:1715.

Baseline 25(OH) VD levels were significantly lower in patients with ADEH (37±20 nmol/L) than in patients with AD (61±28 nmol/L; *p<0.001*).

Only 2 patients with ADEH had normal 25(OH) VD levels.

AD: atopic dermatitis
ADEH: atopic dermatitis eczema herpeticum

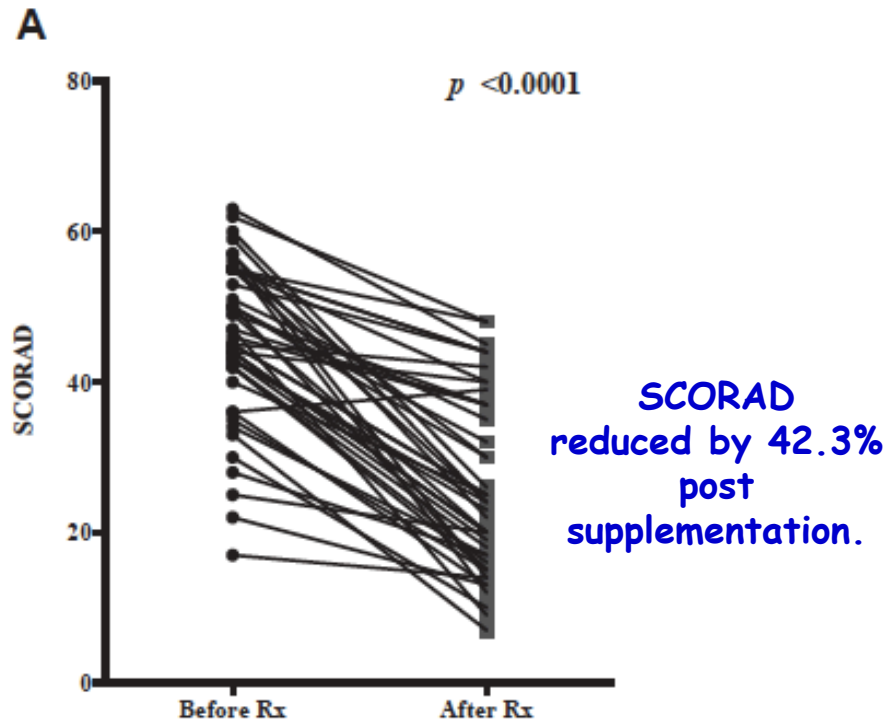
Children with ADEH (black dots,n=45) with lower VD levels compared with children with AD (gray squares, n=45).



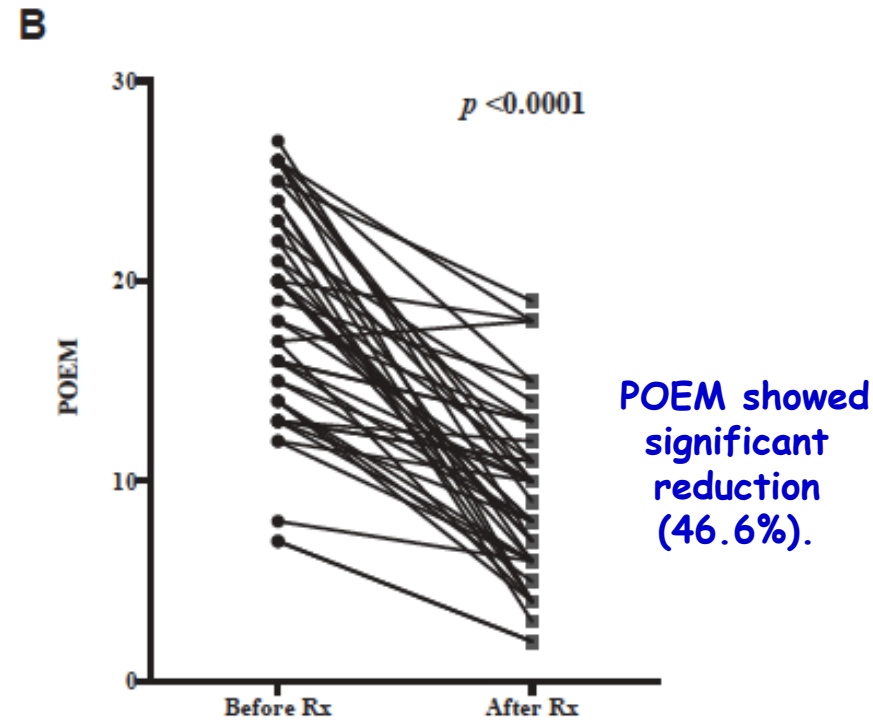
Vitamin D and antimicrobial peptide levels in patients with atopic dermatitis and atopic dermatitis complicated by eczema herpeticum: A pilot study.

Albenali LH , JACI 2016;138:1715.

Post vitamin D supplementation analysis



SCORAD reduced by 42.3% post supplementation.



POEM showed significant reduction (46.6%).

SCORAD: SCORing Atopic Dermatitis

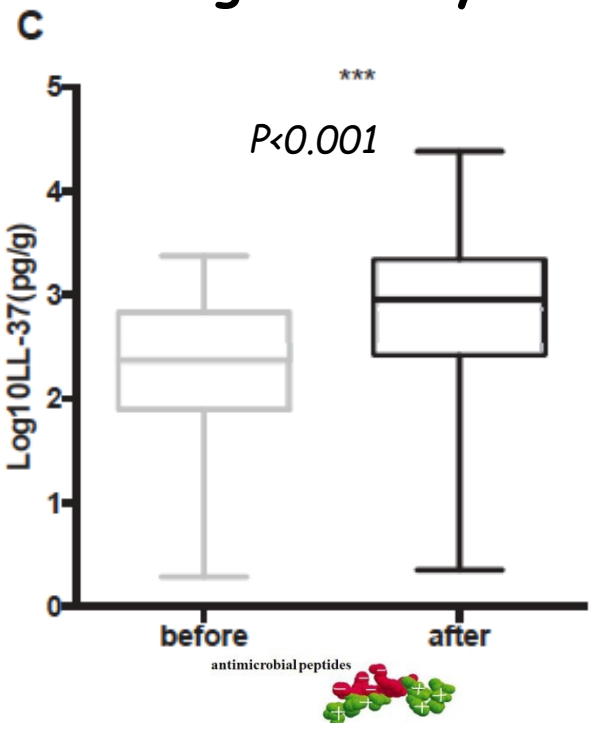
POEM: Patient Oriented Eczema Measure

Vitamin D and antimicrobial peptide levels in patients with atopic dermatitis and atopic dermatitis complicated by eczema herpeticum: A pilot study.

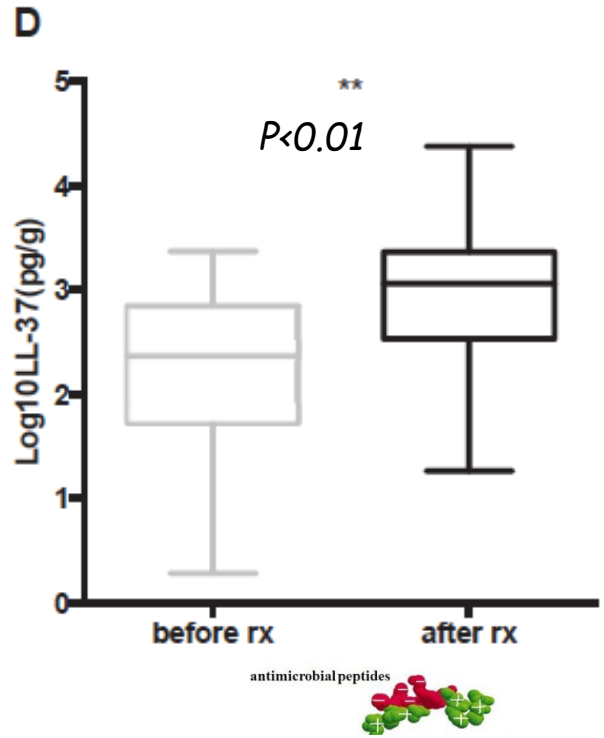
Albenali LH , JACI 2016;138:1715.

Postsupplementation analysis (n=47).

