Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

- ✓ **Introduction**
- ✓ Immunomodulation related to allergy
- ✓ Fetal development
- ✓ 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

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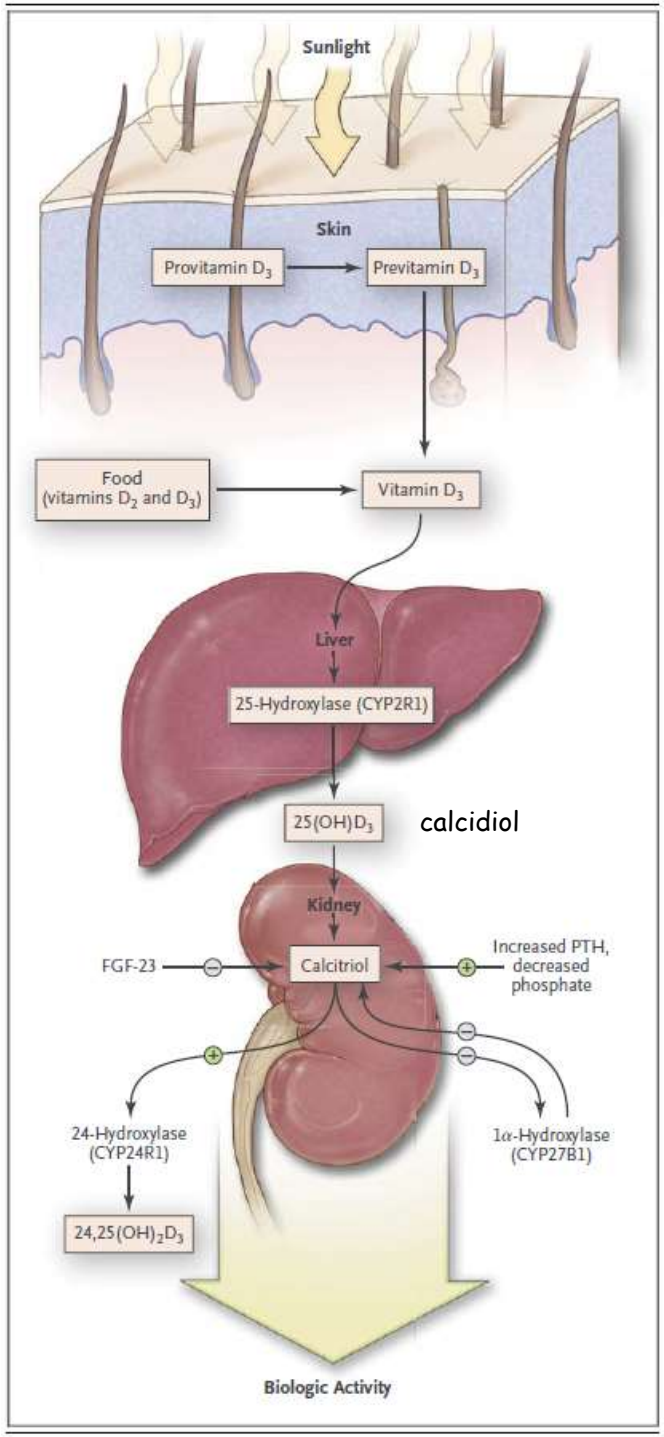
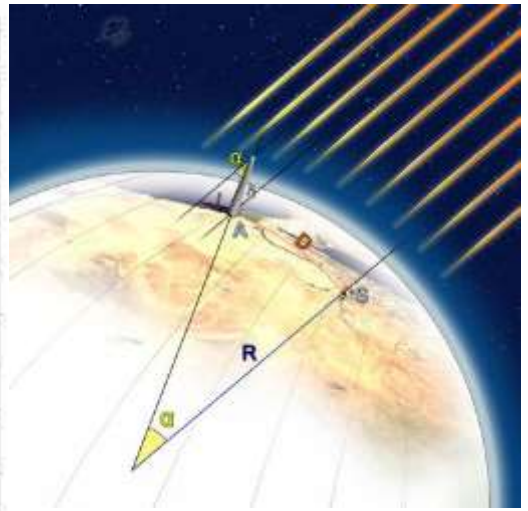
Synthesis and Metabolism of Vitamin D.

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.





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

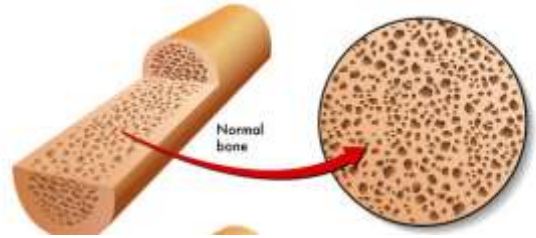
Global Consensus Recommendations on Prevention and Management of Nutritional Rickets

Munns CF. J Clin Endocrinol Metab. 2016;101:394–415.

Vitamin D status

classification of vitamin D status, based on serum 25-hydroxyvitamin D (25OHD) levels:

- Sufficiency, >50 nmol/L (> 20 ng/mL)
- Insufficiency, 30–50 nmol/L (12-20ng/mL)
- Deficiency, <30 nmol/L (<12 ng/mL)



Vitamin D toxicity

- Toxicity is defined as hypercalcemia and serum 25OHD > 250 nmol/L (100ng/mL) with hypercalciuria and suppressed PTH

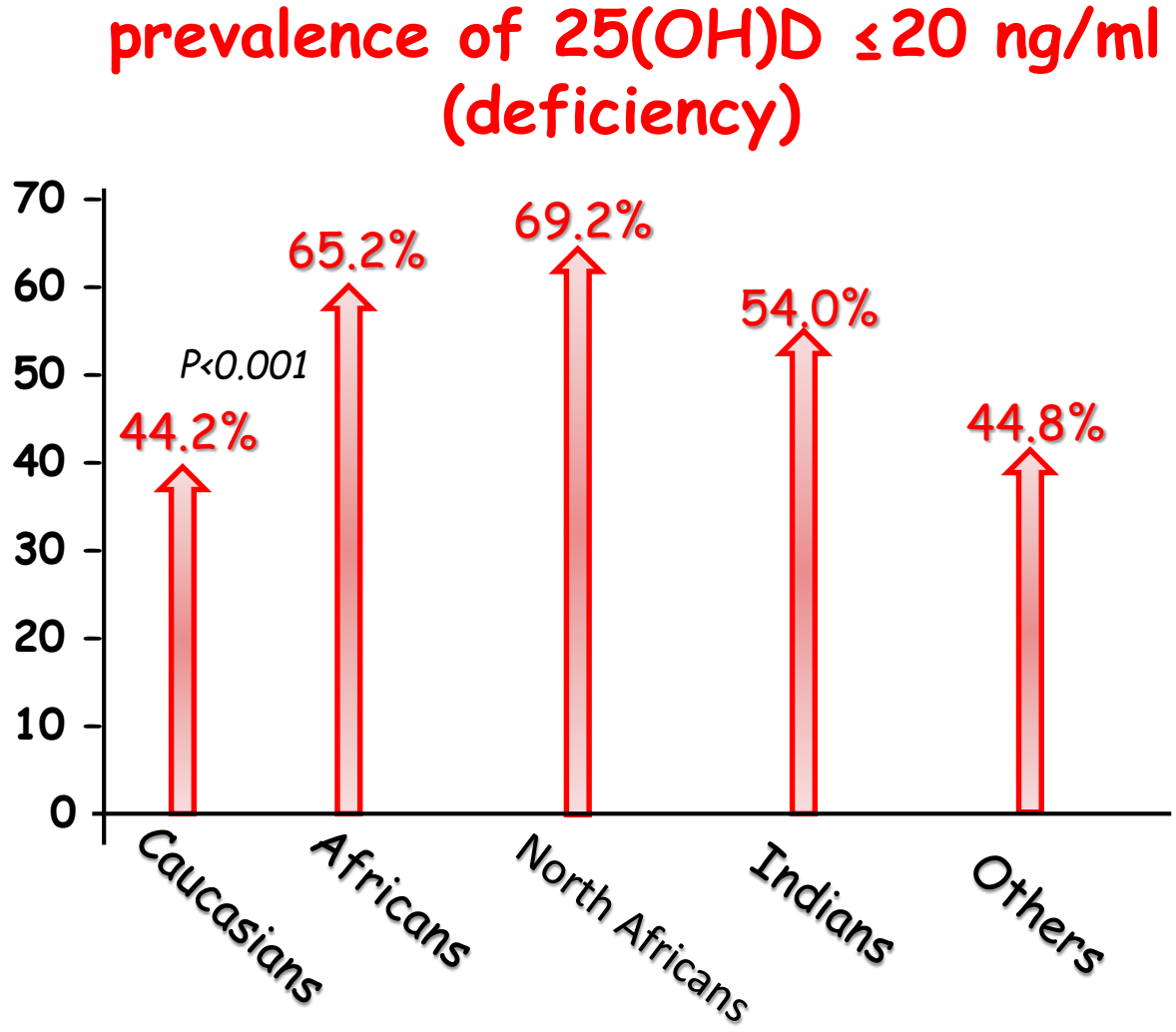
To convert 25-OH vitamin D concentrations from nanomoles per liter to ng/mL, devide by 2.496.

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)



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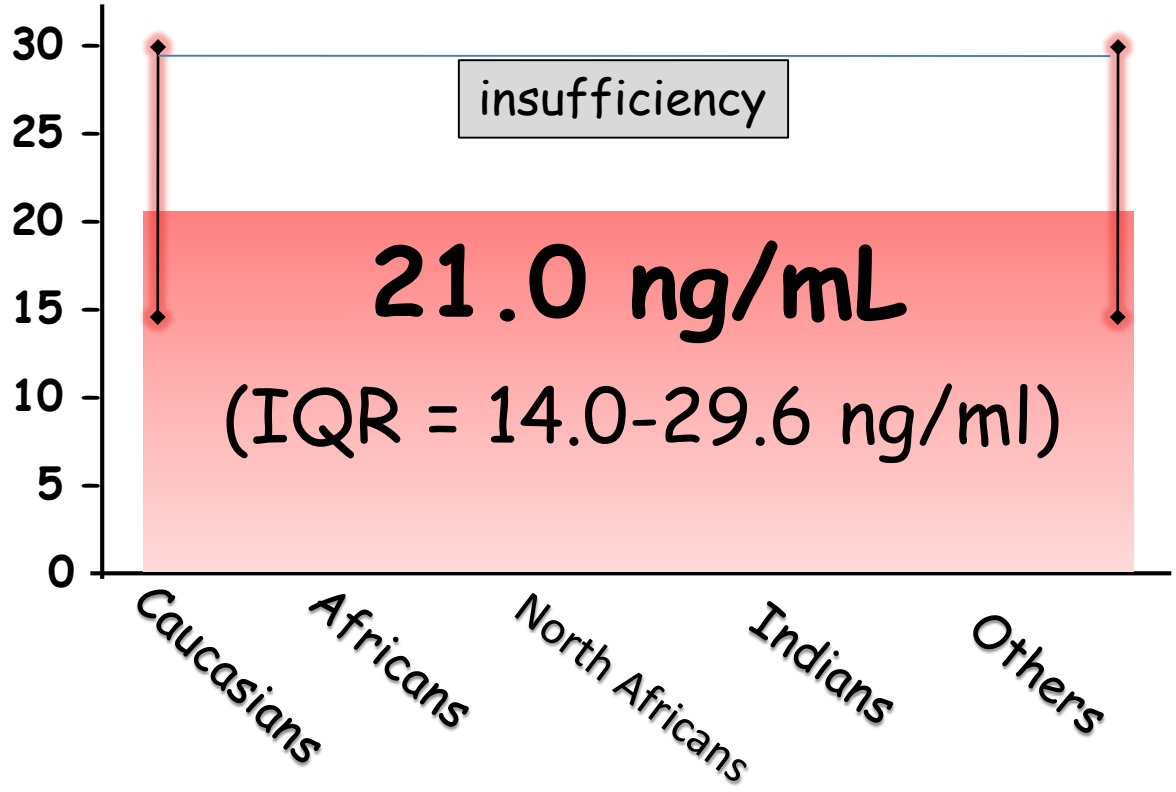
Median 25(OH)D ng/ml for the entire cohort



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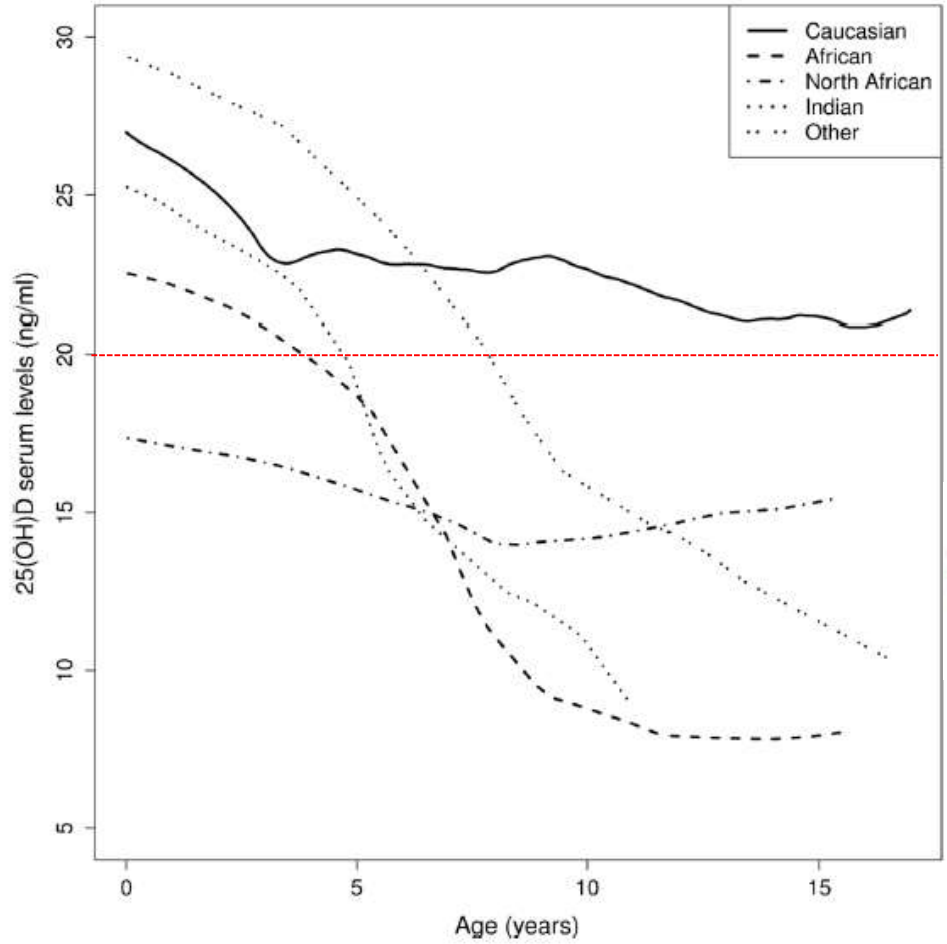
Mean serum levels of 25(OH)D as a function of age and by ethnicity



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. [Epub ahead of print]

✓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)*.

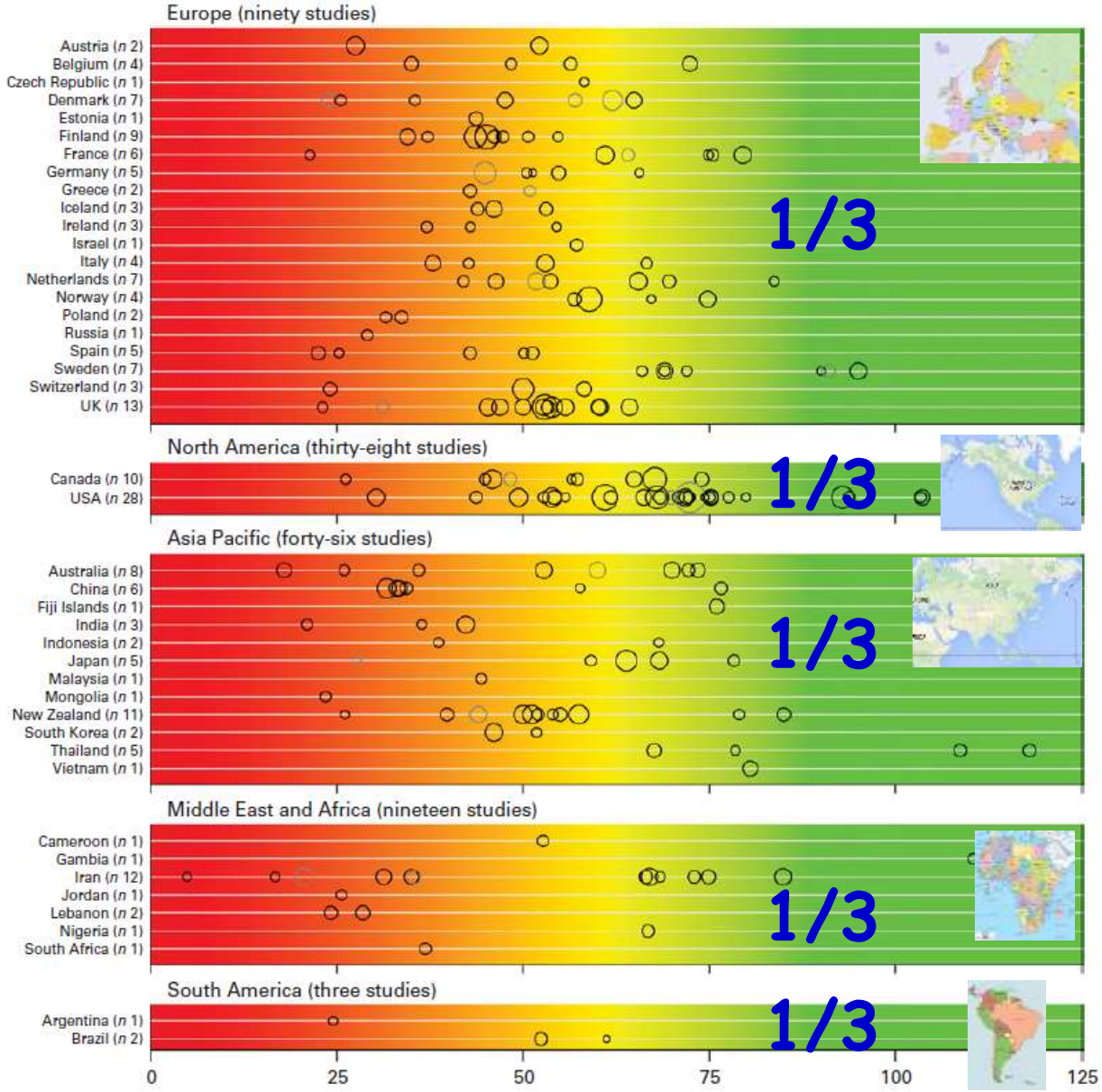
Approximately one-quarter of circulating cobalamin (vitamin B-12) binds to transcobalamin (holoTC) and is thereby available for the cells of the body. For this reason, holoTC is also referred to as active vitamin B-12.