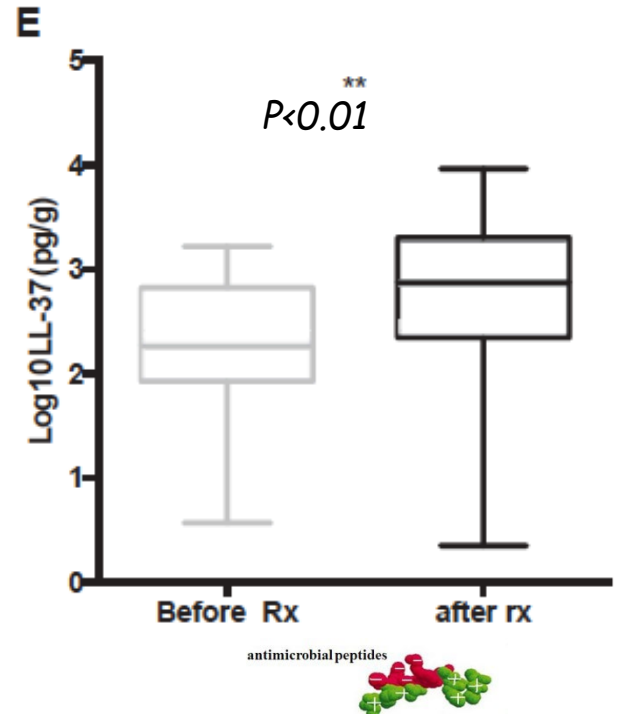
LL-37 levels increased significantly



Lesional LL-37 levels increased



Non-Lesional LL-37 levels increased

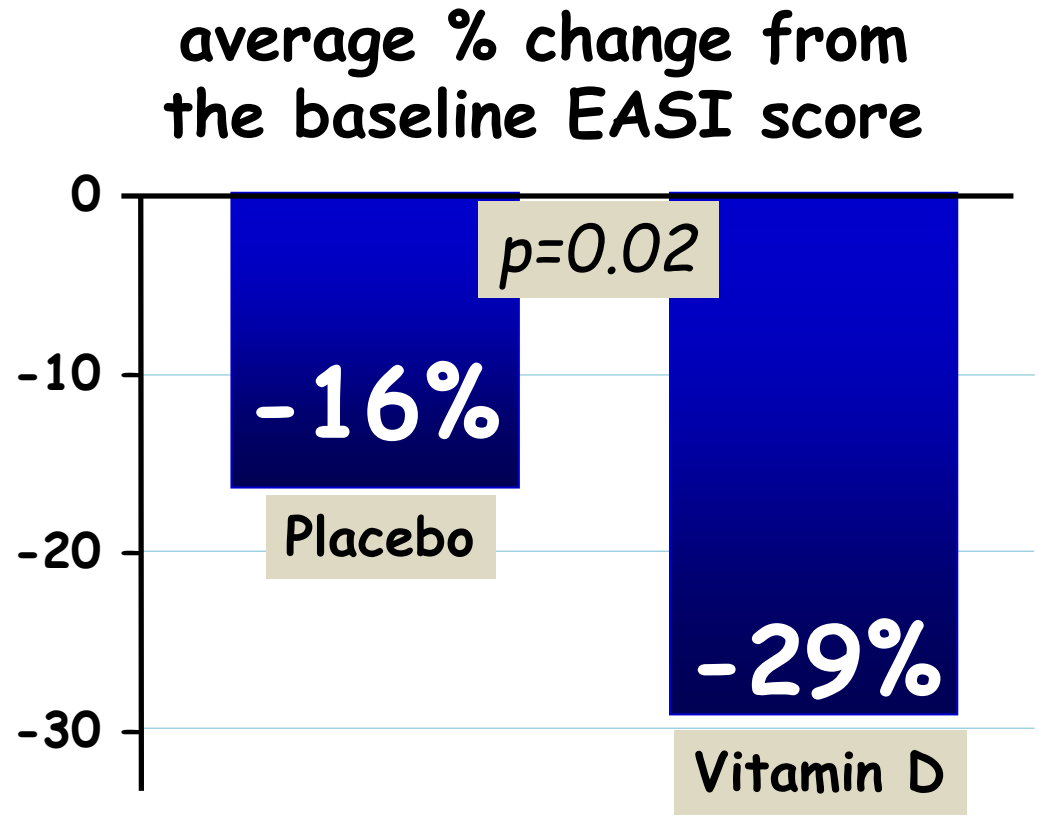


cathelicidin LL-37 levels were quantified from superficial samples of stratum corneum

Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children.

Camargo CA Jr, J Allergy Clin Immunol. 2014;134(4):831-835.

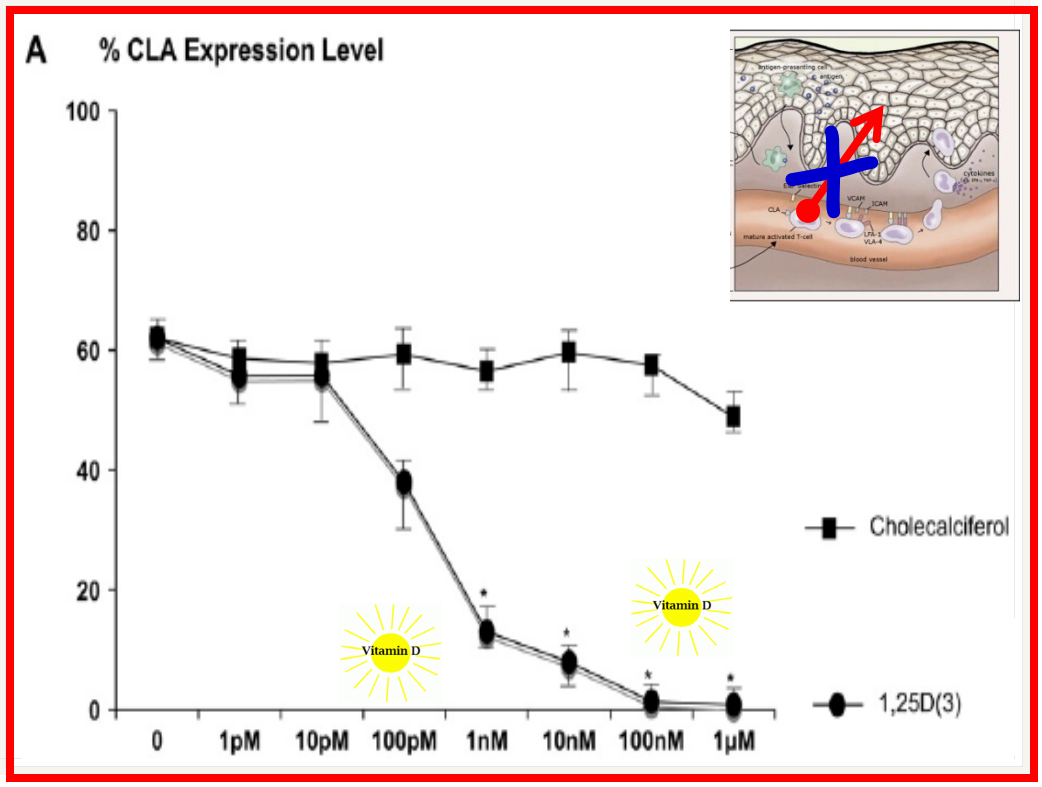
- ✓104 Mongolian children with winter-related AD (age 2-17 yrs)
- ✓AD score 10 to 72 using the Eczema Area and Severity Index (EASI)
- ✓oral cholecalciferol (1000 IU/day) versus placebo for 1 month.

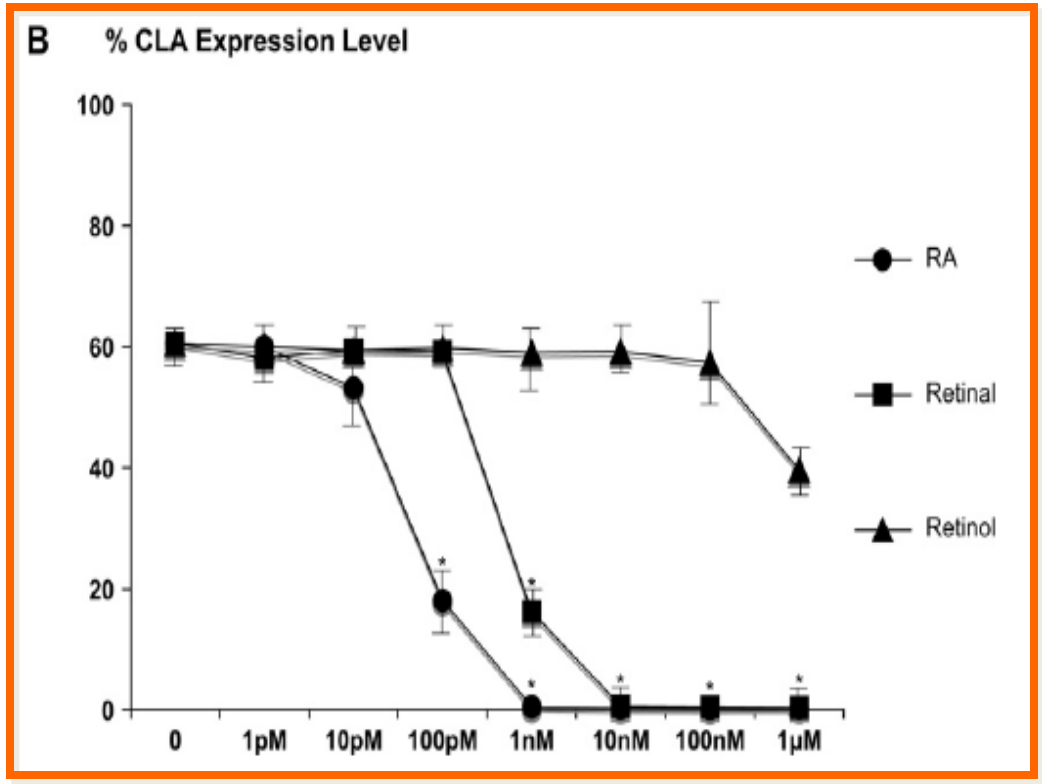


Vitamins A and D are Potent Inhibitors of Cutaneous Lymphocyte-Associated Antigen Expression

Yamanaka JACI 2008;121:148

NORMAL T CELLS WERE CULTURED WITH VITAMIN D OR VITAMIN A





CLA expression levels were reduced with 1nM 1,25D(3) whereas cholecalciferol, an inactive precursor of vitamin D, had no effect * *P<0.05*

CLA expression levels were also decreased with 100 pM RA, 1 nM retinal and 1μM retinol. * *P<0.05*

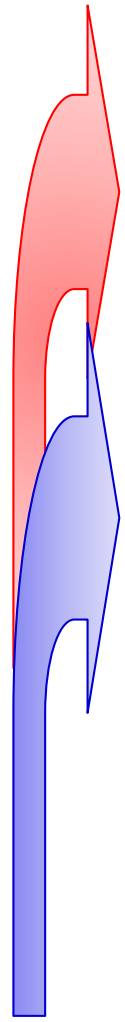
Is vitamin D level associated with the natural course of atopic dermatitis?

Dogru M. Allergol Immunopathol (Madr). 2018 Nov - Dec;46:546-551

✓69 patients with AD and 70 healthy children

✓SPTs , eosinophil counts, sIgE and serum 25OHD3 levels

✓After at least 4 years of follow-up, patients were re-evaluated for natural course of AD.



- There was a negative correlation between 25OHD3 levels and severity of AD (r=-0.480; p=0.001).

- **In patients reassessed after 4 years**: age, the age of AD onset, vitamin D deficiency, SCORAD level and severe AD were higher in the persistent group vs. remission group, **25OHD3 levels were higher in the remission group vs. persistent group** *(p<0.05)*.

Use of Vitamin D and Immunity: *Why supplementation are needed?*

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- ✓ Fetal development
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- ✓ Prevention and modification of asthma & COPD
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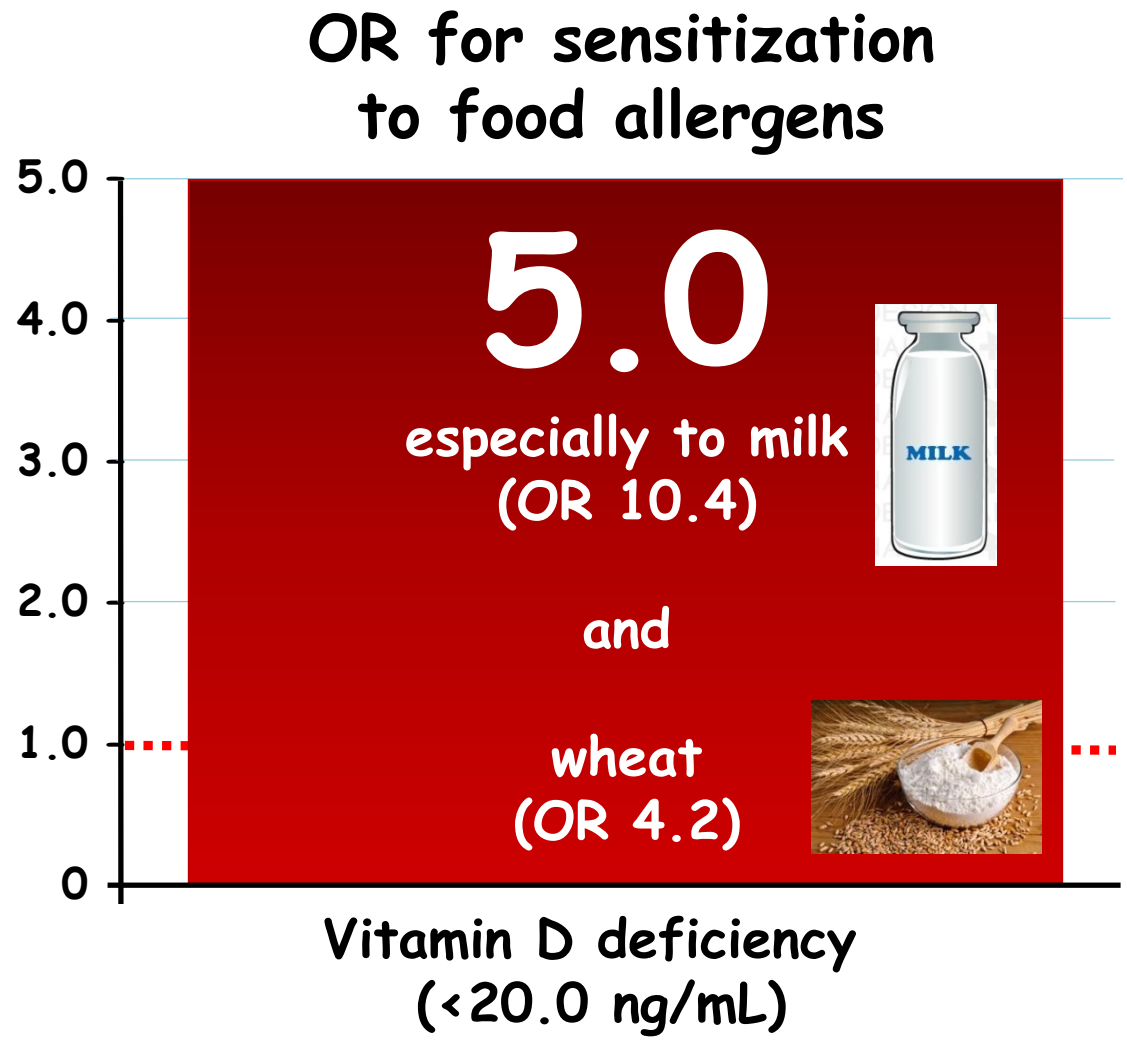
- ✓ Prevention and modification of atopic dermatitis
- ✓ **Prevention and modification of food allergy anaphylaxis, urticaria**
- ✓ Autoimmunity
- ✓ Other Diseases
- ✓ Conclusions

The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy. *Baek JH, J Pediatr. 2014;165(4):849-54.*

✓226 infants with atopic dermatitis or food allergy

✓serum 25-hydroxyvitamin D (25[OH]D) and sIgE levels to common or suspected food allergens

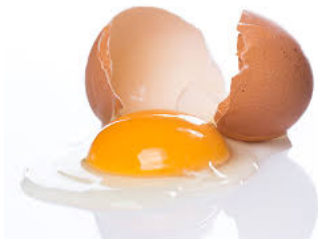
✓serum 25(OH)D category levels: <20.0 ng/mL (deficiency), 20.0-29.0 ng/mL (insufficiency), ≥ 30.0 ng/mL (sufficiency)

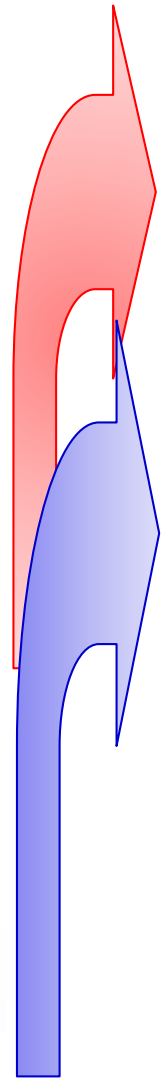


Early life innate immune signatures of persistent food allergy.

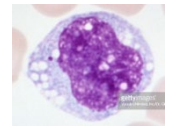
Neeland MR, J Allergy Clin Immunol. 2018 Sep;142(3):857-864.e3

✓Longitudinally collected PBMC samples from a population-based cohort of challenge-confirmed egg-allergic infants with either persistent or transient egg allergy outcomes in childhood to phenotype and quantify the functional innate immune response associated with clinical phenotypes of egg allergy.





- infants with persistent egg allergy exhibit an increased numbers of circulating monocytes and dendritic cells that produce more inflammatory cytokines .



- follow-up analysis revealed that this unique innate immune signature continues into childhood in those with persistent egg allergy and that increased serum vitamin D levels correlate with changes in innate immune profiles observed in children who developed natural tolerance to egg by age 2 years.

Higher latitude and lower solar radiation influence on anaphylaxis in Chilean children.

Hoyos-Bachiloglu R, Pediatr Allergy Immunol. 2014;25(4):338-43

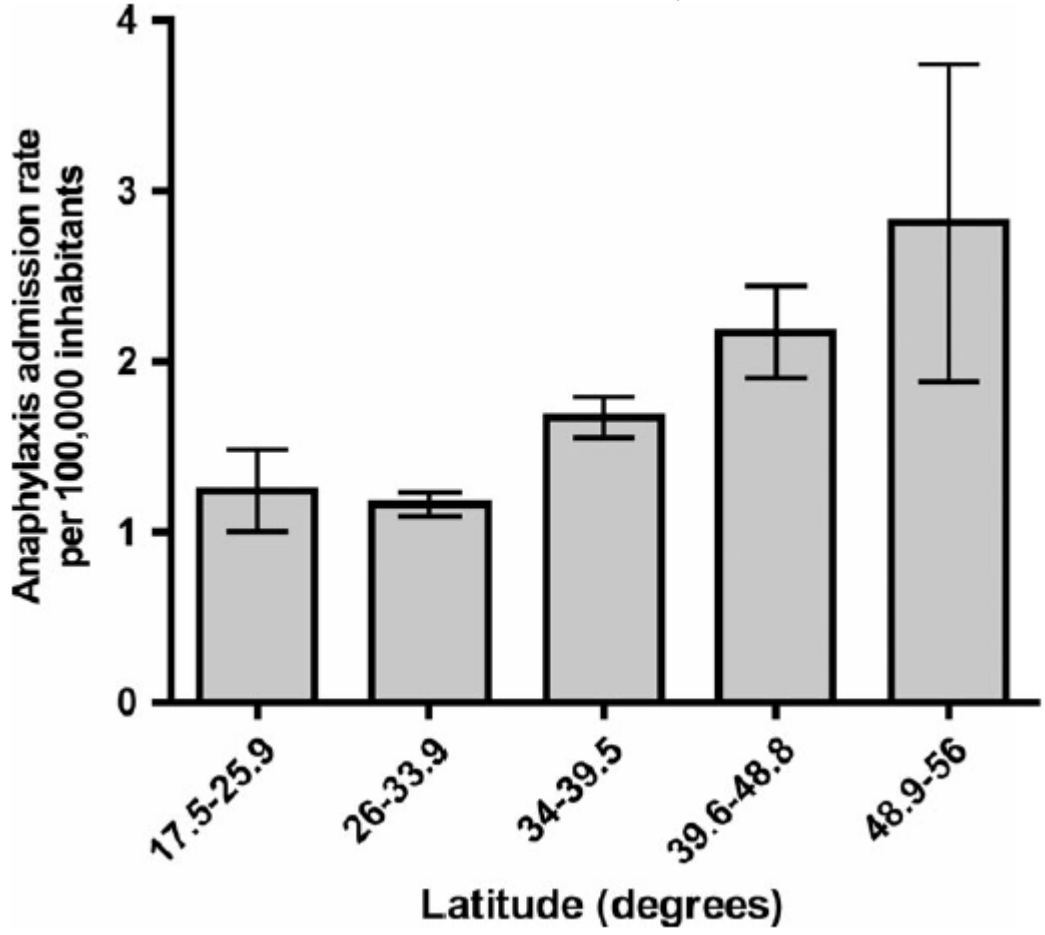
✓2316 anaphylaxis admissions

✓Median age of patients 41 yr;