A systematic review of vitamin D status in populations worldwide. *Hilger J. British J Nut 2014;111:23-45.*

✓25-hydroxyvitamin D (25(OH)D) levels in 195 studies conducted in 44 countries involving more than 168 000 participants.

✓median 25-hydroxyvitamin D (25(OH)D) values, by geographical region and country.

✓values falling within the intensely red zone are most consistent with severe vitamin D deficiency; those in the green zone reflect adequate vitamin D levels (≥ 75 nmol/L). Values within the yellow zone are those thought to be indicative of insufficiency



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

	Calcium		Vitamin D		100 IU=2.5μg
Life-stage group (age and gender)	RDA (mg/d) (intake that covers needs of ≥97.5% of population)	UL (mg/d)[a]	RDA (IU/d) (intake that covers needs of ≥97.5% of population)	Serum 25OHD level (ng/ml) (corresponding to the RDA)[b]	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

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

Maternal Preferences for Vitamin D Supplementation in Breastfed Infants. *Umaretiya PJ, Ann Fam Med. 2017;15:68-70.*

✓140 mothers with exclusively breastfed infants, and 44 who used both breast and formula milk

✓maternal preferences for vitamin D supplementation

- Only 101 **(55%)** had supplemented their infants with vitamin D in the preceding week (median 5 d/wk), and
- 77 infants **(42%)** received the 400 IU recommended.
- A total of 134 **(73%)** reported that their clinician had recommended infant vitamin D supplementation

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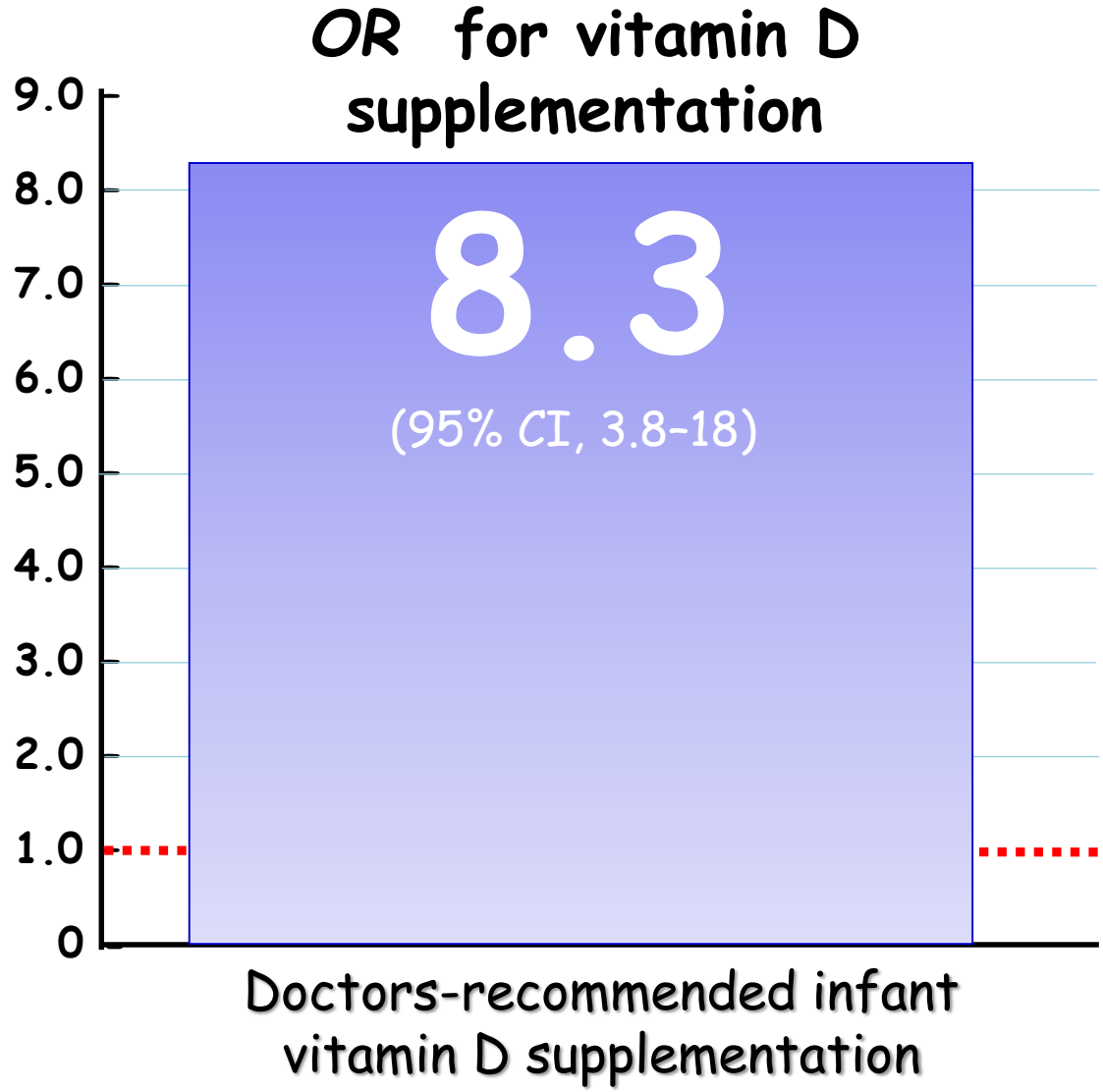

Maternal Preferences for Vitamin D Supplementation in Breastfed Infants. *Umaretiya PJ, Ann Fam Med. 2017;15:68-70.*

Regarding reasons for not supplementing infants with vitamin D, many mothers indicated:

1) lack of knowledge about supplementation,

2) some believed that breast milk provided infants with adequate vitamin D,

3) others chose not to supplement because of inconvenience or their infant's apparent dislike of the supplement.

Themes	Quotes
Lack of knowledge about supplementation	"I didn't know I should"
	"Too young – will start soon"
	"Never even knew vitamin D supplementation was needed"
Assumption that fortified milk provides infant with needed vitamin D	"I gave vitamin D supplement when she was breast milk-fed, provider told us to discontinue when formula started"
	"My baby went to exclusive soy formula at 2 months old, which has vitamin D supplement"
	"Baby formula has all that is needed and recommended"
	"Stopped giving it when I stopped nursing and started to give formula"
Assumption that breast milk provides infant with needed nutrition	"Find it hard to believe the whole population is so deficient in Vitamin D, especially in breast milk"
	"I feel like my breast milk was designed by God to give my baby what she needs. Babies have been fine and healthy without Vitamin D supplementation for generations"
Inconvenience/ Dislike	"It causes her to spit up"
	"I forget to because she doesn't take it well and doesn't seem to like the taste"

Maternal Preferences for Vitamin D Supplementation in Breastfed Infants. *Umaretiya PJ, Ann Fam Med. 2017;15:68-70.*

The great majority of breastfeeding mothers (88.4%) preferred supplementing themselves rather than their infants with vitamin D.

if infant is not receiving 400 IU/d and is breastfed the mother's requirement, is 4,000–6,000 IU/d
Holick MF, J Clin Endocrinol Metab 2011;96:1911–30.

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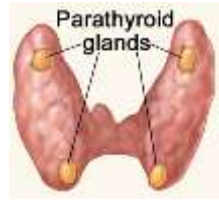
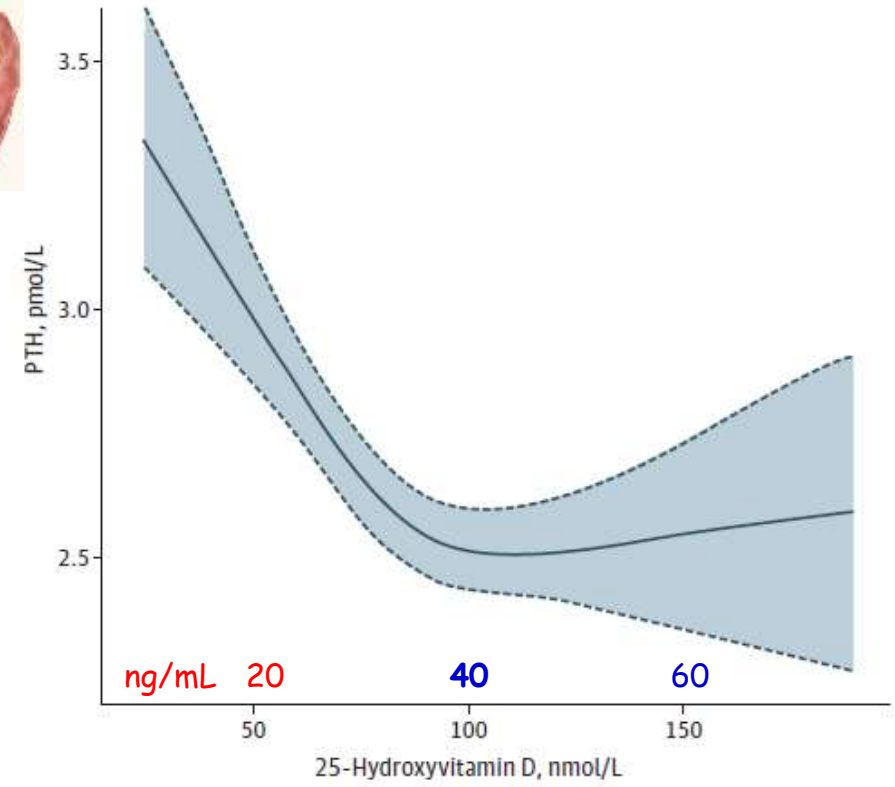
Parathyroid Hormone as Functional Indicator of Vitamin D Sufficiency in Children

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

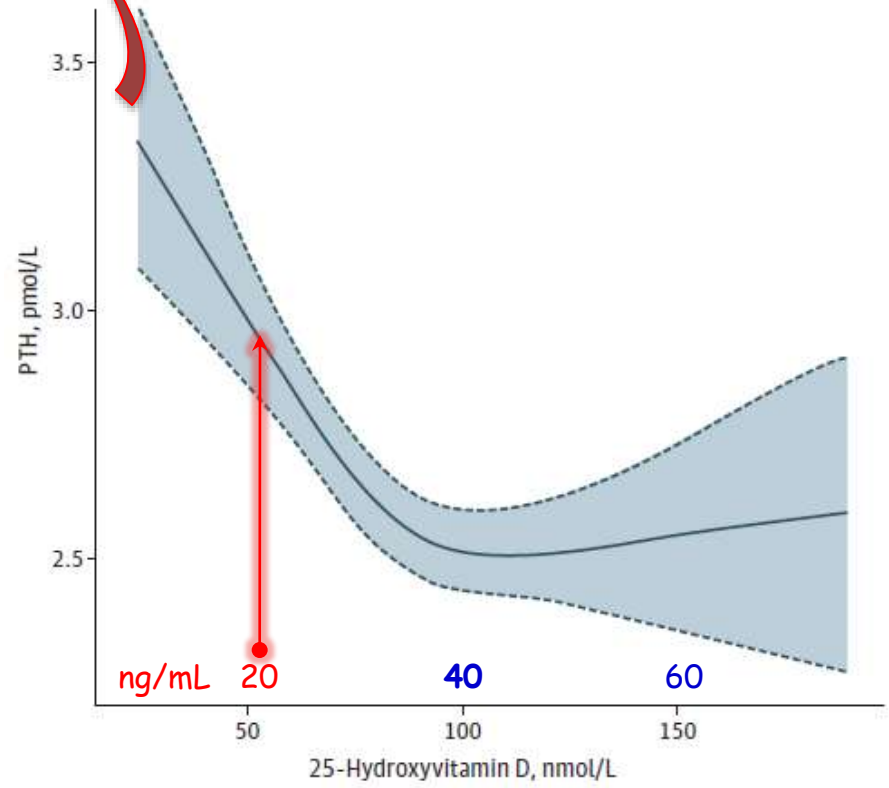
Maguire JL, JAMA Ped 2014;168;383-384

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

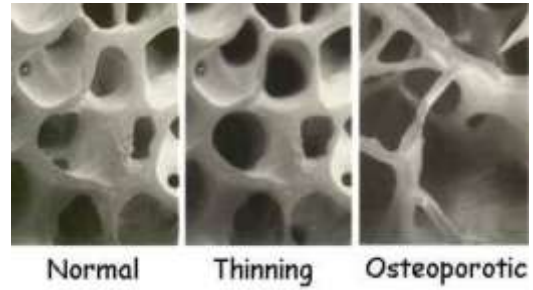
Plot of the Regression Model for 25-Hydroxyvitamin D and Parathyroid Hormone (PTH)



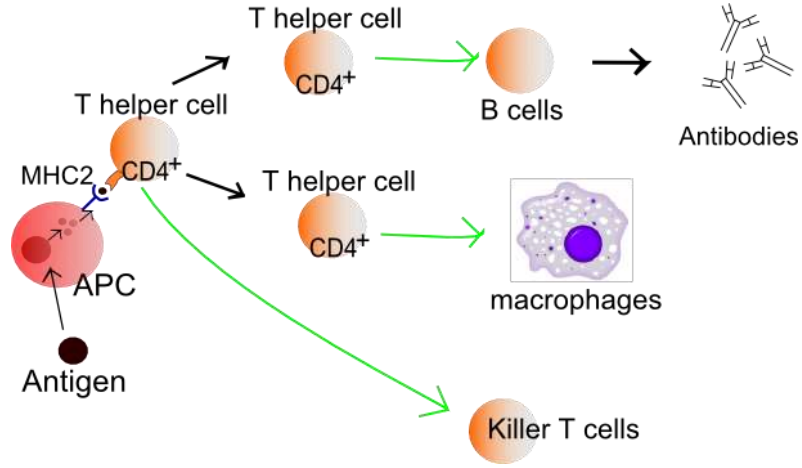
Shaded areas inside the dashed lines represent 95% confidence intervals.

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.*

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- ✓Other diseases
- ✓Conclusions

Vitamin D and immunomodulation related to allergy

Vitamin D has immunomodulatory effects on allergen induced inflammatory pathways

Hossein-nezhad A, Mayo Clin Proceed Mayo Clin 2013; 88:720–55.

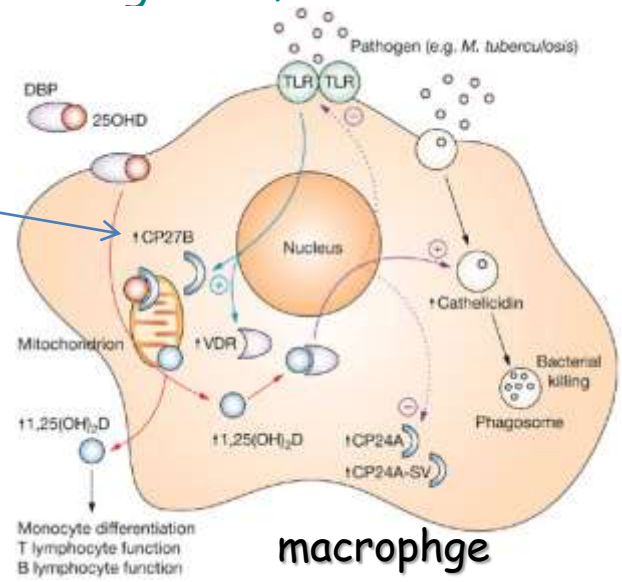
25OHD → 1,25OHD

Many cells, such as activated macrophages and dendritic cells, are capable of synthesizing biologically active vitamin D from circulating 25OHD.

- *Adams JS, Nat Clin Pract Endocrinol Metab 2008;4:80–90.*
- *Barbour GL, New Engl J Med 1981;305:440-3.*
- *Adams JS, J Clin Investig 1983;72:1856–60.*

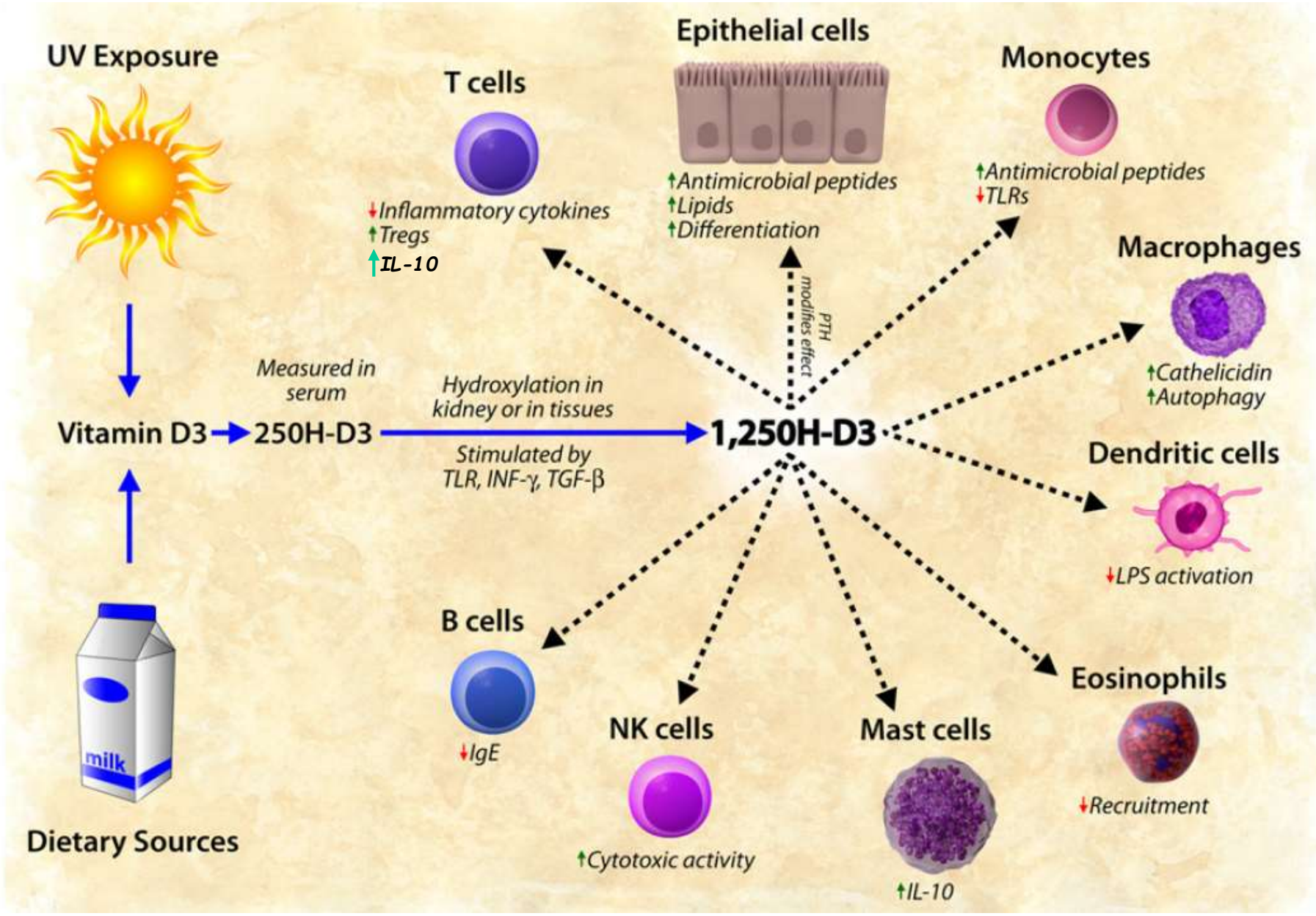
The **extrarenal expression of CP27B1 (25OHD-1hydroxylase)**, enables immune cells to rapidly increase local levels of vitamin D, potentially needed to shape adaptive immune responses.