- 17.5 S

- 56.0 S

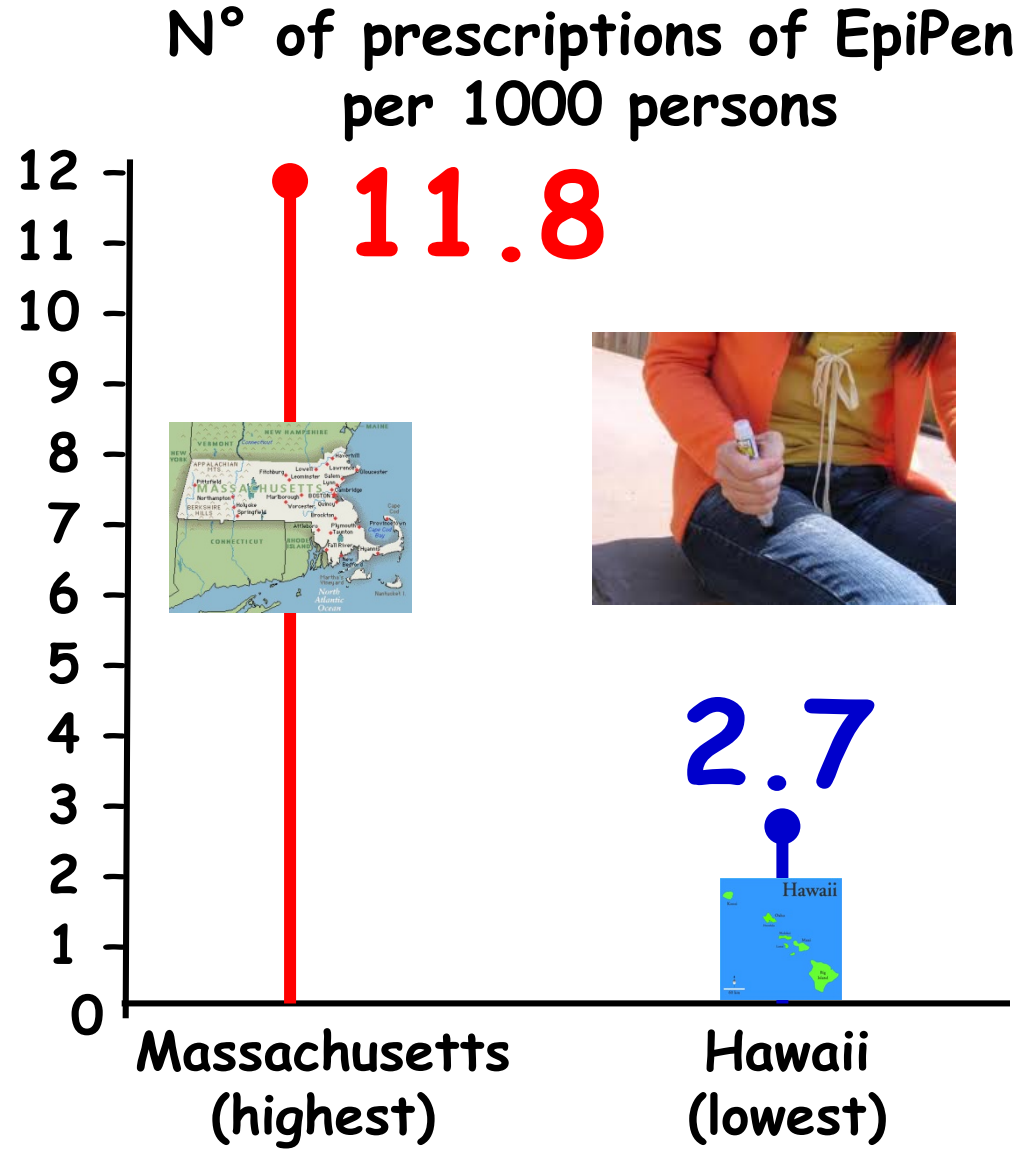
Latitudinal distribution of anaphylaxis admissions in Chile, 2001–2010.



Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D.

Camargo CA Jr, J Allergy Clin Immunol. 2007;120(1):131-6

- ✓ EpiPen prescriptions in 2004 were obtained for all 50 states and Washington;
- ✓ There were 1,511,534 EpiPen prescriptions
- ✓ On average, there were 5.71 EpiPens prescribed per 1000 persons



Chronic urticaria and Vitamin D

1) Low vitamin D level in patients with chronic urticaria:

Thorp WA. J Allergy Clin Immunol. 2010;126(2):413-4.
Grzanka A, J Inflamm (Lond). 2014;11(1):2.

2) Low vitamin D level are related to severity of chronic urticaria:

Abdel-Rehim AS, Egypt J Immunol. 2014;21:85-90
Woo YR, Ann Dermatol. 2015;27(4):423-30.

3) Vitamin D treatments leads to improvment/resolution of chronic urticaria:

Sindher SB, Ann Allergy Asthma Immunol. 2012;109(5):359-60
Rorie A, Ann Allergy Asthma Immunol. 2014;112(4):376-82.
Rorie A. Expert Rev Clin Immunol. 2014;10(10):1269-71.
Boonpiyathad T, Dermatoendocrinol. 2014;6:e29727.
Rasool R, World Allergy Organ J. 2015;8:15.
Oguz Topal I. J Dermatolog Treat. 2016;27(2):163-6.

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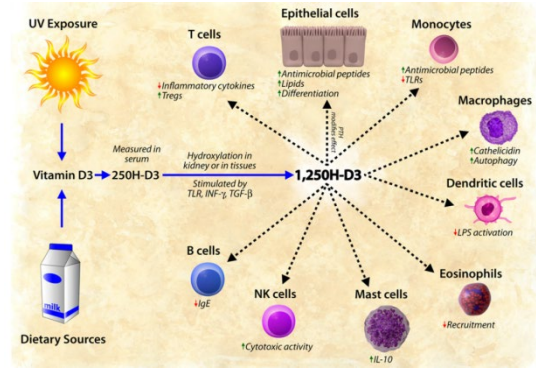
- ✓ Prevention and modification of food allergy anaphylaxis, urticaria
- ✓ **Autoimmunity**
- ✓ Other Diseases
- ✓ Conclusions

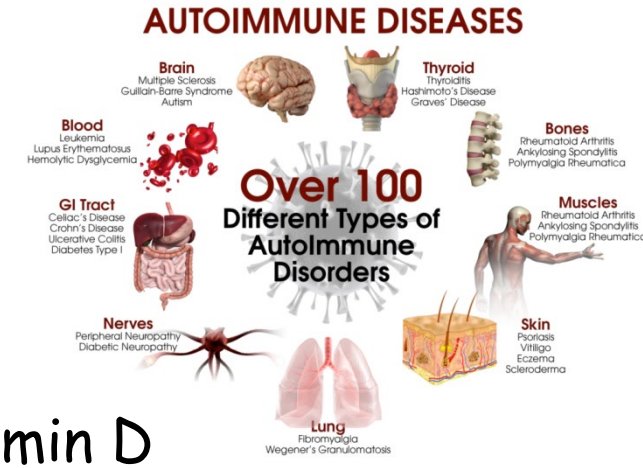
Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential.

Dankers W, Front Immunol. 2017 Jan 20;7:697.



- An important extra-skeletal effect of vitamin D is the modulation of the immune system.

- In the context of **autoimmune diseases**, this is illustrated by correlations of vitamin D status and genetic polymorphisms in the vitamin D receptor with the incidence and severity of the disease.

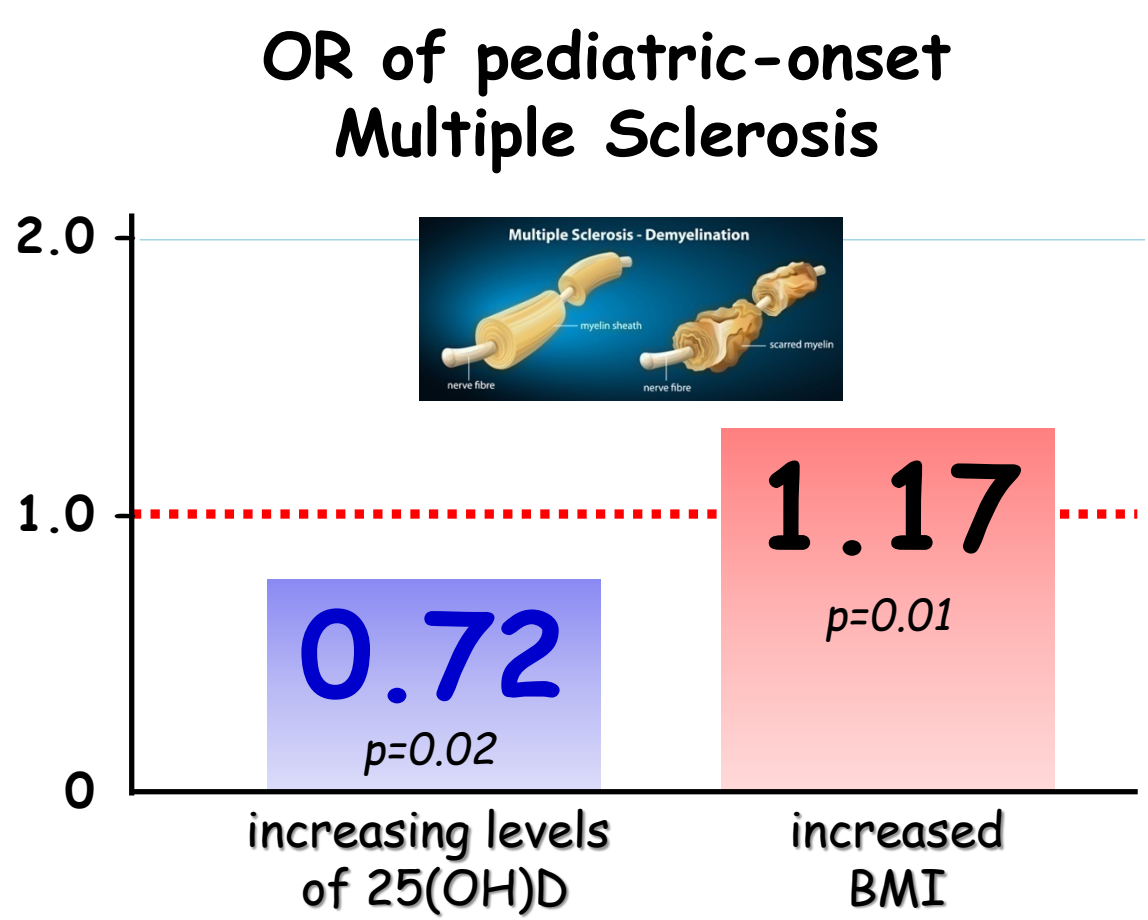


- In recent years, several clinical trials have been performed to investigate the therapeutic value of vitamin D in **multiple sclerosis**, **rheumatoid arthritis**, **Crohn's disease**, **type I diabetes**, **systemic lupus erythematosus**, and **coeliac disease**.

Evidence for a causal relationship between low vitamin D, high BMI, and pediatric-onset multiple sclerosis.

Gianfrancesco MA, Neurology. 2017 Apr 25;88(17):1623-1629.

- ✓individuals recruited in the USA (n = 394 cases, 10,875 controls) and Sweden (n = 175 cases, 5,376 controls; total n = 16,820).
- ✓Serum levels of 25(OH)D
- ✓body mass index (BMI)
- ✓genetic risk scores (GRS).



Evidence for a causal relationship between low vitamin D, high BMI, and pediatric-onset multiple sclerosis.

Gianfrancesco MA, Neurology. 2017 Apr 25;88(17):1623-1629.