Baeke F, Curr Opin Pharmacol 2010; 10:482–96.



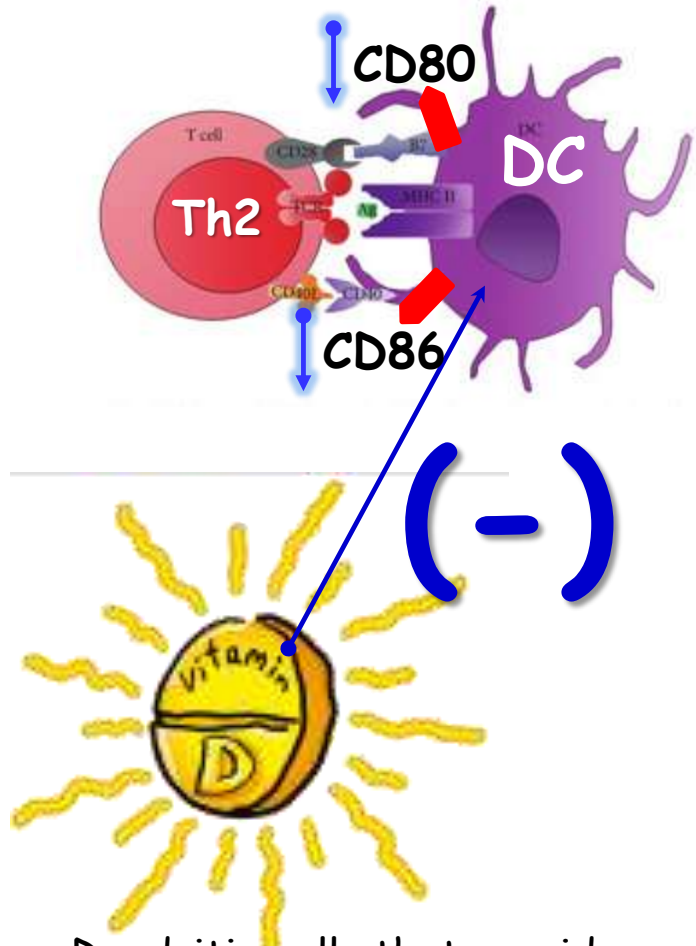
macrophge

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



Vitamin D regulates immunoglobulin mucin domain molecule-4 expression in dendritic cells.

Liu ZQ, Clin Exp Allergy. 2017 [Epub ahead of print]



BACKGROUND:
Dendritic cell (DC)-derived immunoglobulin domain molecule (TIM)4 (CD80, CD86) plays a critical role in the initiation of T helper (Th)2 polarization. Vitamin D (VitD) involves the regulation of a number of immune responses.

OBJECTIVES:
This study tests a hypothesis that VitD regulates TIM4 expression in DCs.

(TIM4: T cell immunoglobulin mucin domain molecule-4)
Cluster of differentiation 80,86 (also **CD80, CD86**) is a protein found on Dendritic cells that provides a costimulatory signal necessary for T cell activation and survival.

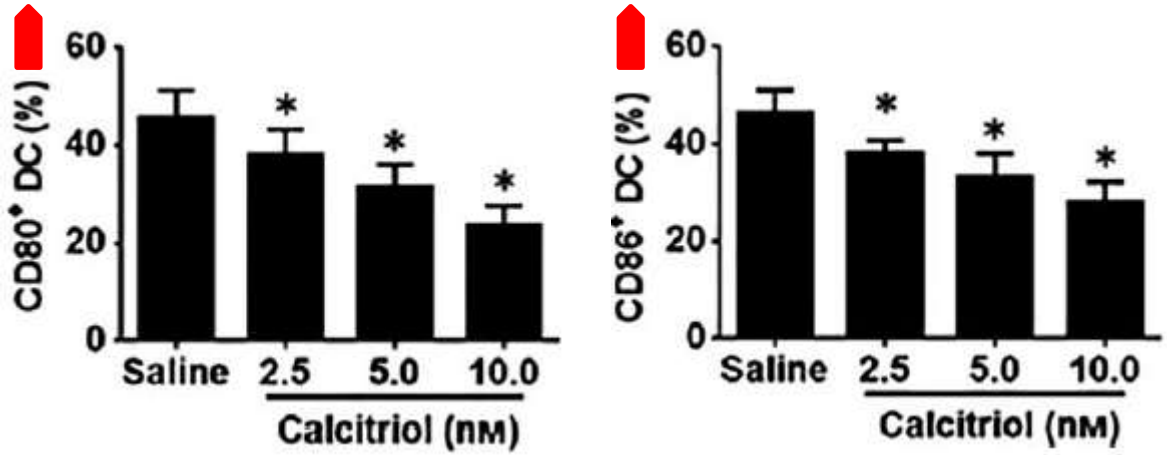
Vitamin D regulates immunoglobulin mucin domain molecule-4 expression in dendritic cells.

Liu ZQ, Clin Exp Allergy. 2017 [Epub ahead of print]

✓Peripheral blood samples from patients with allergic rhinitis and healthy subjects.

✓Dendritic cell (DCs) isolated from the samples and analyzed for the expression of TIM4 (CD80, CD86)

in DCs a negative correlation was identified between the data of serum calcitriol (1,25-dihydroxyvitamin D_3) and TIM4 (CD80, CD86) which provide costimulatory signals necessary for T cell activation and survival



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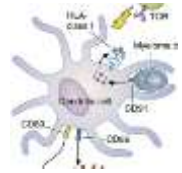
TIM4 (CD80, CD86) in DCs.



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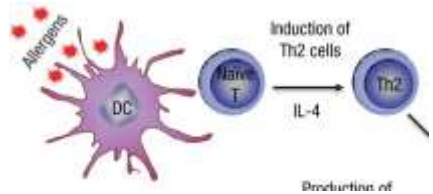
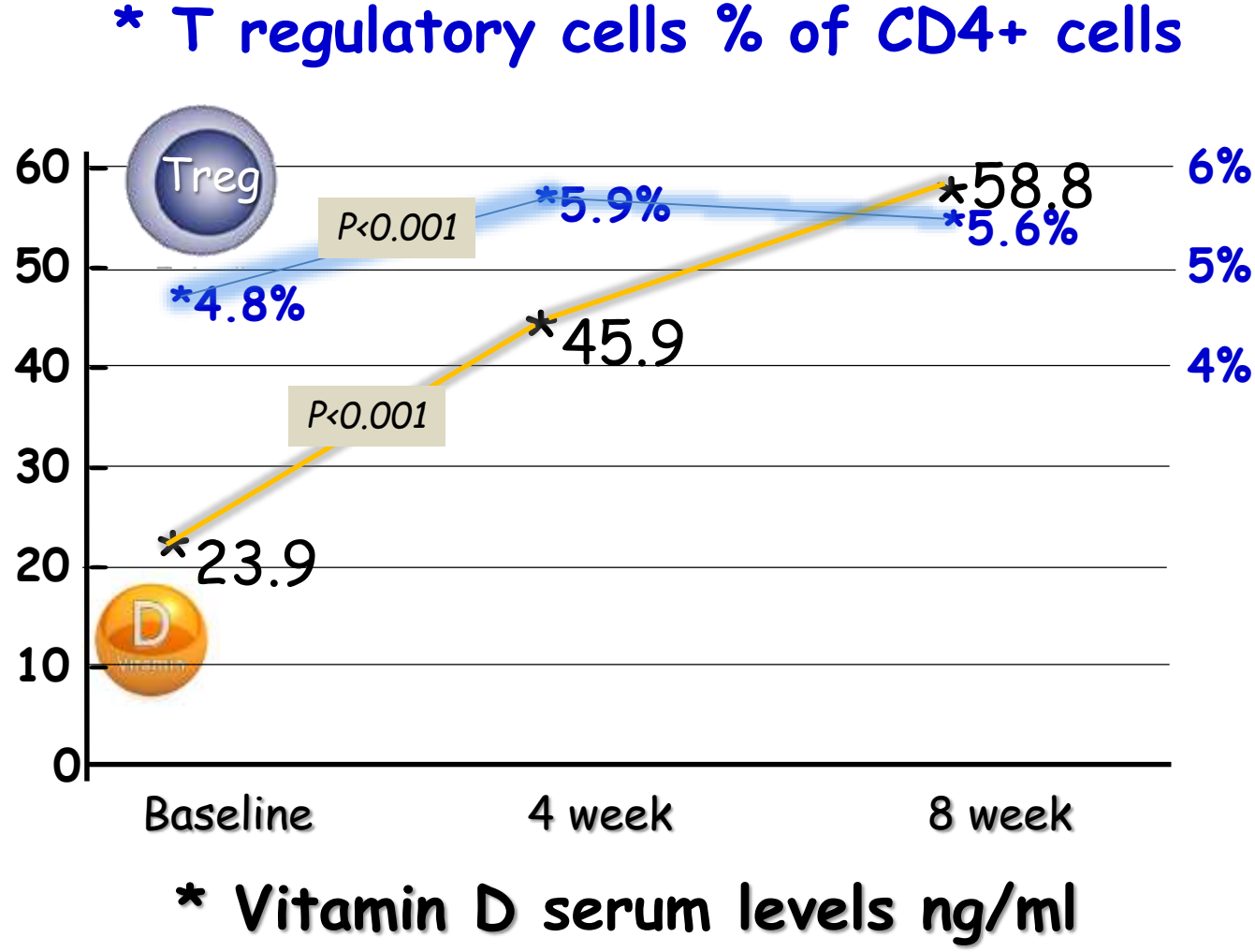
T helper (Th)2 polarization



Vitamin D supplementation and regulatory T cells in apparently healthy subjects: vitamin D treatment for autoimmune diseases? *Prietl B, Isr Med Assoc J. 2010;12:136-9.*

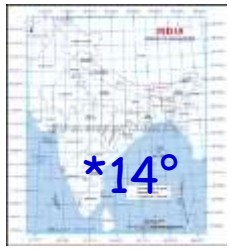
- ✓46 apparently healthy subjects
- ✓Oral supplementation of Vitamin D 140,000 IU at baseline and after 4 weeks.
- ✓follow-up visit 8 weeks after the baseline examination.



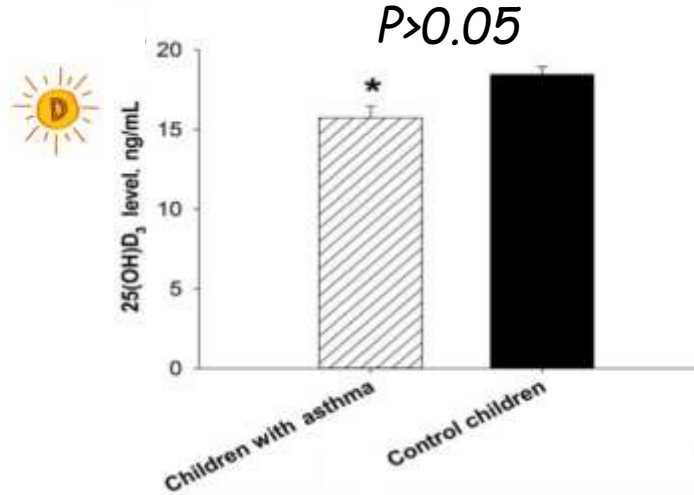
Association of T-regulatory cells and CD23/CD21 expression with vitamin D in children with asthma

Chary AV Ann Allergy Asthma Immunol 2016;116:447-454

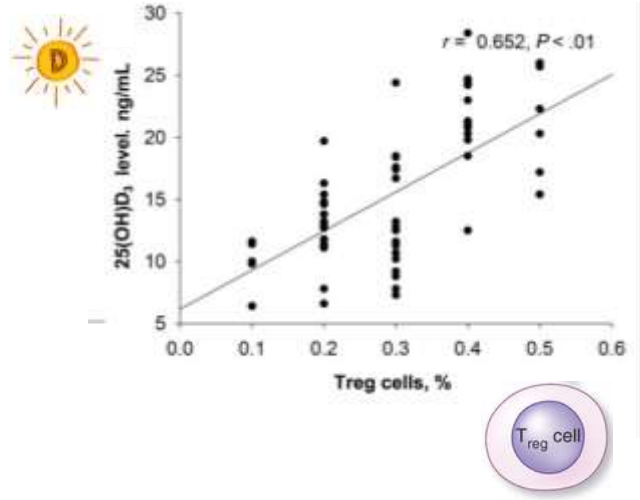
- ✓60 children (2-6 years old) with asthma and 60 age-matched healthy children



- ✓Treg cells and CD23/CD21 (IgE receptors) by flow cytometry
- ✓25[OH]D3 by high-performance liquid chromatography



25(OH)D3 concentrations in asthmatic and control children



Correlation of 25(OH)D3 and Treg cells.

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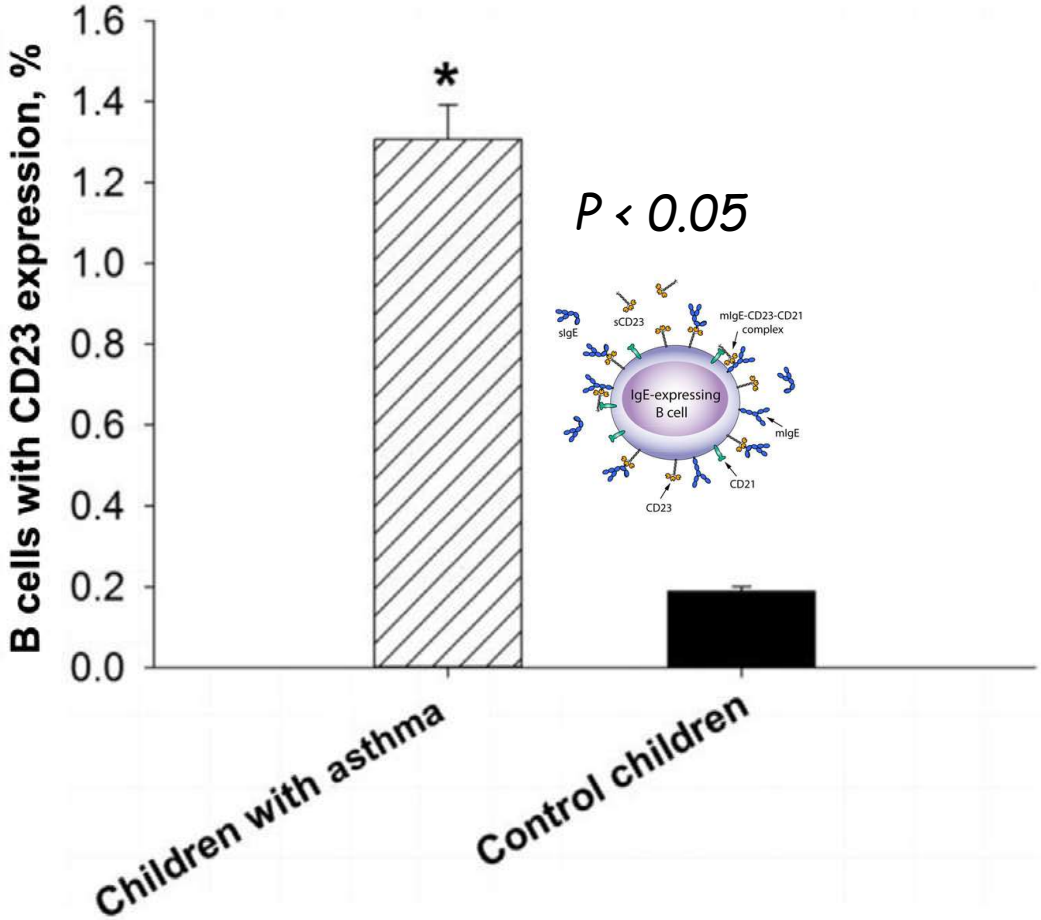
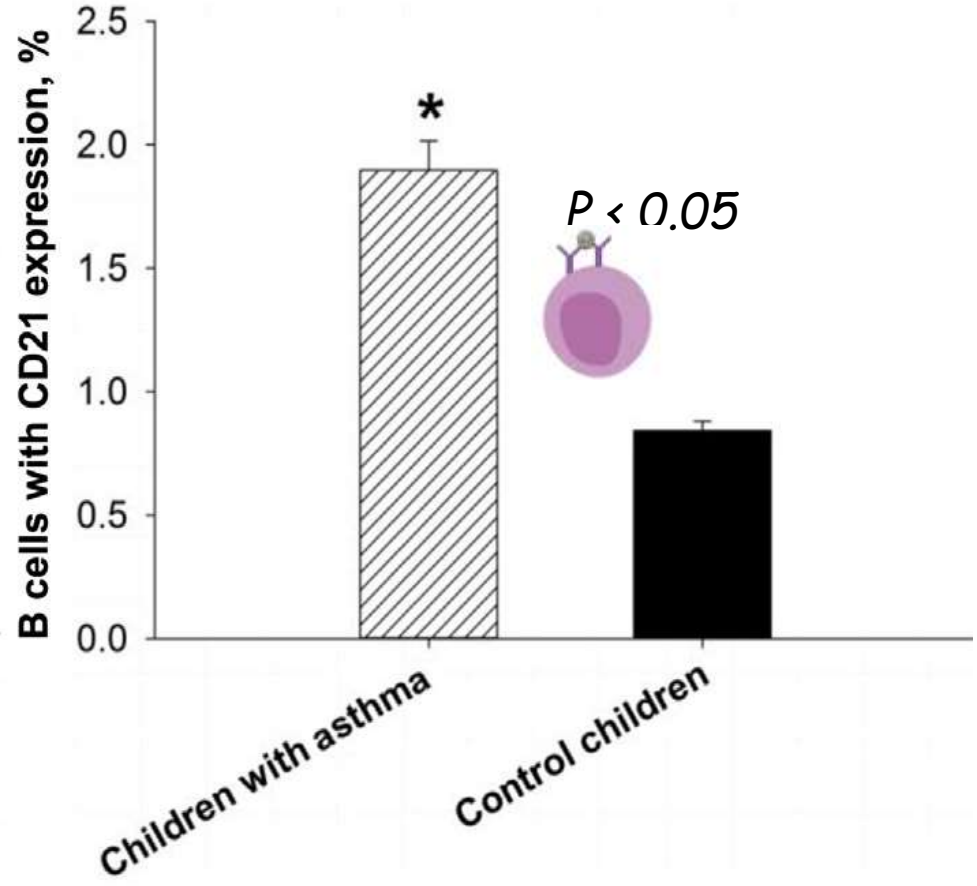
B cells with CD23
(IgE receptor) expression