Protective effect confirmed:

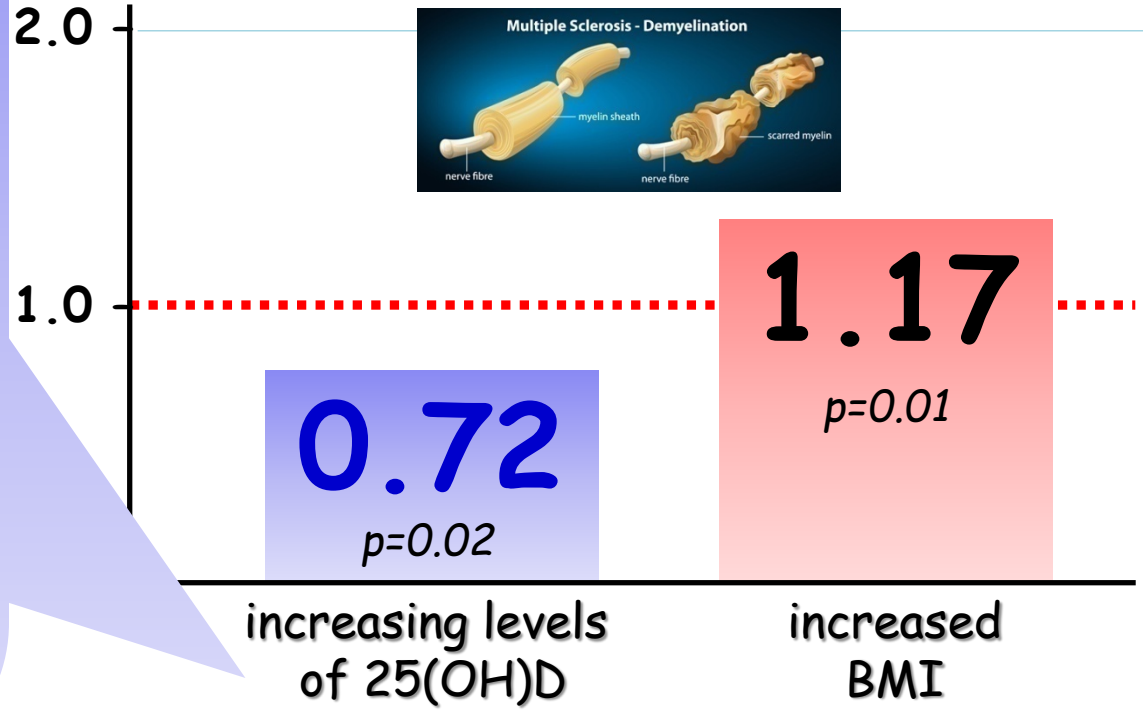
Sikes EM, Pediatric Health Med Ther. 2018 Mar 6;9:17-25.

Yamamoto E, J Child Neurol. 2018 Jan;33(1):98-105.

Yılmaz Ü, Eur J Paediatr Neurol. 2017 Nov;21(6):864-872.

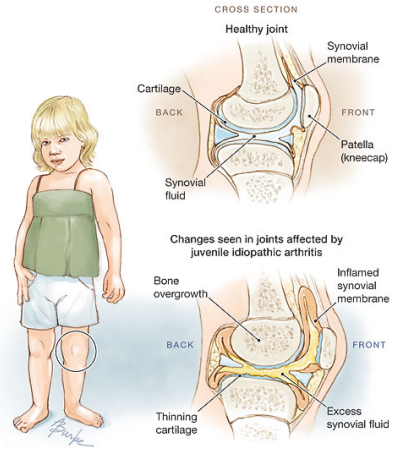
Mowry EM. J Neurol Sci. 2011 Dec 15;311(1-2):19-22.

OR of pediatric-onset Multiple Sclerosis



Determinants of vitamin D levels in children, adolescents, and young adults with juvenile idiopathic arthritis

Stagi S, J Rheumatol 2014;41:1884-1892



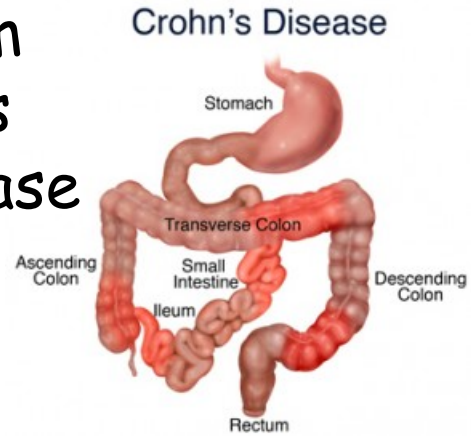
- ✓ 152 patients with juvenile idiopathic arthritis (JIA) (mean age 16.2 ± 7.4 yrs).
- ✓ A control group.
- ✓ Plasma 25(OH)D, parathyroid hormone.

- Patients with JIA showed reduced 25(OH)D levels compared to controls *($p < 0.001$).*
- Patients with active disease and/or frequent relapses had reduced 25(OH)D levels compared to patients with no active disease and no frequent flares *($p < 0.005$).*
- JIA patients had significantly higher PTH levels compared to controls *($p < 0.0001$).*

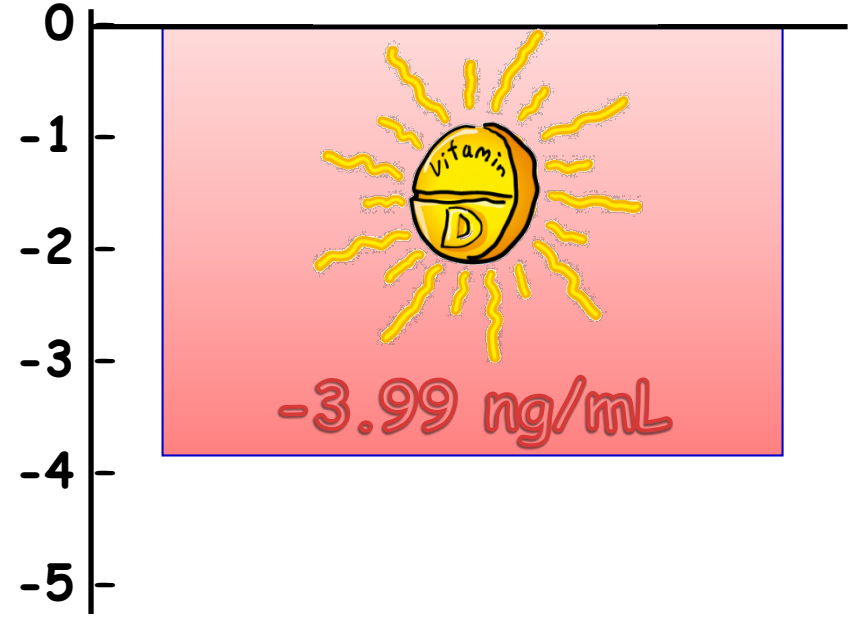
Vitamin D status in relation to Crohn's disease: Meta-analysis of observational studies

Sadeghian M, Nutrition 2016;32:505-514

- ✓ 63 observational studies assessing serum vitamin D levels in crohn's disease (CD) patients.



Mean levels of 25(OH)D in CD patients compared with healthy controls



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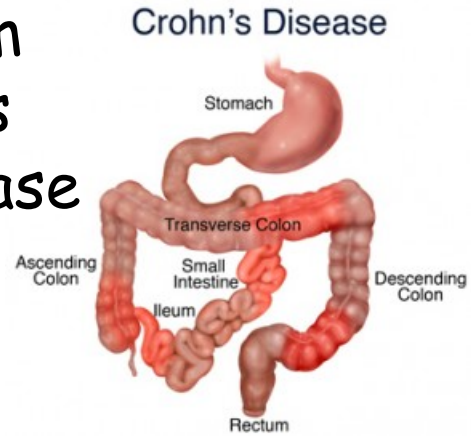
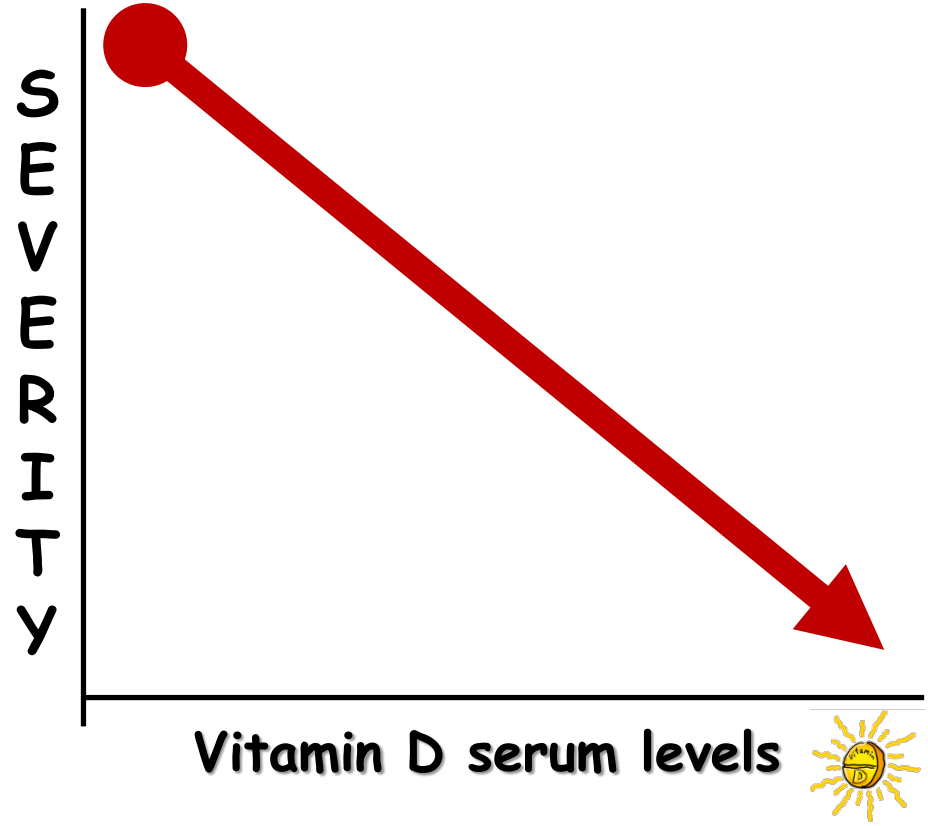


Inverse association was observed between serum vitamin D and severity of CD

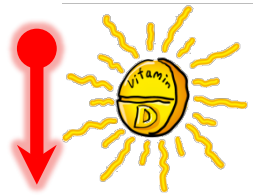


Vitamin D status in children with systemic lupus erythematosus and its association with clinical and laboratory parameters

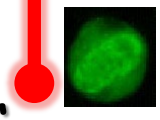
AlSaleem A, Clin Rheumatol 2015;34:81-84

- ✓ 28 Saudi children with systemic lupus erythematosus (SLE) (mean age of 9.7 years).
- ✓ 25-OH vitamin D and its association with clinical, laboratory variables and disease activity.

- 86% patients had low levels of serum 25-OH vitamin D levels, with a mean of 51.1 ± 33.6 nmol/L.



- Levels of 25-OH vitamin D correlated inversely with anti-nuclear autoantibodies.

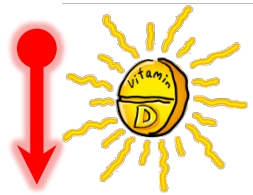


Vitamin D status in children with systemic lupus erythematosus and its association with clinical and laboratory parameters

AlSaleem A, Clin Rheumatol 2015;34:81-84

After 3 months, treatment of vitamin D3 (2000 IU daily) and Calcium (600 mg twice daily), 17 patients had improvement in (Systemic Lupus Erythematosus Disease Activity Index) SLEDAI score and autoimmune markers.

- 86% patients had low levels of serum 25-OH vitamin D levels, with a mean of 51.1 ± 33.6 nmol/L.



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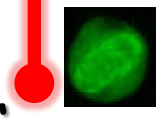


Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis.

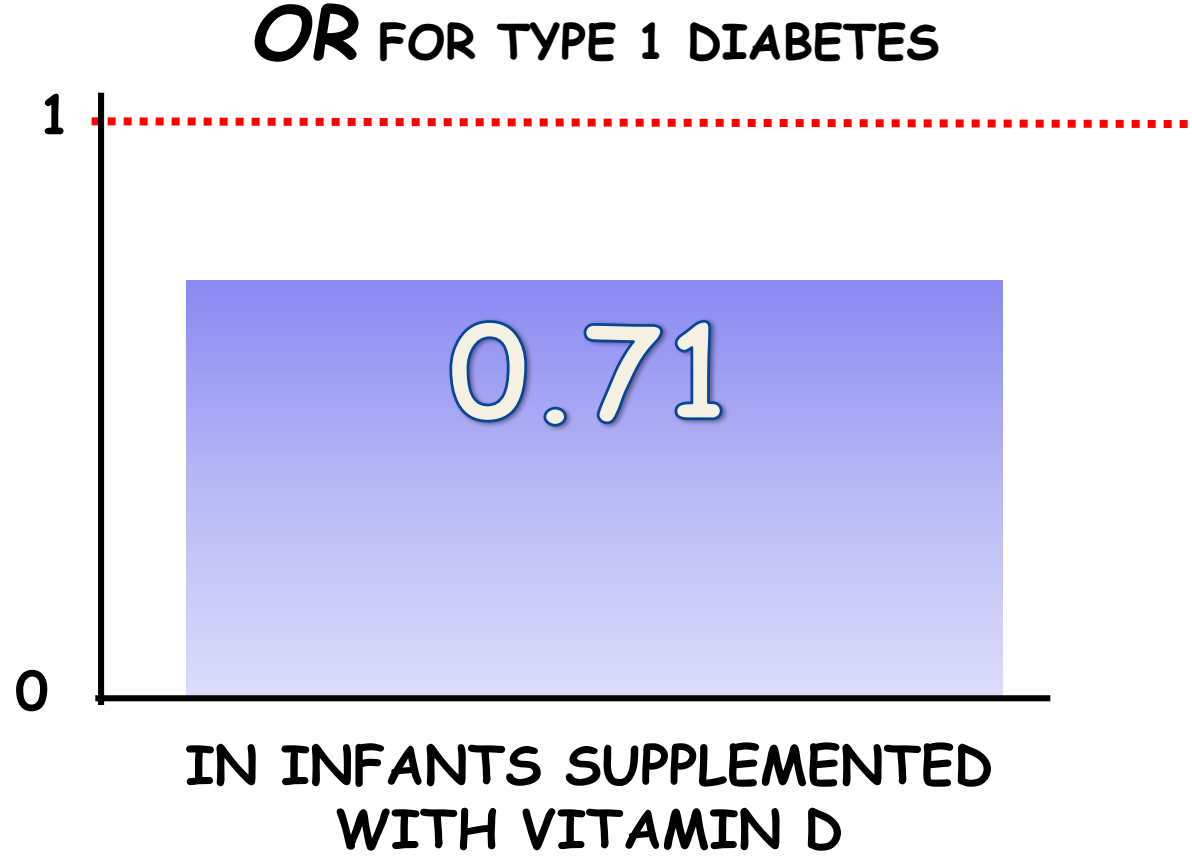
Zipitis Arch Dis Child 2008;93:512

1. Type 1 diabetes is characterized by autoimmune destruction of insulin-producing β cells in the pancreas.
2. There is a marked geographic variation in incidence, with a child in Finland being about 400 times more likely than a child in Venezuela to acquire the disease.

Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis.

Zipitis Arch Dis Child 2008;93:512

- ✓ 5 studies (4 case-control studies and 1 cohort study).

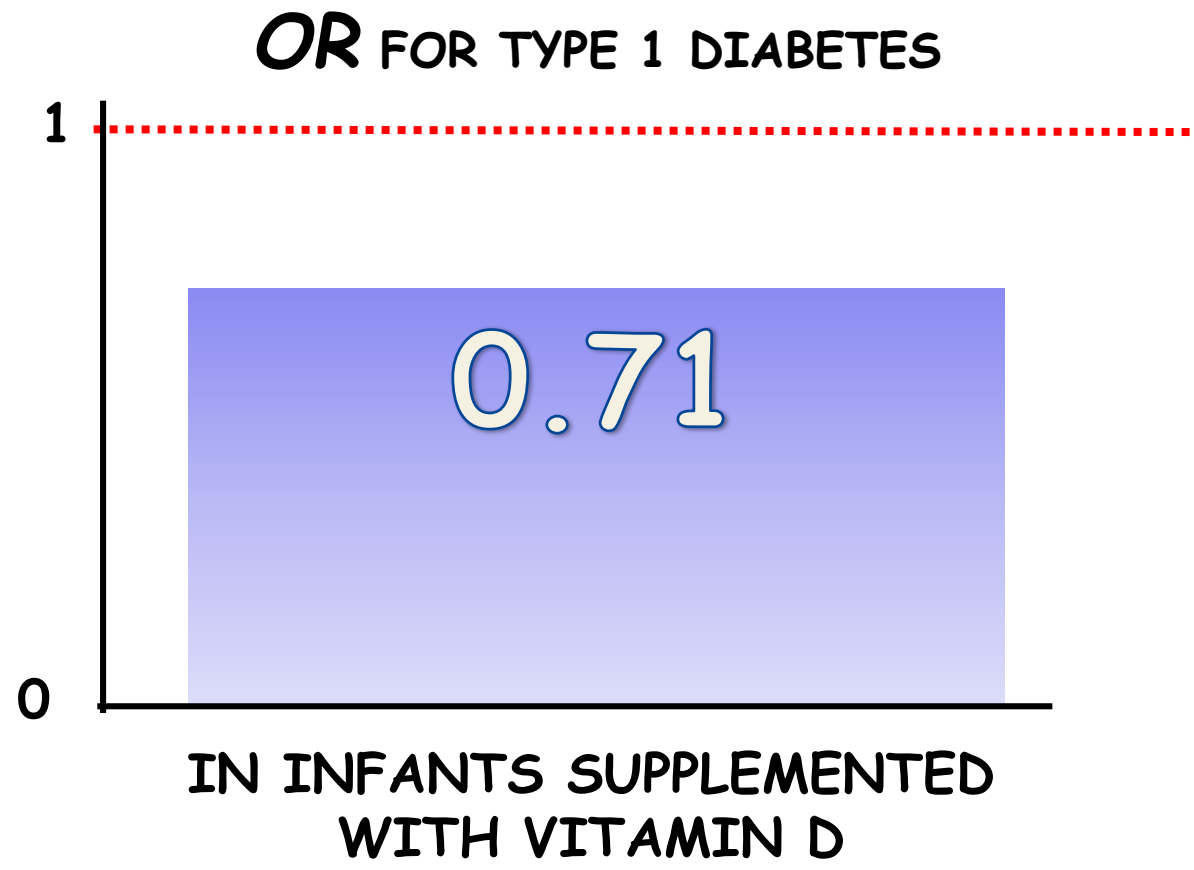


Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis.

Zipitis Arch Dis Child 2008;93:512

✓ 5

There was also some evidence of a dose-response effect.



Vitamin D at the onset of type 1 diabetes in Italian children. *Franchi B, Eur J Pediatr. 2014;173(4):477-82.*

✓vitamin D levels in children at the onset of T1DM (n= 58) compared with children with other diseases (n= 166)

✓between May 2010 and July 2012

- Median 25(OH)D was significantly lower in the diabetic patients (36.2 nmol/l,) than in controls (48.7 nmol/l), *p = 0.010.*

- Median 25(OH)D level was significantly lower in patients admitted with diabetic ketoacidosis (30.2 nmol/l,) than in patients without ketoacidosis (40.7 nmol/l), *p = 0.019*

Vitamin D at the onset of type 1 diabetes in Italian children. *Franchi B, Eur J Pediatr. 2014;173(4):477-82.*