B cells with CD21
(IgE receptor) expression



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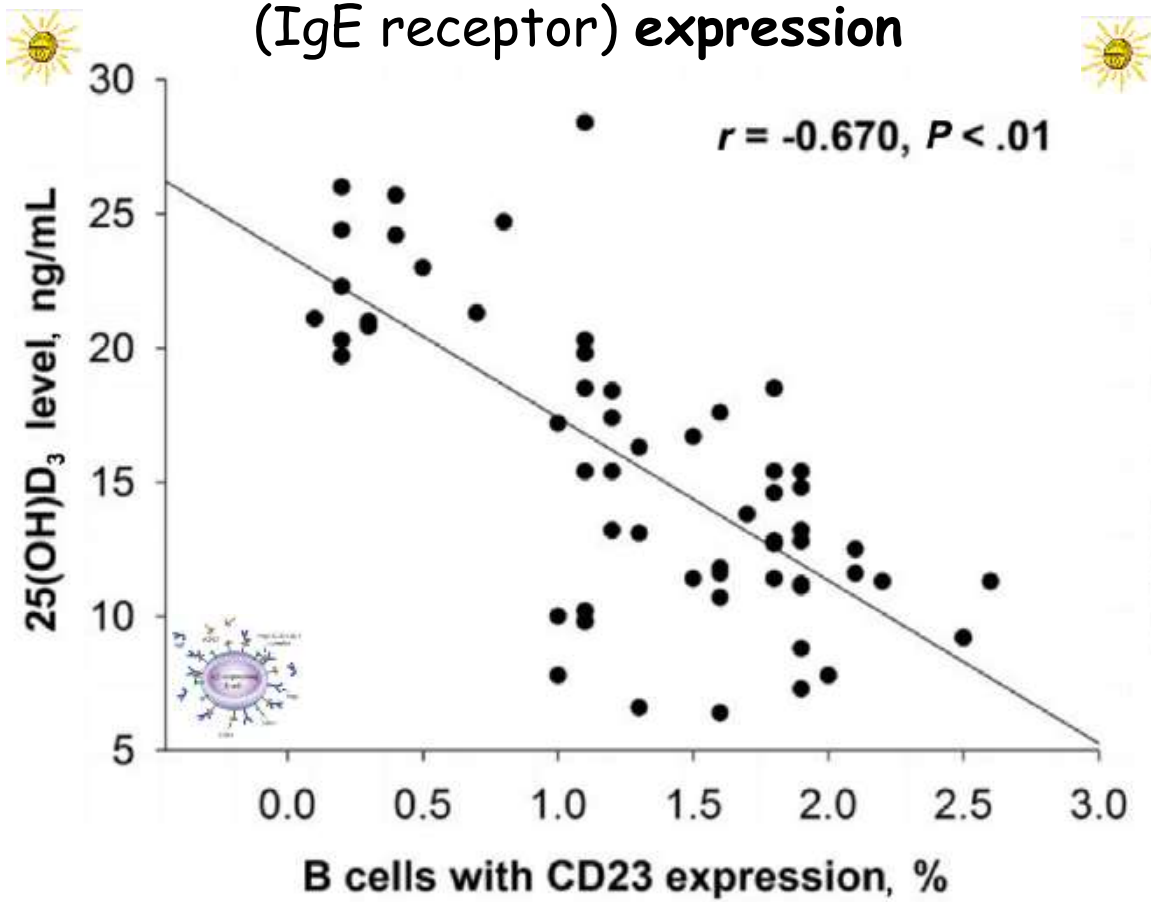
Correlation of 25(OH)D3 and B cells with CD23 (IgE receptor) **expression**



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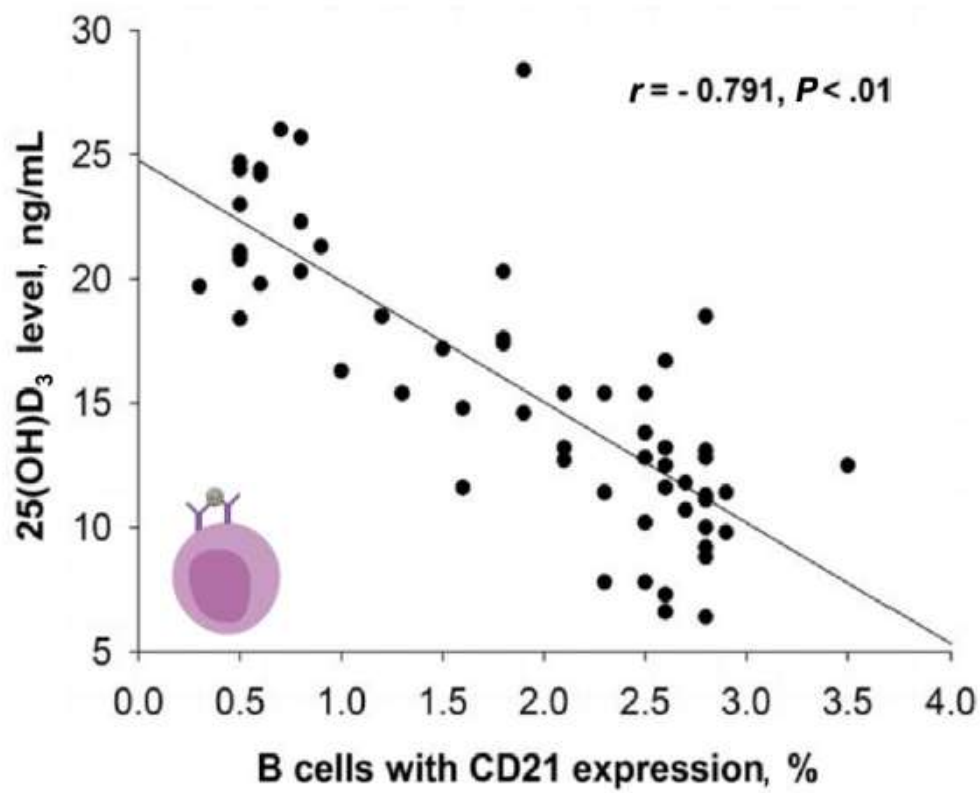
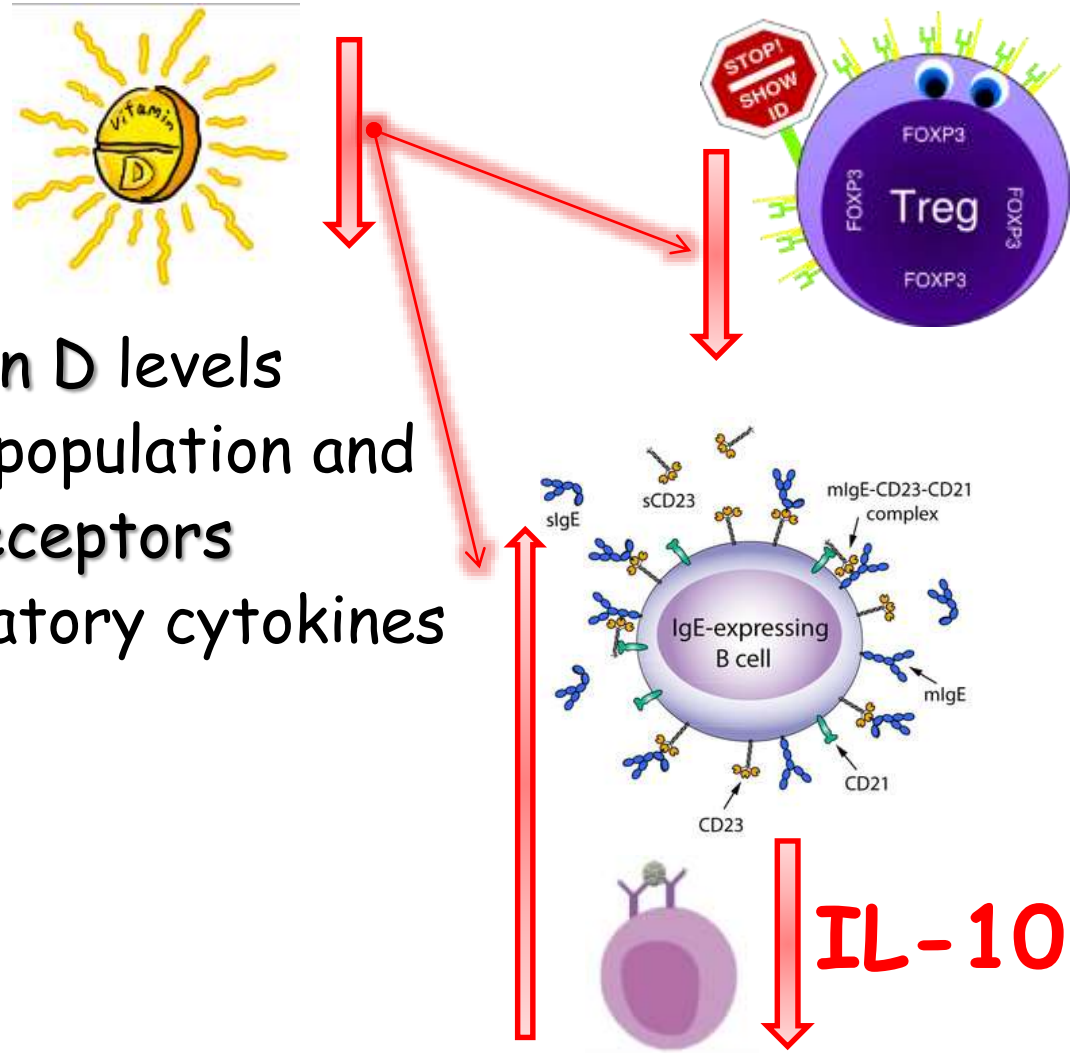


Association of T-regulatory cells and CD23/CD21 expression with vitamin D in children with asthma

Chary AV Ann Allergy Asthma Immunol 2016;116:447-454

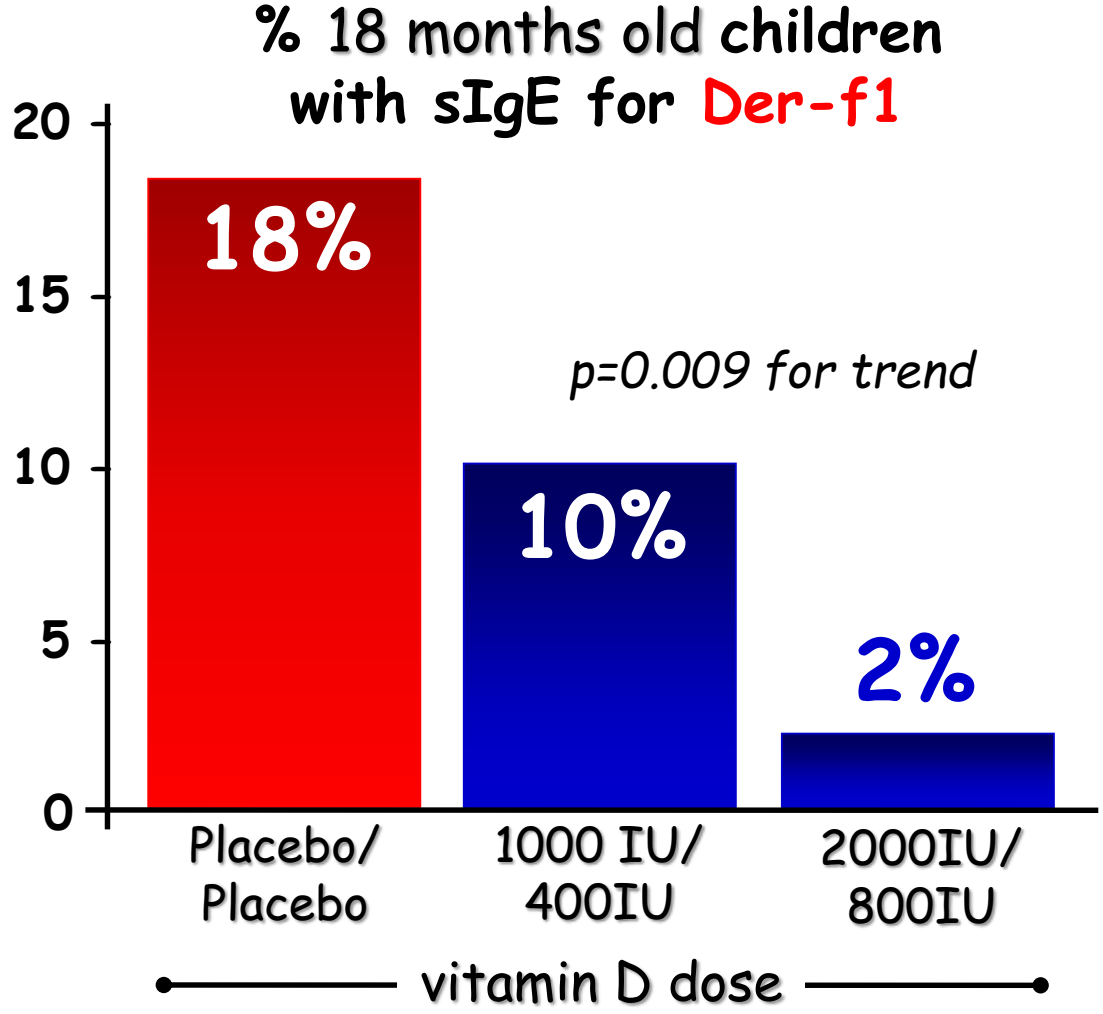
Conclusion:

The current study found low vitamin D levels associated with impaired Treg cell population and high numbers of B cells with IgE receptors (CD23 and CD21) and altered regulatory cytokines in children with asthma, suggesting impaired immune regulation.



Vitamin D supplementation during pregnancy and infancy reduces aeroallergen sensitization: a randomized controlled trial *Grant C.C. Allergy 2016;71:1325-34*

- ✓ Pregnant women, from 27-week gestation to birth, and then their infants, from birth to 6 months, randomized to placebo or one of two dosages of daily oral vitamin D.
- ✓ Placebo/placebo, 1000 IU/400 IU or 2000 IU/800 IU.
- ✓ serum-sIgE in children 18 months old.

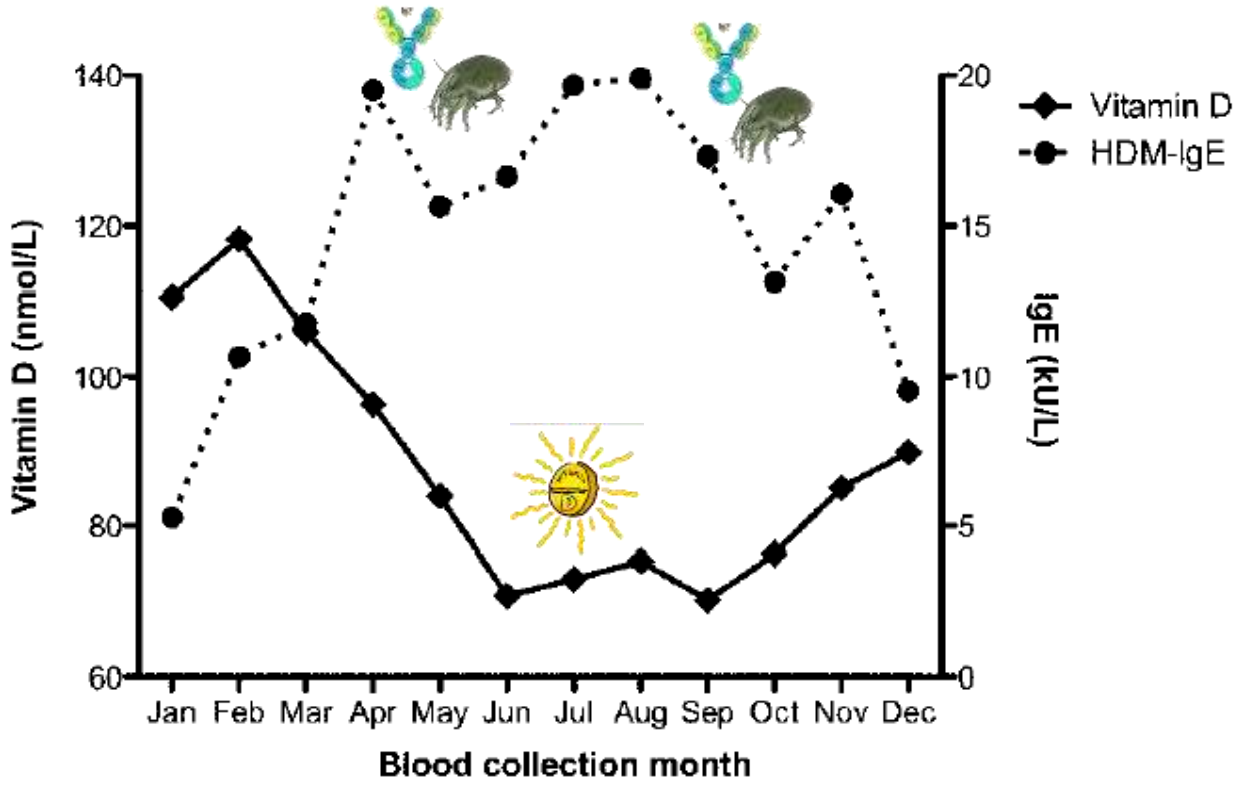


Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study.

Hollams EM, Eur Respir J. 2011;38:1320-27.

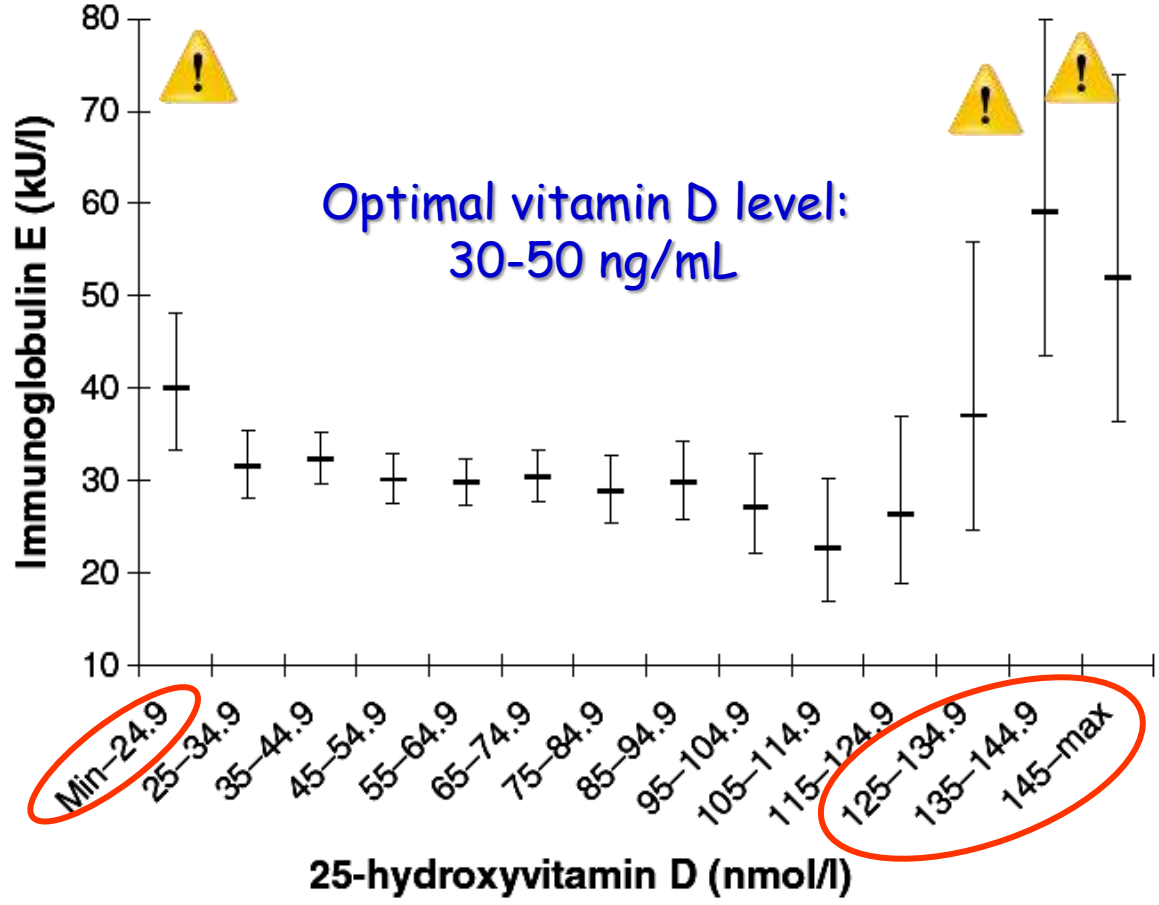
- ✓an unselected community birth cohort in Australia
- ✓6-year-olds (n=989) and 14-year-olds (n=1380);
- ✓associations between vitamin D status and biological signatures indicative of allergy and asthma development in children aged 6 and 14 years

Mean vitamin D levels and mean HDM-IgE titers combined over the three year period



Serum 25-hydroxyvitamin D and IgE a significant but nonlinear relationship *Hyppönen Allergy 2009;64:613*

- ✓ 9377 participants in the 1958 British birth cohort.
- ✓ Assessment at 45 years of age.



Variation in the average immunoglobulin E by 25-hydroxyvitamin D concentration in the 1958 British cohort at the age of 45 years.

Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

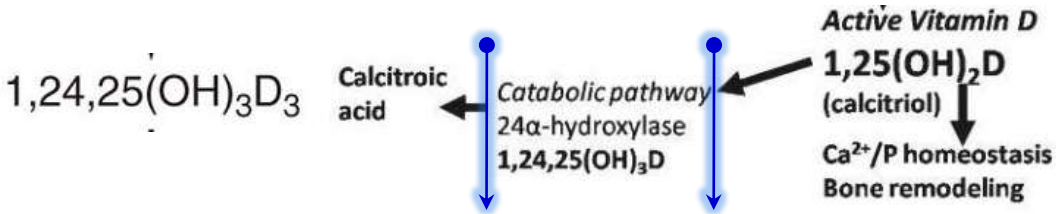
Attilio Boner
University of Verona, Italy
attilio.boner@univr.it

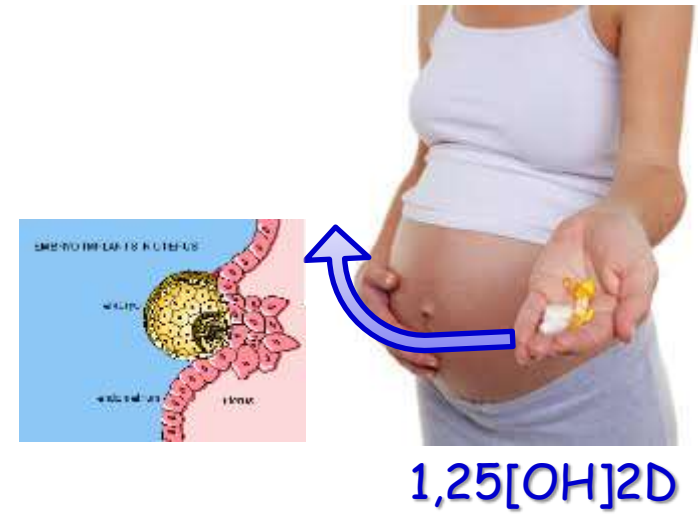
- ✓ Introduction
- ✓ Immunomodulation related to allergy
- ✓ **Fetal development**
- ✓ Prevention and modification of asthma & COPD
- ✓ Prevention and modification of allergic rhinitis
- ✓ Prevention and modification of atopic dermatitis
- ✓ Prevention and modification of food allergy anaphylaxis, urticaria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

Vitamin D in pregnancy and foetal development

- Active vitamin D (1,25[OH]2D) dramatically rises during pregnancy, with levels reaching up to 124% to 135% of normal values which may promote proper foetal implantation (by enhancing Treg cells) and regulates placental development.

- *Papapetrou PD. Hormones 2010;9:136–44.*
- *Brannon PM, Annu Rev Nut 2011;31:89–115.*
- *Liu NQ, Arch Biochem Biophys 2012; 523:37–47.*
- *Rebut-Bonneton C, Gynecol Obstet Invest 1991;32:134–8.*





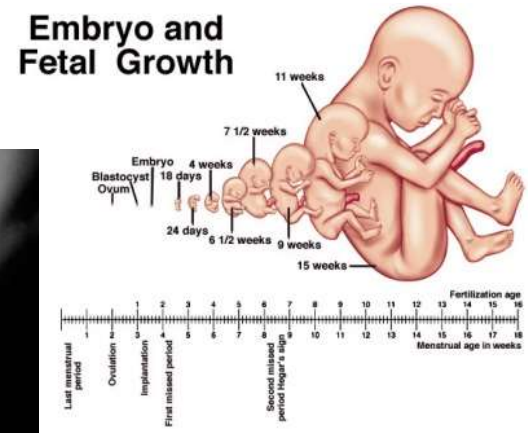
1,25[OH]2D

Mirzakhani H. Clin Exp All 2015;45:114

Vitamin D in pregnancy and foetal development

- Vitamin D is necessary for normal foetal development and organ function.

Brannon PM. Proc Nutr Soc 2012;71:205–12.



- Several observational studies suggest that low 25OHD level promotes intrauterine growth restriction and low birth weight and has modest effects on preterm birth.

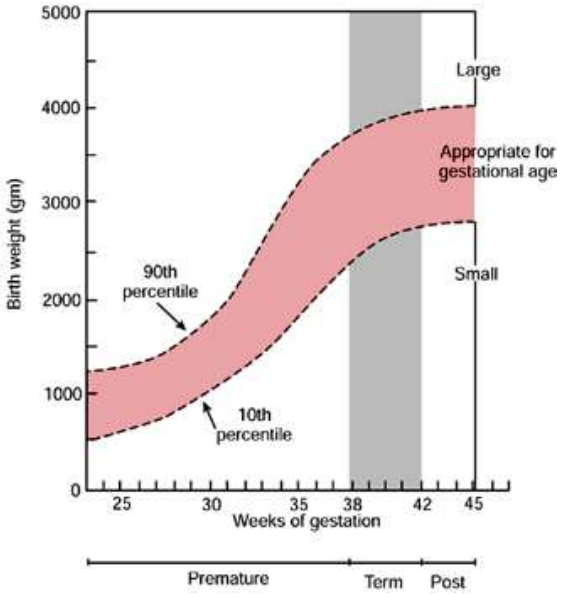
Gernand AD, J Clin Endocrinol Metabolism 2013;98:398–404.
Gernand AD, J Clin Endocrinol Metabolism 2013;98:398–404.

Mirzakhani H. Clin Exp All 2015;45:114

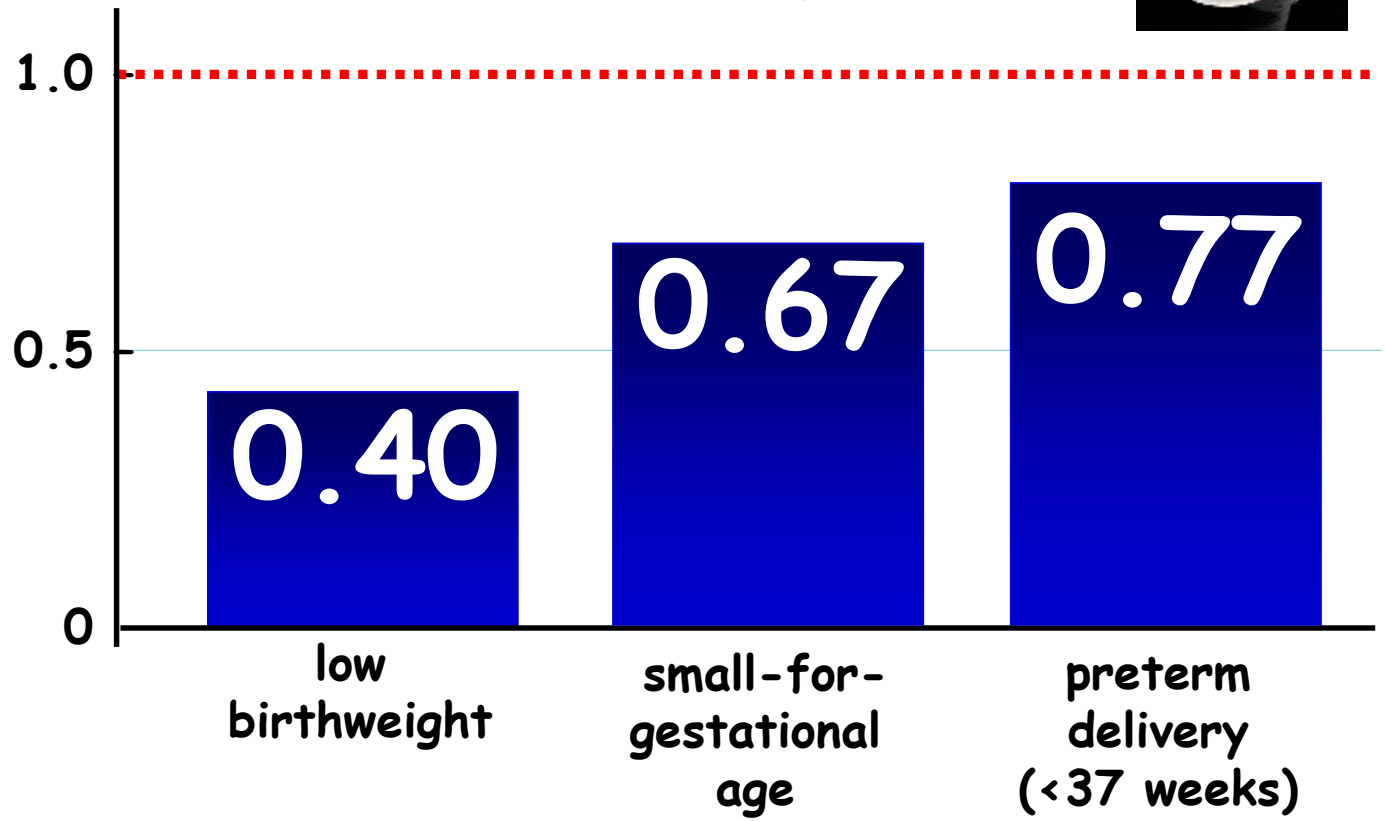
Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis.

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.



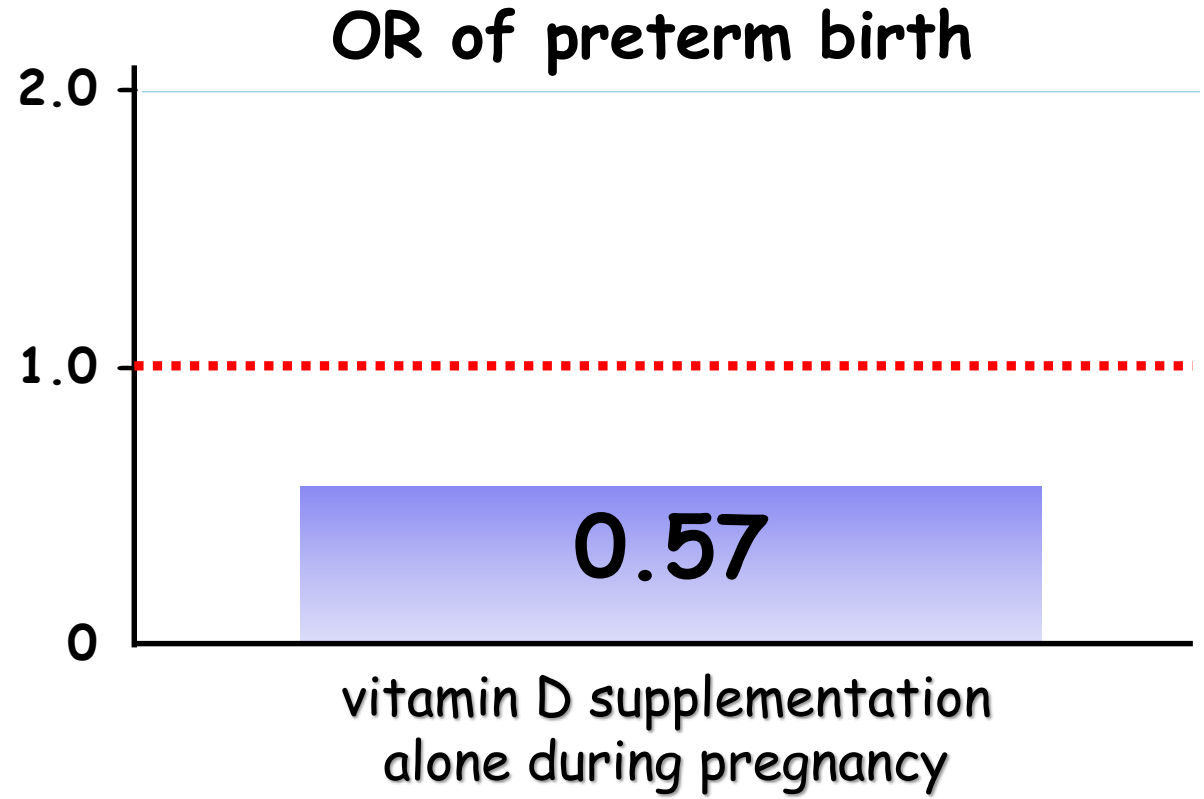
In vitamin D supplemented mother RR for



Vitamin D and risk of preterm birth: Up-to-date meta-analysis of randomized controlled trials and observational studies.

Zhou SS, J Obstet Gynaecol Res. 2017;43(2):247-256.

✓ 24 articles
(6 RCT and
18 observational
studies)



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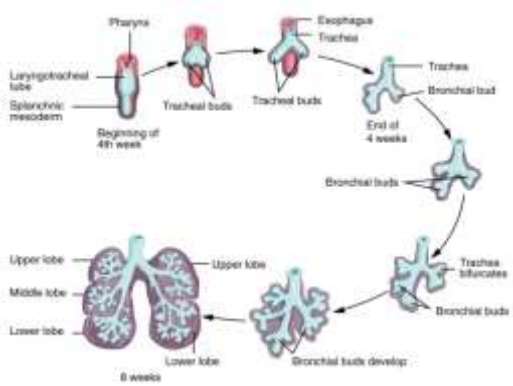
- ✓ Conclusions

Vitamin D and lung development

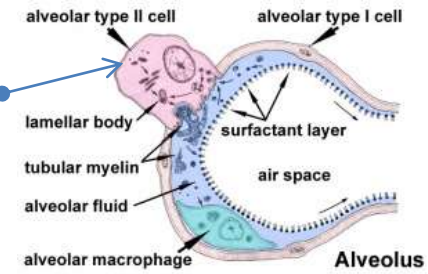


- Vitamin D influence fetal lung development.