- ✓vitamin D levels in children at the onset of T1DM (n= 58) compared with children with other diseases (n= 166)
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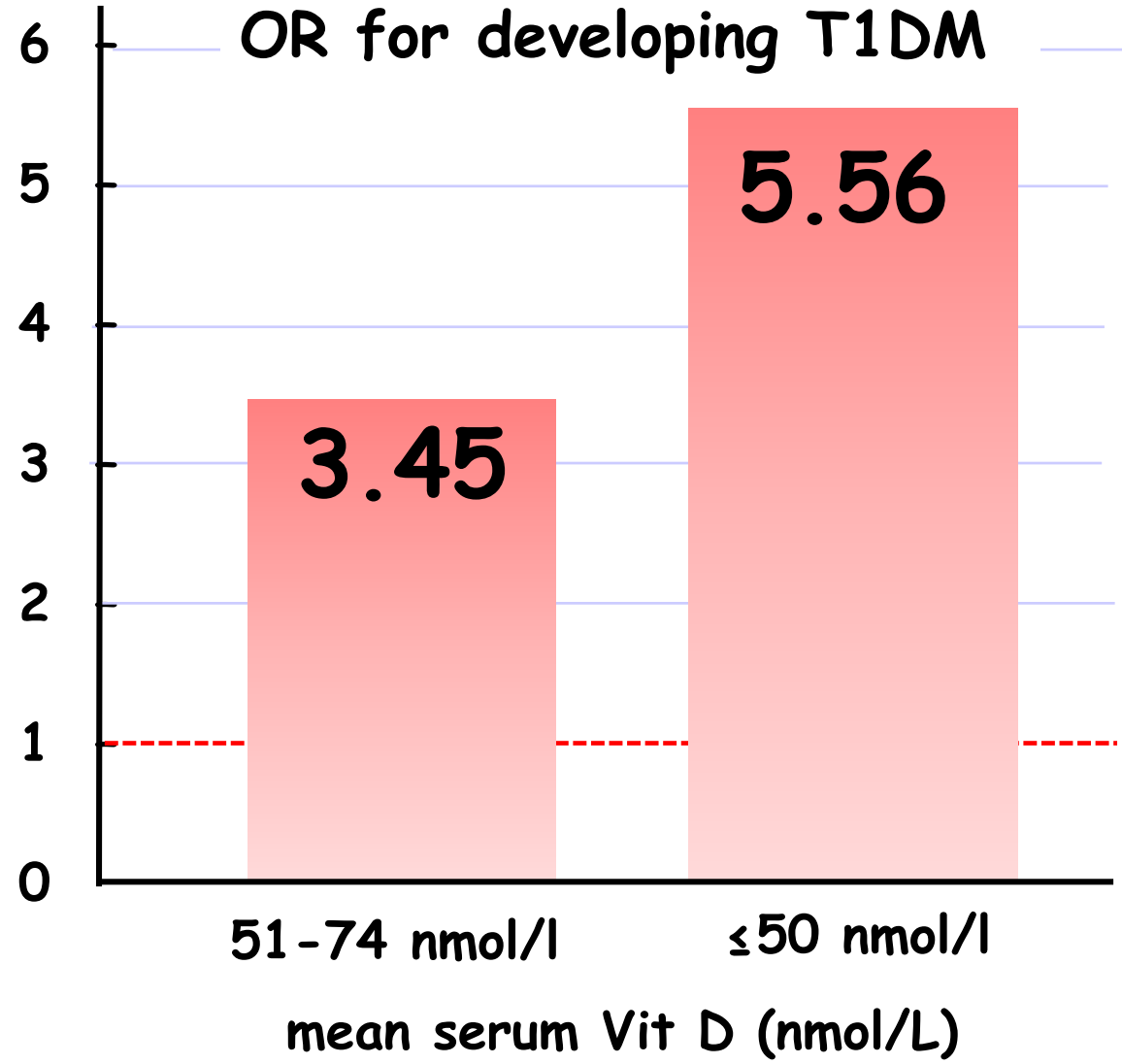
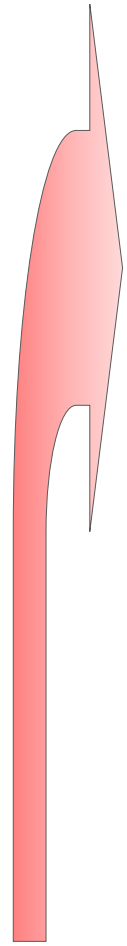


Vitamin D and Incidence of Prediabetes or Type 2 Diabetes: A Four-Year Follow-Up Community-Based Study.

Gao Y, Dis Markers. 2018 Mar 18;2018:1926308.

✓a 4-year follow-up study

✓490 participants
(aged 18–70 years)
free of prediabetes
and
type 2 diabetes mellitus
(T2DM) at baseline



low 25(OH)D levels
were associated
with the risk
of onset of

- prediabetes [OR 3.01, *P* = 0 002]
- T2DM [OR 5.61 P = 0 004]

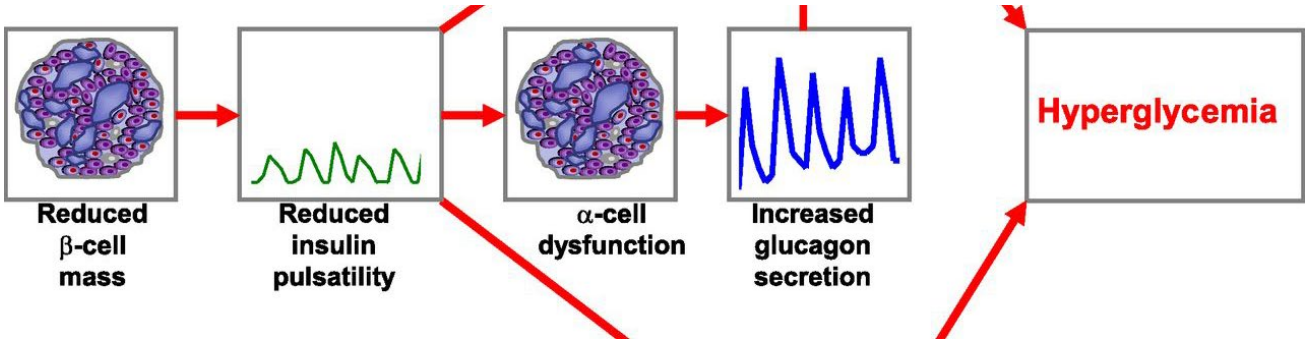
Vitamin D Switches BAF Complexes to Protect β Cells.

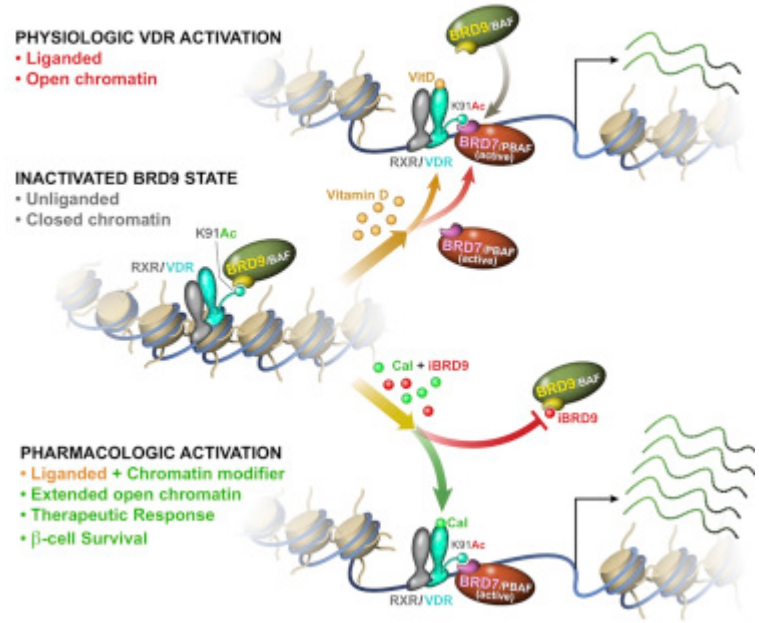
Wei Z, Cell. 2018 May 17;173(5):1135-1149.e15

- A primary cause of disease progression in type 2 diabetes (T2D) is β cell dysfunction due to inflammatory stress and insulin resistance.

- Preventing β cell exhaustion under diabetic conditions is a major therapeutic challenge.

- We identify the vitamin D receptor (VDR) as a key modulator of inflammation and β cell survival.





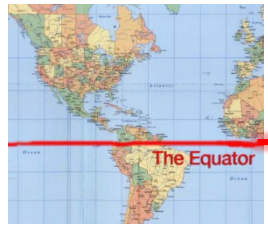
Lower Prevalence of Celiac Disease and Gluten-Related Disorders in Persons Living in Southern vs Northern Latitudes of the United States.

Unalp-Arida A, Gastroenterology. 2017 Jun;152(8):1922-1932.e2

✓gluten-related conditions from the US National Health and Nutrition Examination Survey, from 2009 through 2014, on 22,277 participants 6 years and older.

✓persons with celiac disease, identified on results of serum tests for immunoglobulin A against tissue transglutaminase and endomysium or on both.

OR for Celiac disease



Use of Vitamin D and Immunity: *Why supplementation are needed?*

Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

- ✓ Introduction
- ✓ Immunomodulation
- ✓ Fetal development
- ✓ Infections
- ✓ Prevention and modification of asthma & COPD
- ✓ Prevention and modification of allergic rhinitis
- ✓ Prevention and modification of atopic dermatitis
- ✓ Prevention and modification of food allergy anaphylaxis, urticaria
- ✓ Autoimmunity
- ✓ Other Diseases
- ✓ Conclusions

Is vitamin D useful in the treatment of growing pains?

McNaughten B, Arch Dis Child. 2018 Feb;103(2):203-205

- **Growing pains** is a poorly understood condition and the pathogenesis remains uncertain.

- Estimates of the **prevalence** of growing pains in the UK range **from 2% to 37%.**

- There are **no diagnostic tests** or definitive diagnostic criteria.

- Diagnosis is made clinically on the presence of **typical features and exclusion of symptoms and signs which may point to an underlying pathology** requiring further investigation.

- It has been suggested that **hypovitaminosis D may contribute** to the development of growing pains.

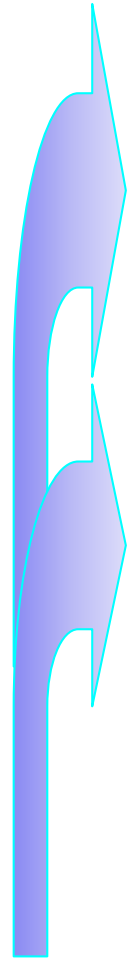
Classification	Serum 25-hydoxy vitamin D (nmols/l)
Deficiency	<25
Insufficiency:	25-50
Sufficiency:	50-125

Is vitamin D useful in the treatment of growing pains?

McNaughten B, Arch Dis Child. 2018 Feb;103(2):203-205

✓PubMed and Medline (1946–present) using the key words: 'Vitamin D' AND 'child* OR adoles*' AND 'growing pains'.

✓The PubMed search yielded 14 results:
5 articles for full-text review



➢It is possible that some children presenting with unexplained lower limb pain may have these symptoms secondary to low vitamin D levels. (Grade C)

➢Vitamin D supplementation in those found to have low vitamin D levels may be associated with pain reduction in those suffering from growing pains. (Grade C)

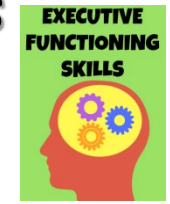
Linking vitamin D status, executive functioning and self-perceived mental health in adolescents through multivariate analysis: A randomized double-blind placebo control trial.

Grung B, Scand J Psychol. 2017;58(2):123-130.

✓50 adolescents were randomly assigned into an intervention group (vitamin D pearls/38μg/die) (1520 IU) or a control group (placebo pearls).

✓Before (pre-test in December/January) and after (post-test in April/May) the intervention period the participants were exposed to a test procedure, consisting of blood draw, completion of cognitive tests (Tower of Hanoi and Tower of London), and the Youth Self-report version of the Child Behavior Checklist.