  Liu NQ, Arch BiochemnBiophys 2012;523:37–47.

- Experimental evidence in rats show that foetal alveolar type II epithelial cells express VDR, suggesting that pulmonary maturation is responsive to vitamin D exposure . *Nguyen TM, Endocrinology 1990;127:1755–62.*
  Marin L, Am J Physiol 1993;265:L45–52.
  Marin L, Biol Neonate 1990; 57:257–60.

Type II (Great Alveolar) cells that secrete pulmonary surfactant



- A number of genes associated with the vitamin D pathway are differently expressed during human foetal lung development

  Kho AT, BMC Med Genomics 2013;6:47.

Mirzakhani H. Clin Exp All 2015;45:114

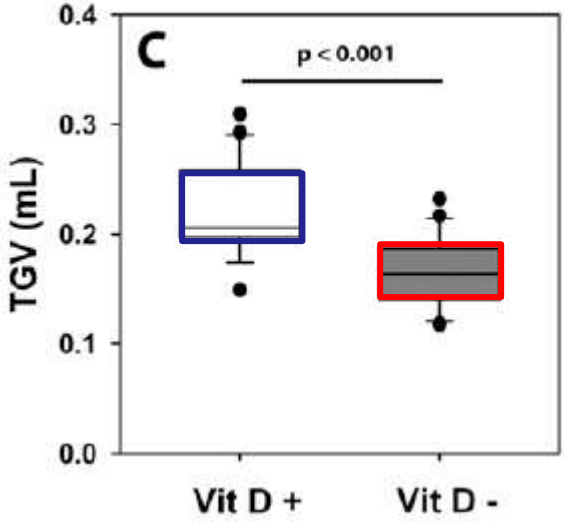
Vitamin D deficiency causes deficits in lung function and alters lung structure. *Zosky GR, AJRCCM. 2011;183:1336-43.*

standard vitamin D sufficient diet

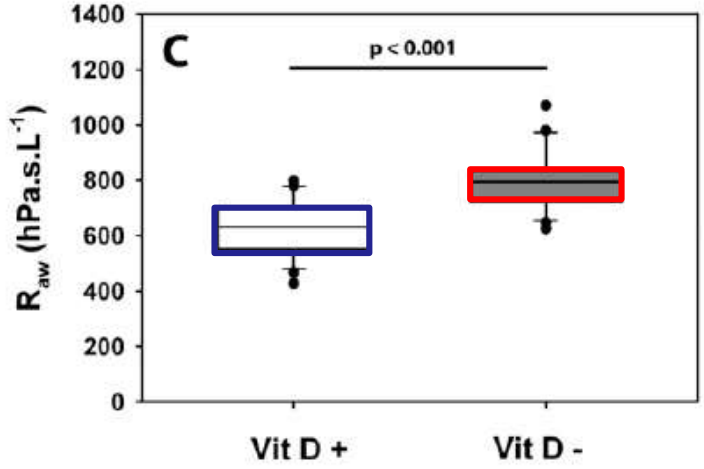
mouse model of vitamin D deficiency by dietary manipulation

Elastance is a measure of the tendency of a hollow organ to recoil toward its original dimensions upon removal of a distending or compressing force. It is the reciprocal of compliance.

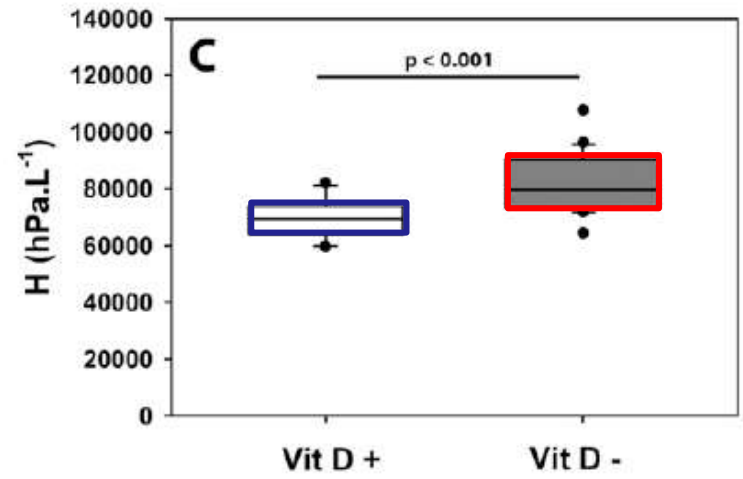
thoracic gas volume



airway resistance



tissue elastance



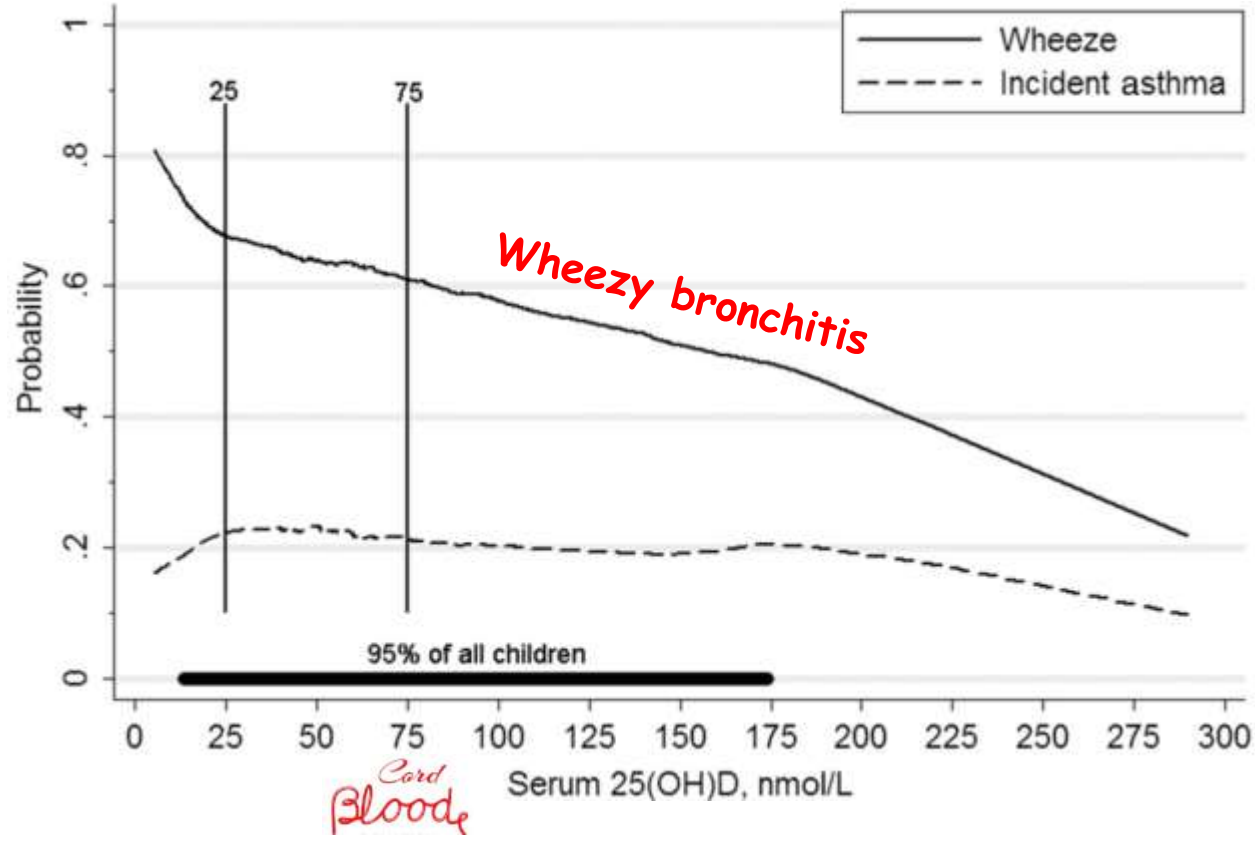
Cord-Blood 25-Hydroxyvitamin D Levels and Risk of Respiratory Infection, Wheezing, and Asthma

Camargo C. Pediatrics 2011;127:180

- ✓ 25(OH)D in cord blood from 922 newborns.
- ✓ History of respiratory infection at 3 mo of age or a history of wheezing at 15 mo and then annually thereafter.
- ✓ Doctor-diagnosed asthma by age 5 years.

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

Associations of cord-blood 25(OH)D levels with probabilities of cumulative wheeze or incident asthma by 5 years of age

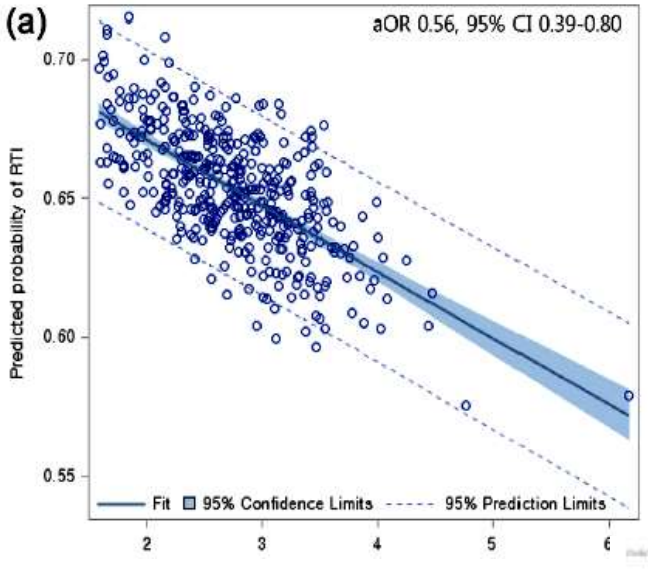


Interaction between 25-hydroxyvitamin D and variants at 17q12-21 on respiratory infections

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

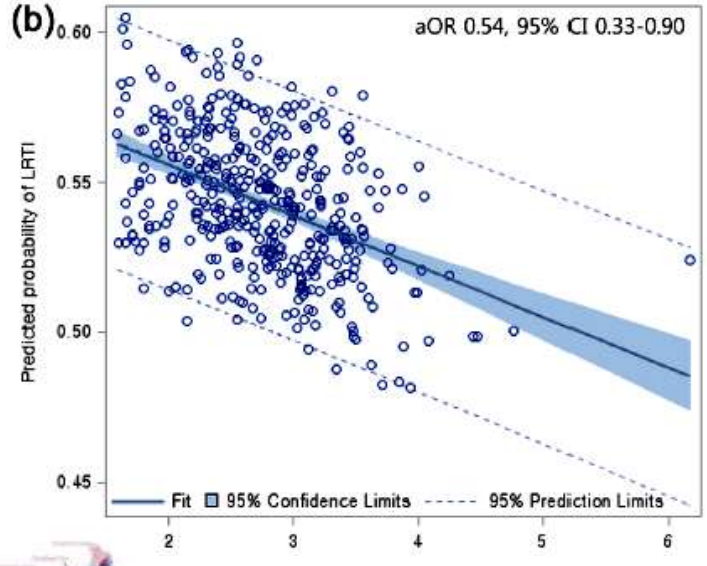
Relationship between cord-blood 25(OH)D levels and within the first year of life, predicted probability of:

respiratory
respiratory-tract infections (RTIs)



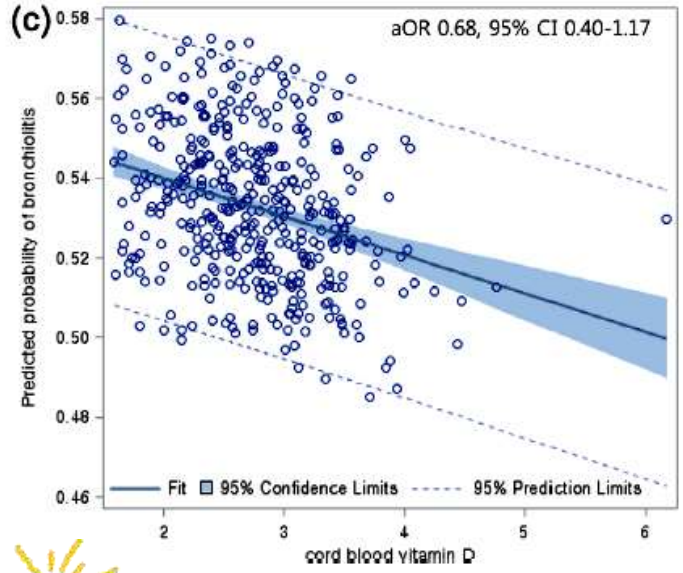
cord-blood vitamin D

lower respiratory-tract infections (LRTIs)



cord-blood vitamin D

bronchiolitis



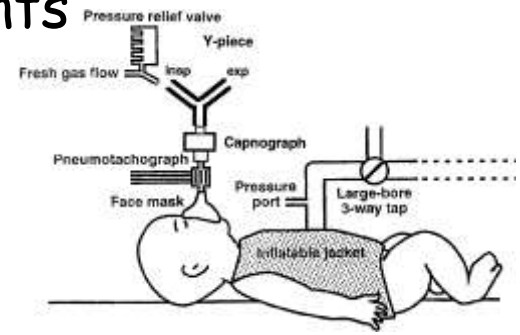
cord-blood vitamin D

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

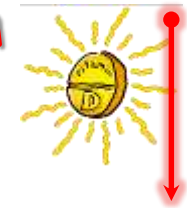
Lai SH. PLoS One. 2017;12(3):e0173268.

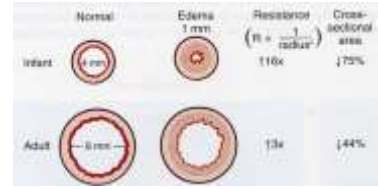
✓122 mother-infant pairs

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



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



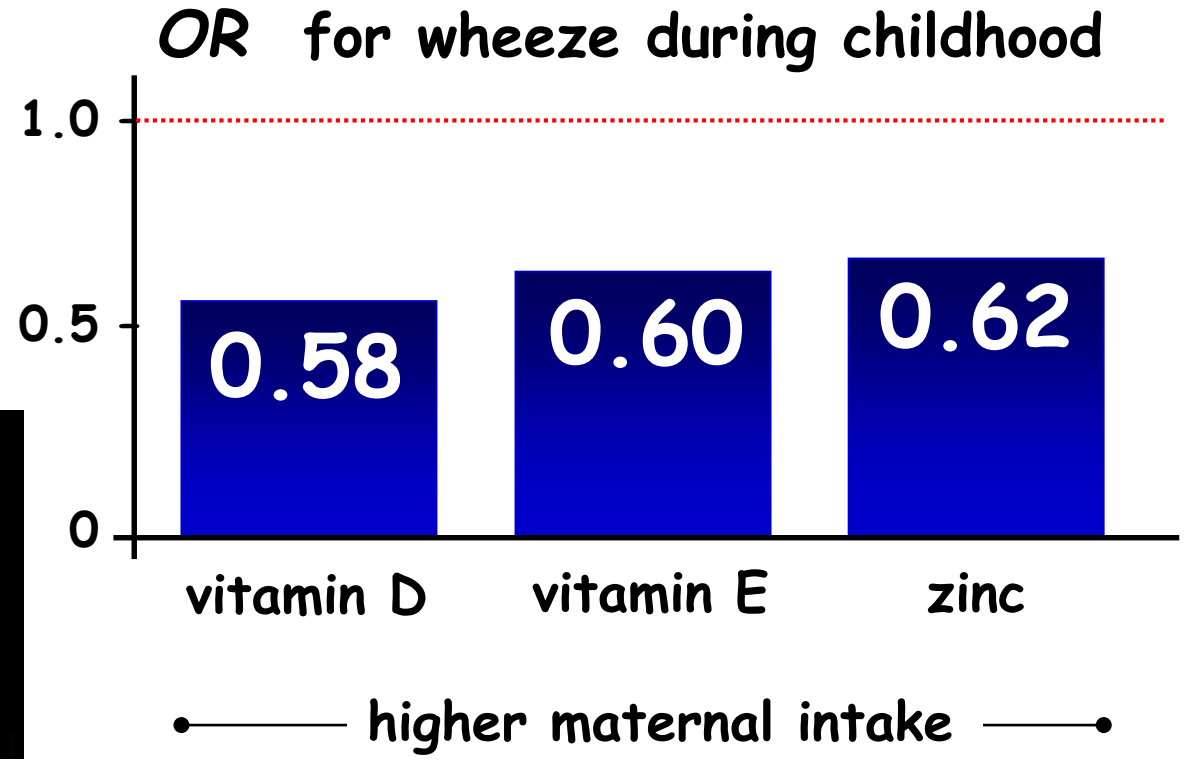


1) higher resistance of respiratory system ($p < 0.01$) and
2) higher risk of a respiratory tract infection (OR=7.6) before the age of 6 months ($p < 0.01$).

Maternal nutrition during pregnancy and risk of asthma, wheeze and atopic diseases during childhood: a systematic review and meta-analysis.

Beckhaus AA, Allergy 2015;70(12):1588-604

- ✓ 32 studies (29 cohorts) included.
- ✓ Data on vitamins, oligo-elements, food groups and dietary patterns during pregnancy.

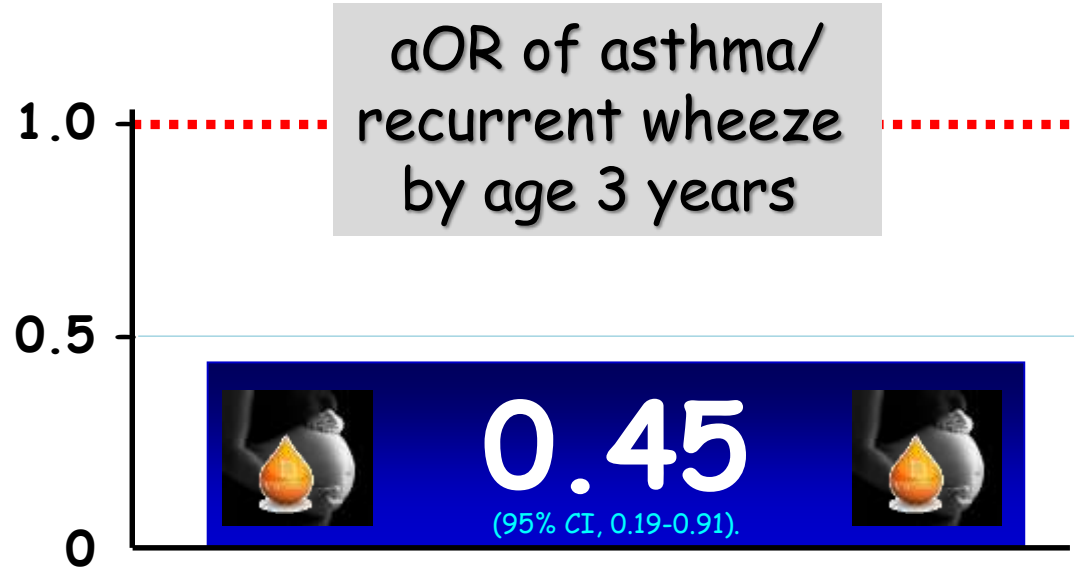


Vitamin D supplementation in pregnancy, prenatal 25(OH)D levels, race, and subsequent asthma or recurrent wheeze in offspring: Secondary analyses from the Vitamin D Antenatal Asthma Reduction Trial.

Wolsk HM, J Allergy Clin Immunol. 2017 [Epub ahead of print]

✓732 pregnant women at risk of having children with asthma randomized to:
4400 international units/d vitamin D or placebo plus 400 international units/d vitamin D.

✓Asthma and recurrent wheezing until age 3 years



Having an initial level > 30 ng/mL and being randomized to the 4400 international units/d *vs* an initial level < 20 ng/mL and receiving placebo

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

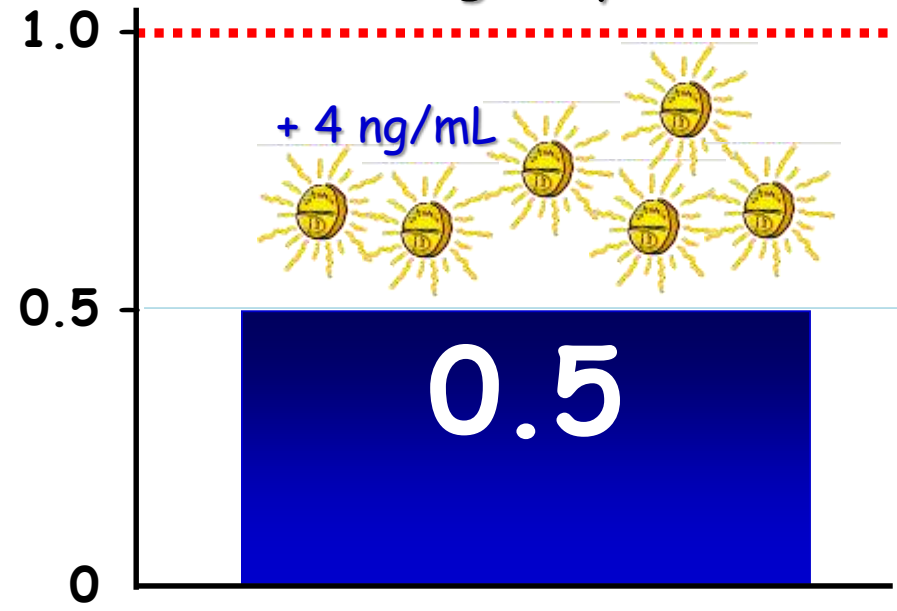
Hollams EM, J Allergy Clin Immunol 2017;139:472-81

✓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

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

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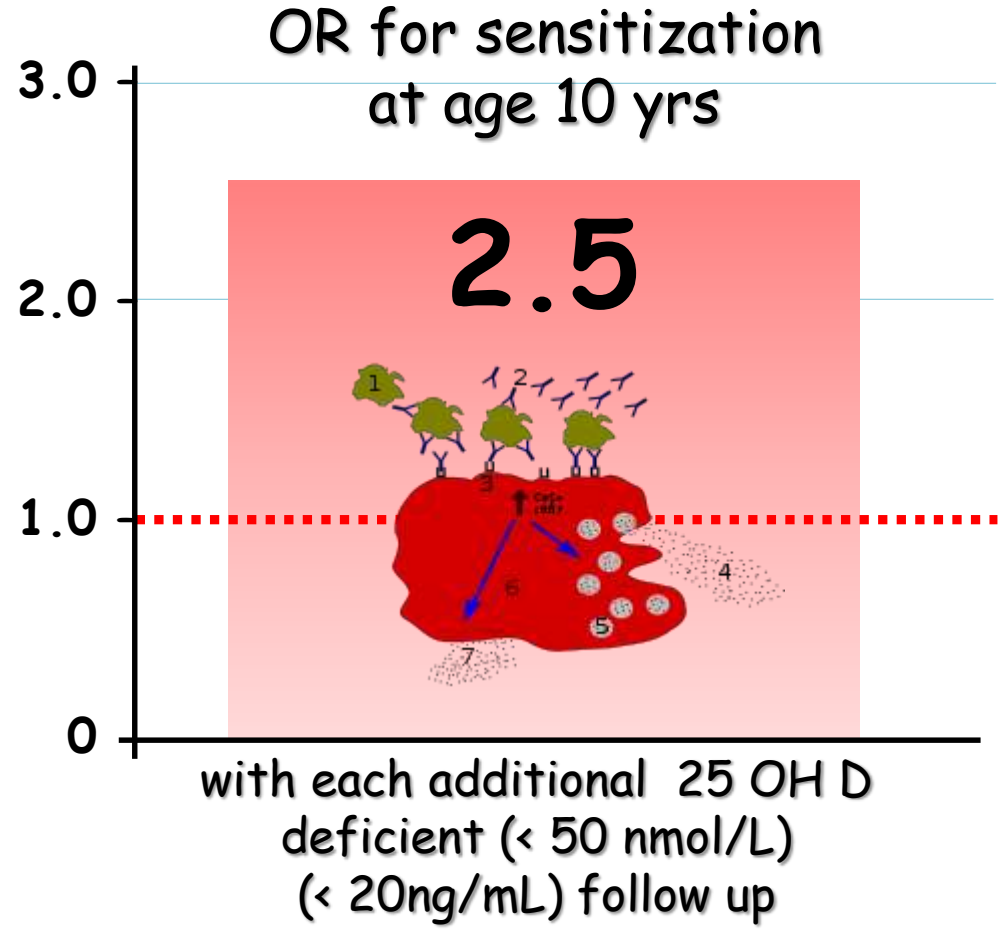
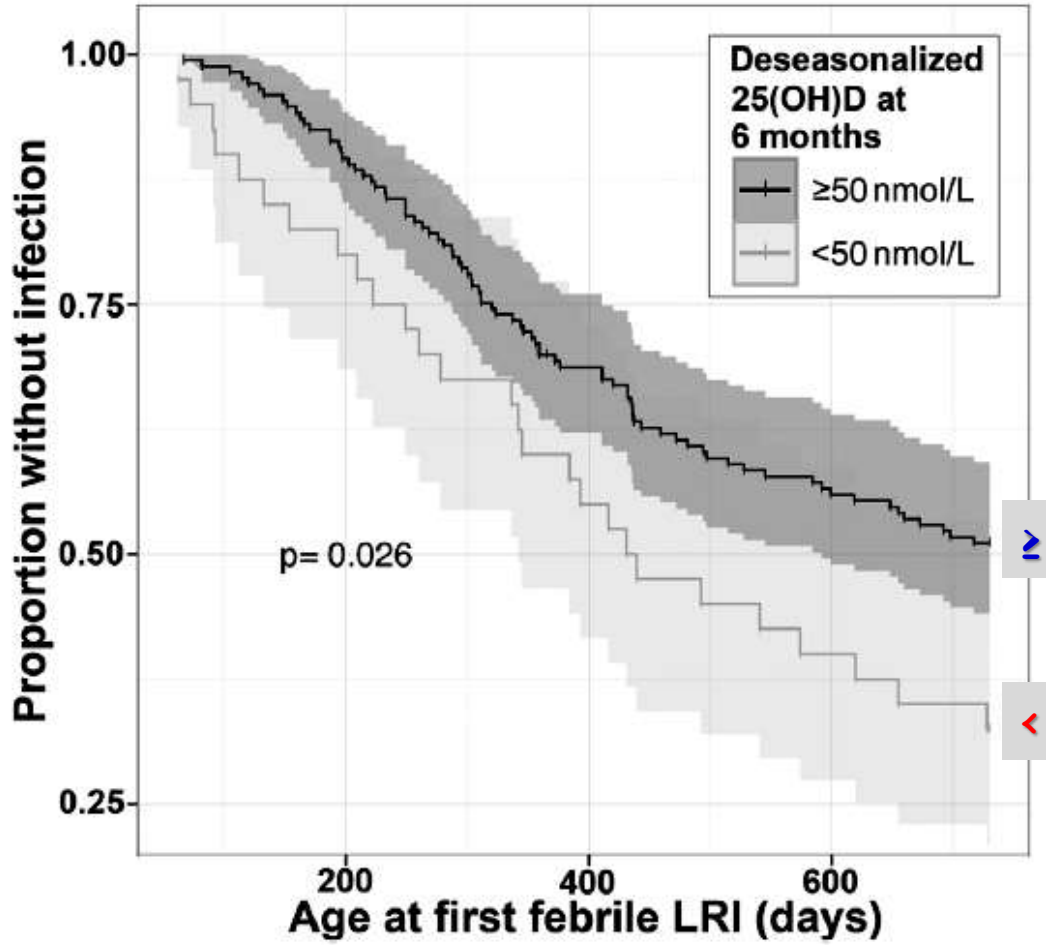
✓8 years follow – up.



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

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

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

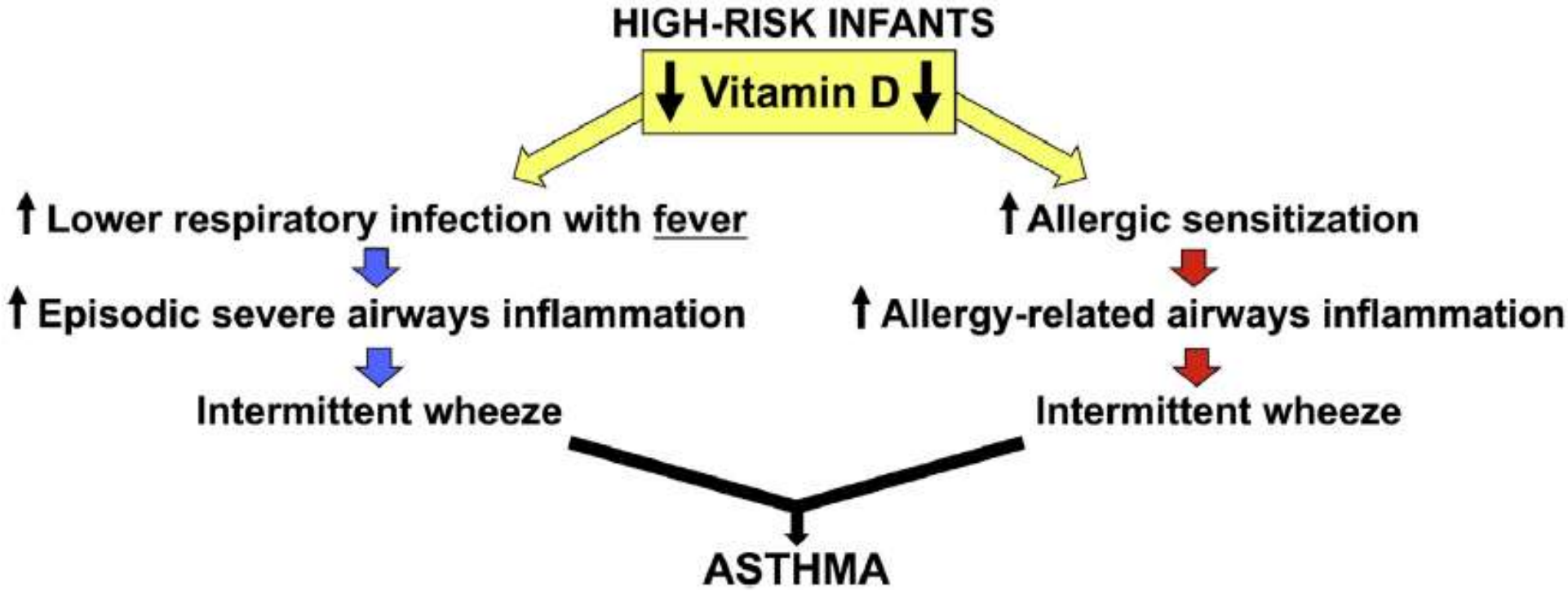


≥ 20ng/mL

< 20ng/mL

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

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

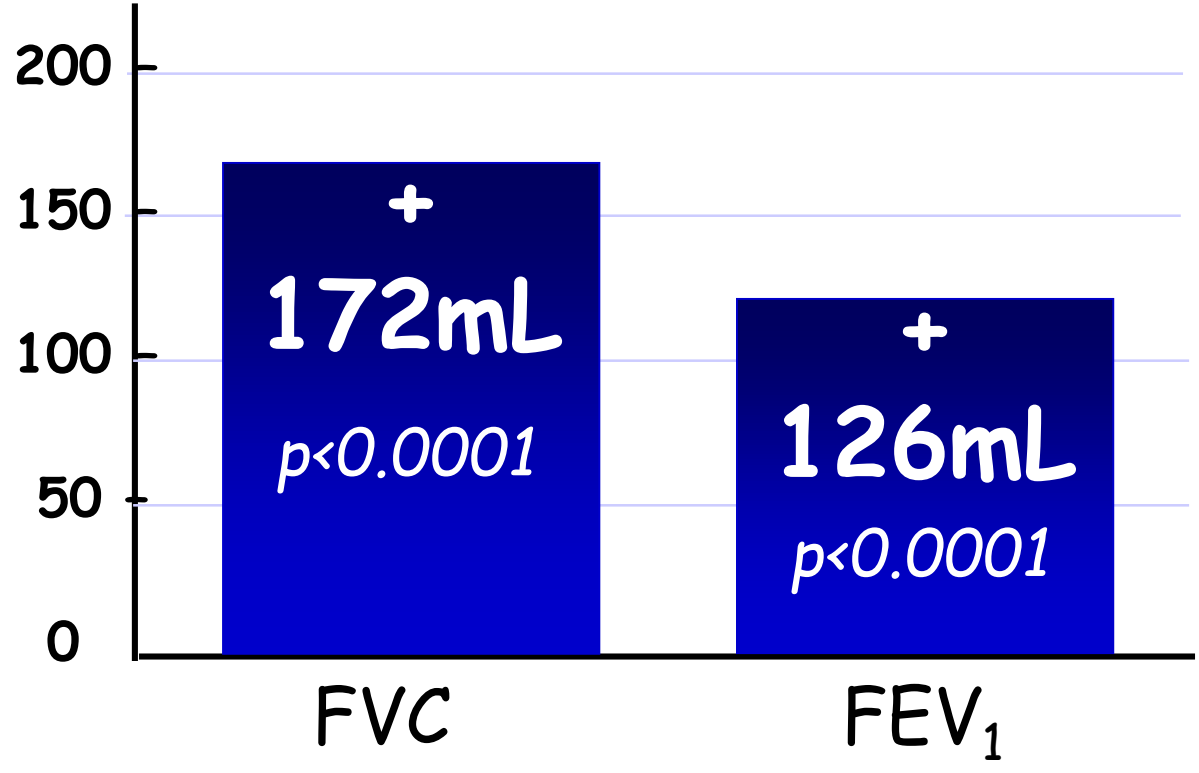


Relationship between serum 25-hydroxyvitamin D and pulmonary function in the Third National Health and Nutrition Examination Survey.

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).

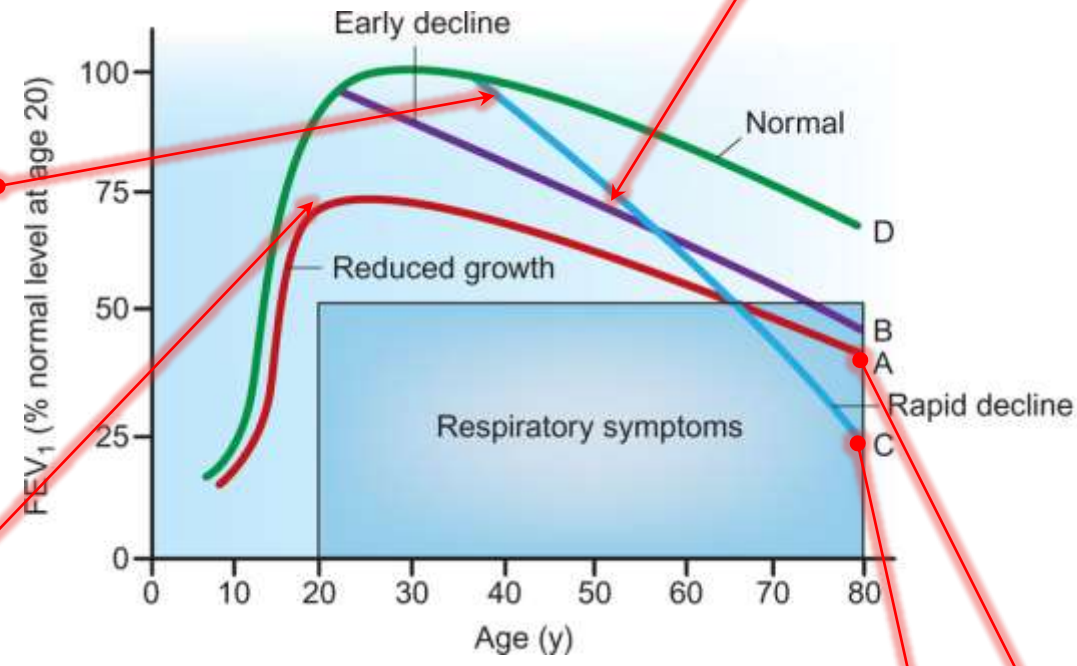


Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease.

Lange P, N Engl J Med. 2015;373(2):111-22.

BACKGROUND:
Chronic obstructive pulmonary disease (COPD) is thought to result from an accelerated decline FEV_1 over time.

Yet it is possible that a normal decline in FEV_1 could also lead to COPD in persons whose maximally attained FEV_1 is less than population norms.