- participants with low vitamin D status scored worse on the Tower of London tests (planning) and the more difficult sub-tasks on the Tower of Hanoi tests (problem-solving).



- They also had a tendency to report higher frequency of externalizing behavior problems and attention deficit.

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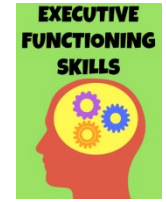
•the intervention group (1520 IU/die for 4 months) improved their performance on the most demanding sub-tasks on the ToH.



•overall, the study indicates that vitamin D status in adolescents may be important for both executive functioning and mental health.

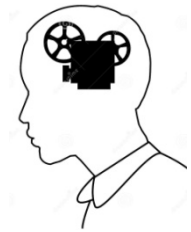
Does high dose vitamin D supplementation enhance cognition?: A randomized trial in healthy adults.

Pettersen JA. Exp Gerontol. 2017;90:90-97.

✓Healthy adults (n=82) from northern British Columbia, Canada (54° north latitude) with baseline 25(OH)D levels ≤100nmol/L randomized and blinded to High Dose (4000IU/d) versus Low Dose (400IU/d) vitamin D3 (cholecalciferol) for 18weeks.

✓Baseline and follow-up serum 25(OH)D and cognitive performance assessed and the latter consisted of: Symbol Digit Modalities Test, verbal (phonemic) fluency, digit span, and the CANTAB® computerized battery

•Nonverbal (visual) memory seems to benefit from higher doses of vitamin D supplementation, particularly among those who are insufficient (<75nmol/L) at baseline, while verbal memory and other cognitive domains do not.



•These findings are consistent with recent cross-sectional and longitudinal studies, which have demonstrated significant positive associations between 25(OH)D levels and nonverbal, but not verbal, memory.

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- ✓ Autoimmunity
- ✓ Other Diseases
- ✓ **Conclusions**

Dietary guidelines for calcium and vitamin D: a new era.

Abrams SA. Pediatrics. 2011 Mar;127(3):566-8.

Selected Calcium and Vitamin D DRI Values for Children and Adolescents

Age	Calcium, mg/d		Vitamin D, IU/d	
	Recommended Intake[a]	Tolerable UL	Recommended Intake[a]	Tolerable UL
0–6 mo	200	1000	400	1000
6–12 mo	260	1500	400	1500
1–3 y	700	2500	600	2500
4–8 y	1000	2500	600	3000
9–18 y	1300	3000	600	4000

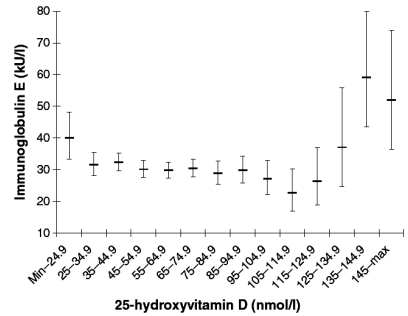
[a] Recommended intake values are the RDA values for children aged 1 year and older and AI values for infants younger than 1 year.

- Advising families that they do not need to give their children dietary or supplemental vitamin D, because there is abundant sunshine, is inappropriate advice and should be abandoned even in southern climates.

- Educational efforts are urgently needed in this regard because of limited compliance with current recommendations

Conclusions

- Vitamin D is a vitamin/hormone with genomic effects that are involved in fetal development and immune function maturation.



- As observed with all hormones both low and high levels are dangerous, but only 1/3 of people is VitD sufficient.

- There is accumulating evidence that appropriate levels of vitamin D (30-40 ng/mL) are useful for the primary prevention of allergic and autoimmune diseases development.

- Supplementation of vitamin D reduce the risk of respiratory infections, improves control of allergic/autoimmune diseaes and is necessary at all ages and not only in infancy.

- Vitamin D has many other functions besides calcium metabolism!!!!

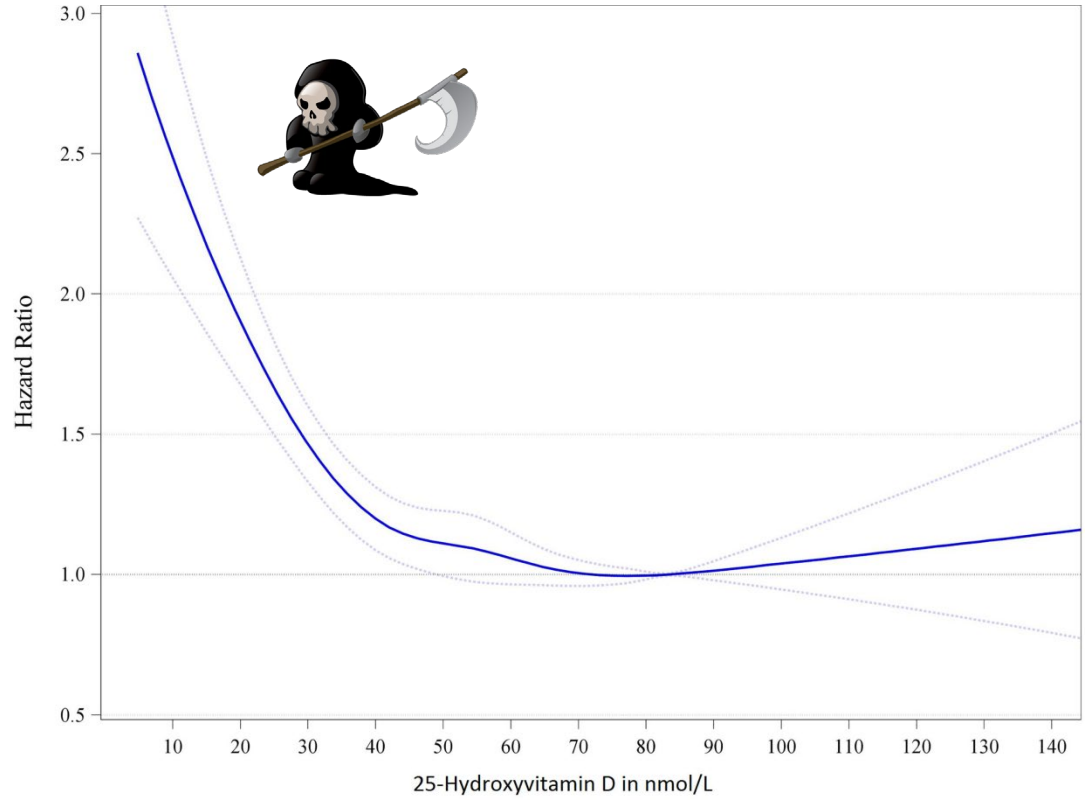
Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium.

Gaksch M, PLoS One. 2017;12(2):e0170791.

✓26,916 study participants (median age 61.6 years, 58% females) with a median 25(OH)D concentration of 53.8 nmol/L.

✓During a median follow-up time of 10.5 years, 6802 persons died.

Dose-response trend of hazard ratios of death from all causes by standardized 25-hydroxyvitamin D.



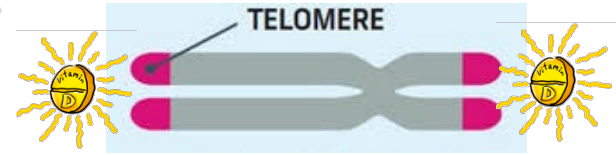
Serum 25-Hydroxyvitamin D Has a Modest Positive Association with Leukocyte Telomere Length in Middle-Aged US Adults. *Beilfuss J. J Nutr. 2017;147(4):514-520.*

✓data from the US NHANES 2001-2002
[1542 young adults (aged 20-39 y), 1336 middle-aged adults (aged 40-59 y), and 1382 older adults (aged ≥60 y)].

✓**Leukocyte telomere length** measured by quantitative polymerase chain reaction.

✓Serum 25(OH)D ≥50 nmol/L were considered optimal.

•In the participants aged 40-59 y, an increment in serum 25(OH)D of 10 nmol/L was associated with a 0.03- ± 0.01-kbp longer LTL, *(P = 0.001)*.



•In the same age group, 25(OH)D concentrations ≥50 nmol/L were associated with a 0.13- ± 0.04-kbp longer LTL than those for 25(OH)D concentrations <50 nmol/L *(P = 0.01)*.

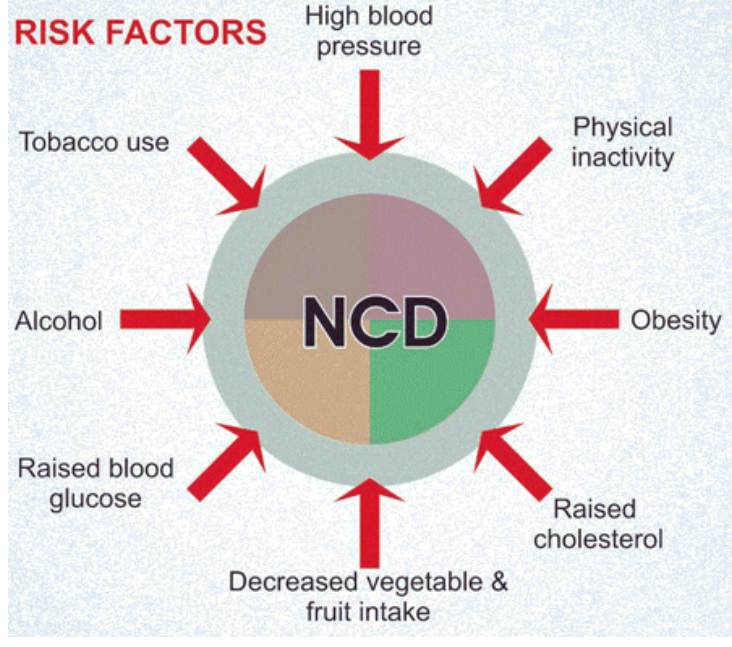
Lifestyle Choices Fuel Epidemics of Diabetes and Cardiovascular Disease Among Asian Indians.

O'Keefe EL, Prog Cardiovasc Dis. 2016;58(5):505-13.

❑India is suffering a rising epidemic of non-communicable diseases (NCDs), including coronary artery disease, type 2 diabetes mellitus, and stroke.

❑The alarming outbreak of cardiovascular disease are due to negative lifestyle factors such as:

- a diet high in added sugar, refined grains and other processed foods,
- physical inactivity,
- vitamin D deficiency,
- smoking/pollution.



Vitamin D deficiency was the cause

Courtesy of Holick MF