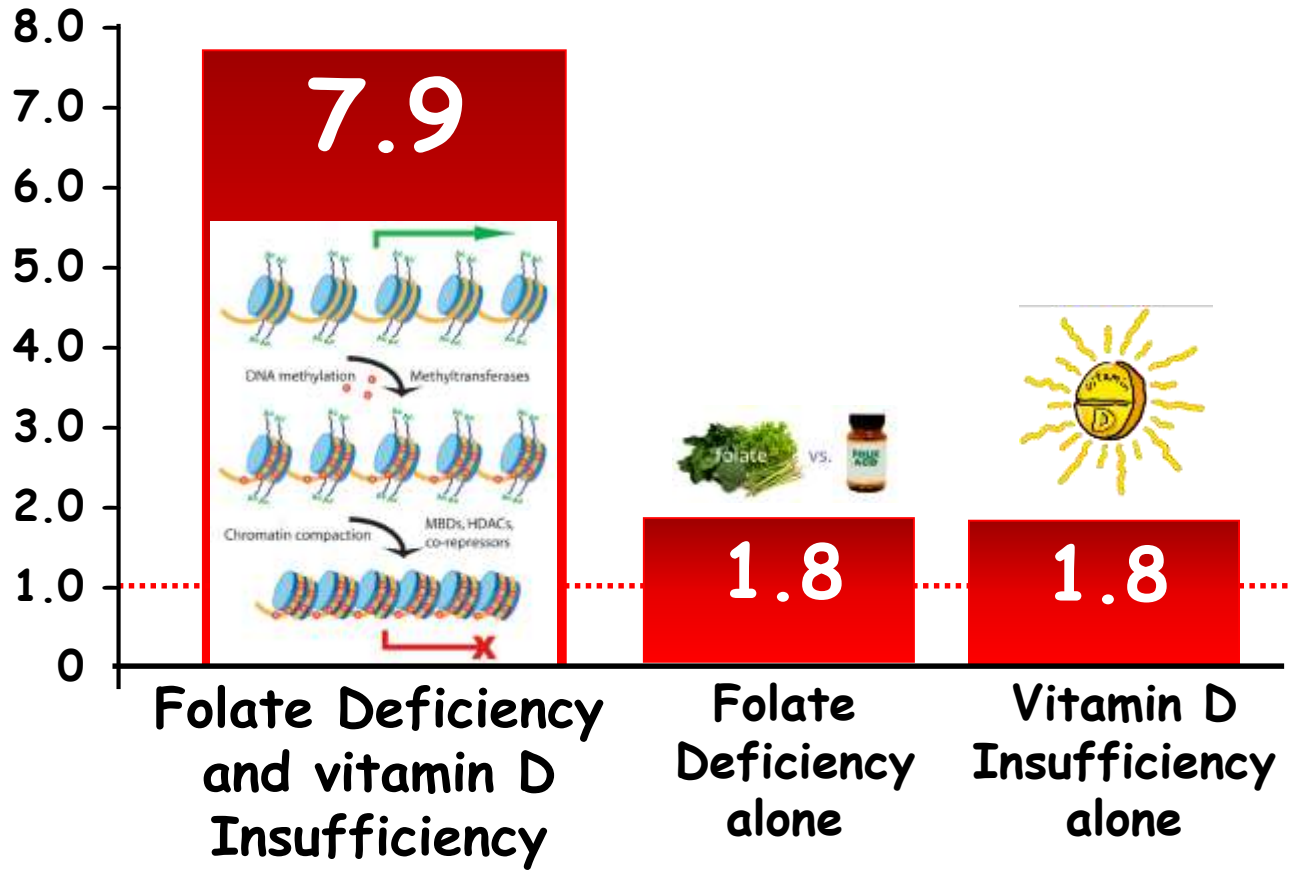


Folate Deficiency, Atopy, and Severe Asthma Exacerbations in Puerto Rican Children

Blatter J, Ann Am Thorac Soc 2016;13:223-230

- ✓ 582 children aged 6 to 14 yrs with (n = 304) and without (n = 278) asthma.
- ✓ Folate deficiency: plasma folate ≤20 ng/ml.
- ✓ Vitamin D insufficiency plasma 25(OH)D <30 ng/ml.

OR for at least one severe asthma exacerbation in the previous year in children with

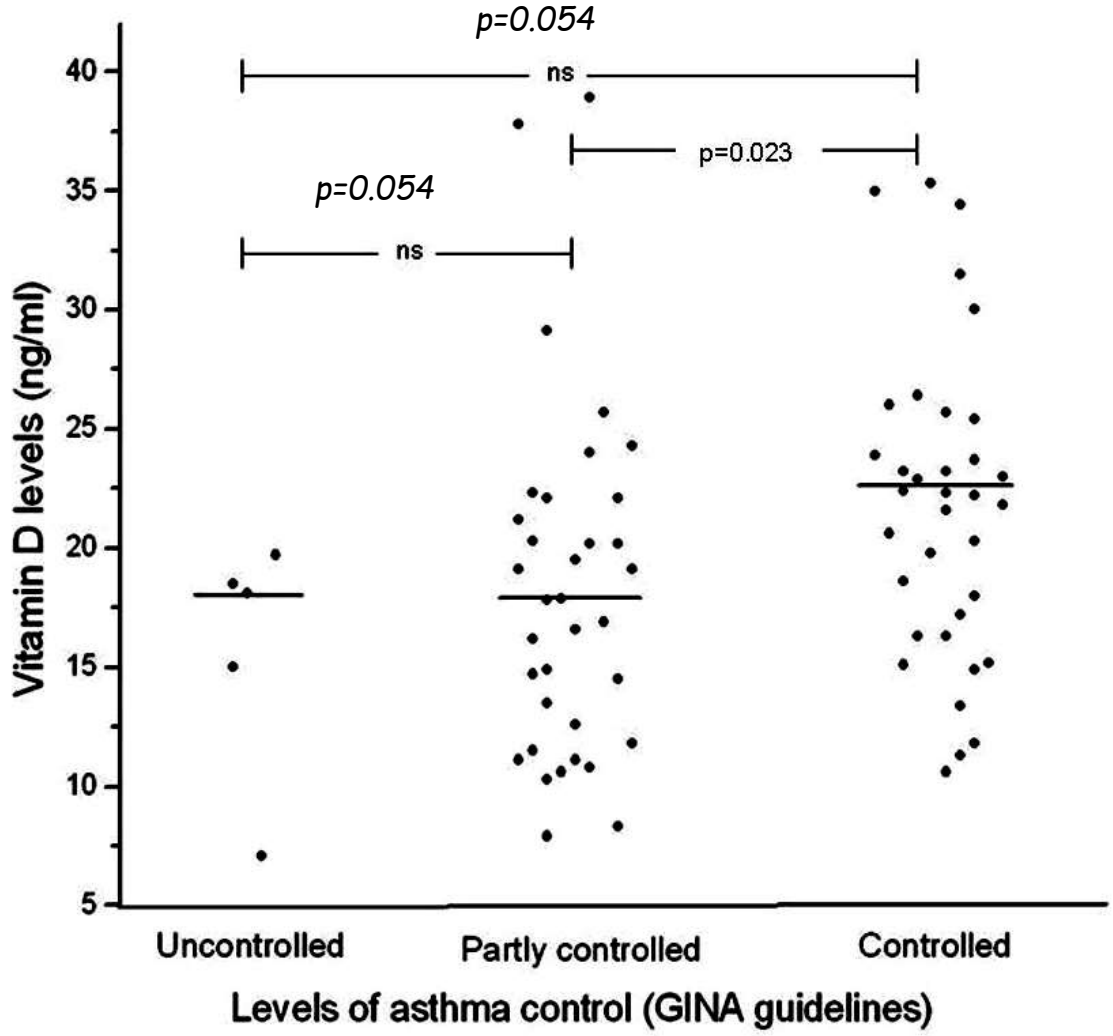


Vitamin D Serum Levels and Markers of Asthma Control in Italian Children *Chinellato I, Boner AL. J Pediatr 2011;158:437*

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

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1)‡	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year*	One in any week†

* Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.
† By definition, an exacerbation in any week makes that an uncontrolled asthma week.
‡ Lung function is not a reliable test for children 5 years and younger.



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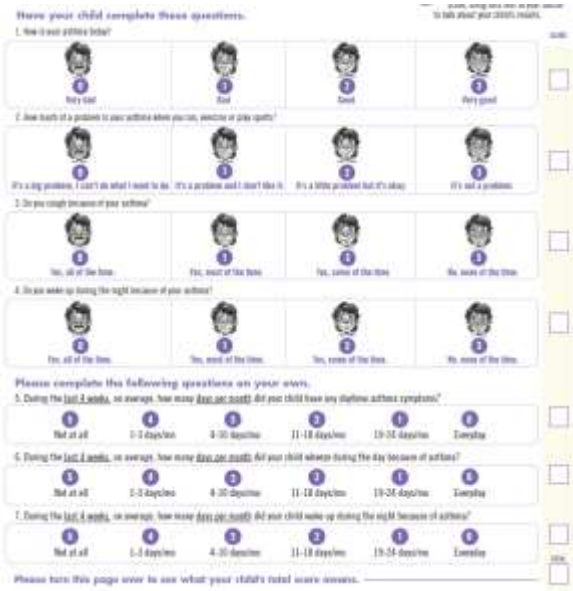
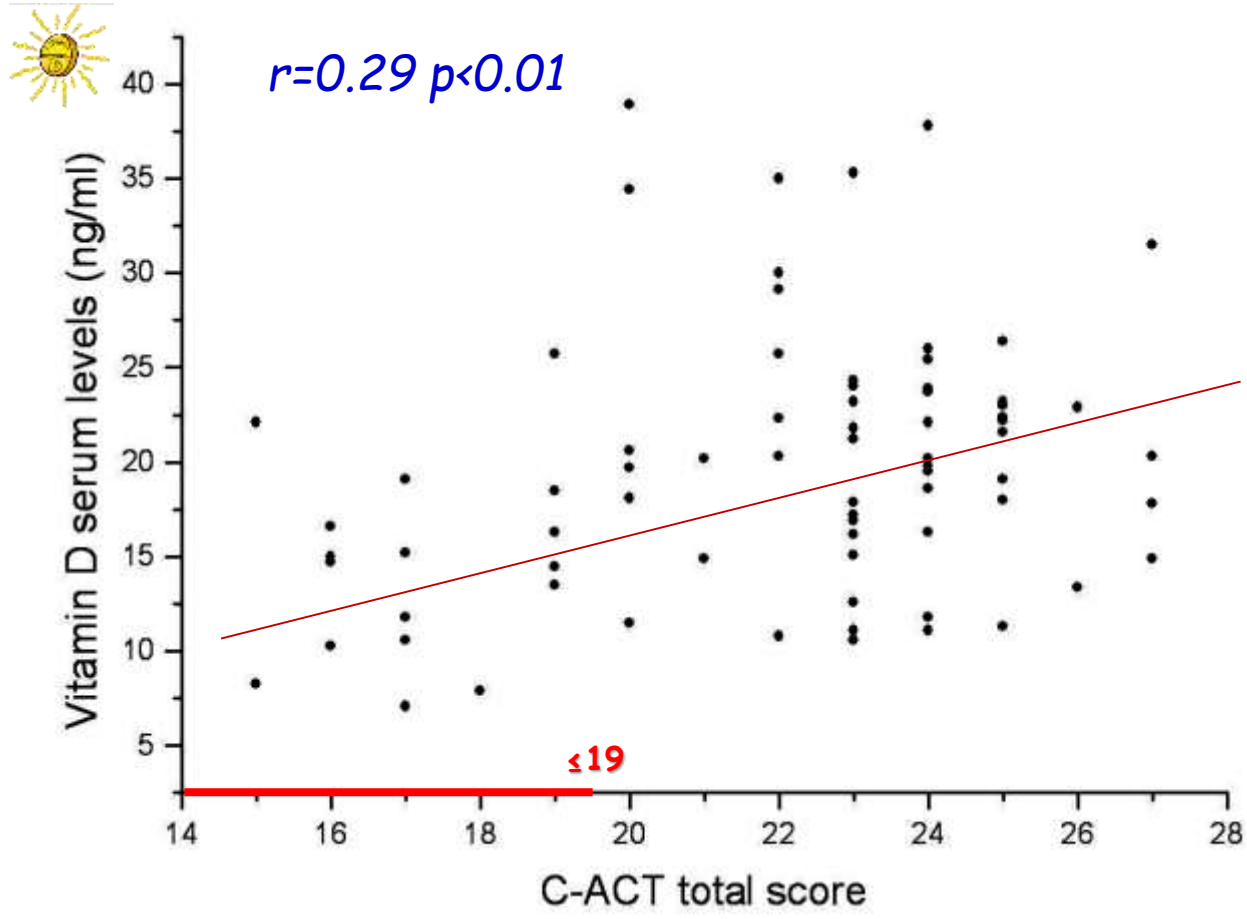
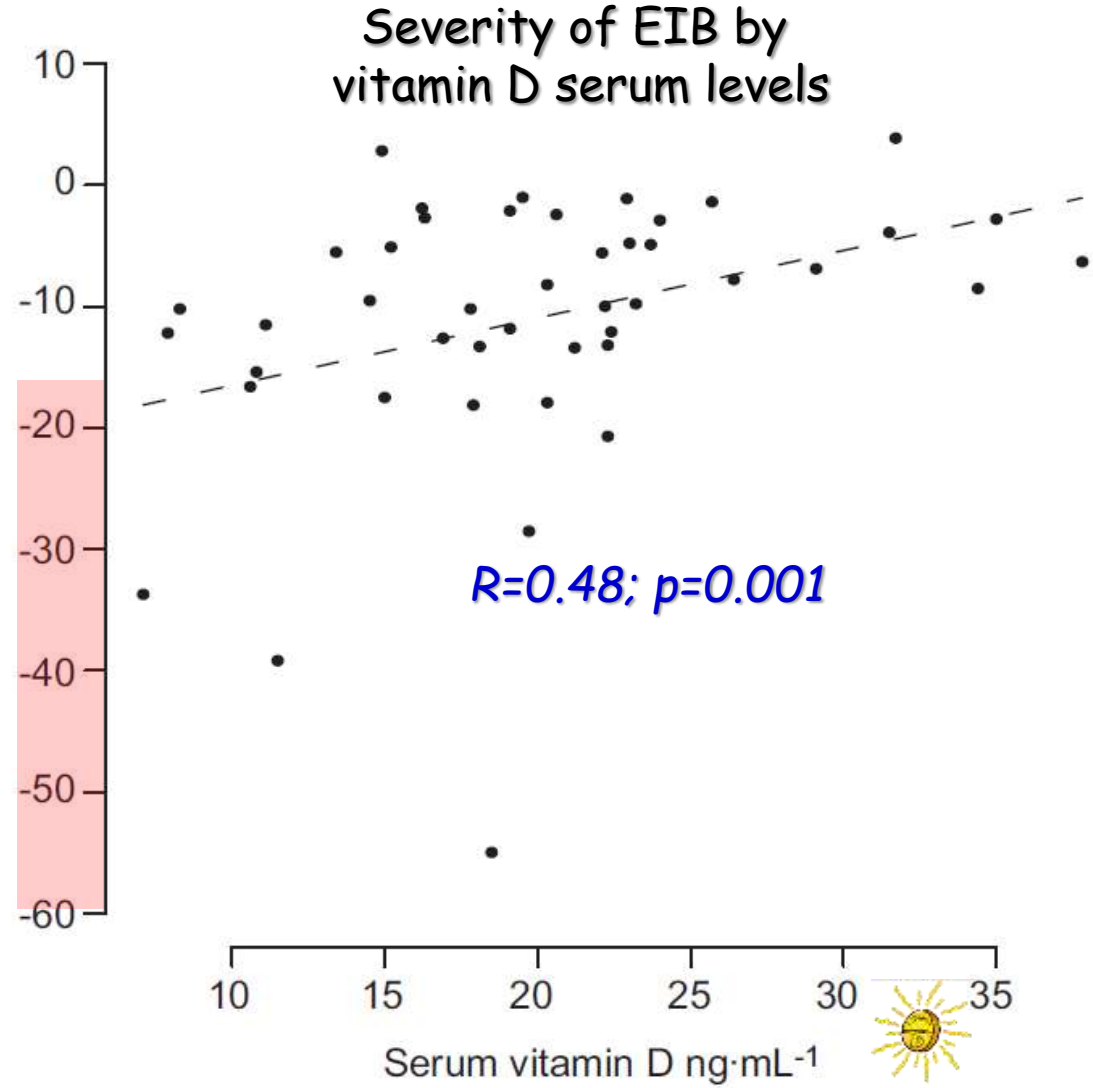




Vitamin D Serum Levels and Lung Function and Exercise Induced Bronchoconstriction in Children with Intermittent Asthma. *Chinellato I, ERJ 2011;37:1366*

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



Vitamin D and pulmonary function in obese asthmatic children

Lautenbacher LA, Pediatr Pulmonol 2016;51:1276-1283

- ✓ 72 obese and 71 normal-weight Hispanic and African-American children with asthma and 25-hydroxyvitamin D (25-OHD).
- ✓ 25-OHD levels ≥30 ng/ml categorized as sufficient, <30 and ≥20 ng/ml as insufficient, and <20 ng/ml as deficient.

Association of Pulmonary Function with Vitamin D in Obese Children with Asthma

	25-OHD sufficient	25-OHD insufficient	25-OHD deficient	*P*-value[b]
FVC	99.7 ± 4.7	98.4 ± 24	92.5 ± 10.4	0.23
FEV_1	94.8 ± 8.4[c]	94.7 ± 14.1[d]	84.5 ± 9.4[c,d]	0.009
FEV_1/FVC	84 ± 5.7	80.3 ± 6.1	80.9 ± 7.4	0.32
$FEF_{25-75\%}$	87.8 ± 25	80.5 ± 23.2	73.2 ± 19.5	0.11
TLC	86.3 ± 9	96.6 ± 10[e]	86.9 ± 14.3[e]	0.01
RV	68.5 ± 27.2	92 ± 36.3	76.8 ± 28.2	0.079
RV/TLC	18.5 ± 6.3	21.5 ± 6.4	20 ± 5	0.35
ERV	73.9 ± 19.3	67.8 ± 22.6	61.7 ± 24.5	0.29
FRC	79.3 ± 19[f]	73.5 ± 19.3	67.5 ± 20.1[f]	0.04
IC	92.1 ± 13.6	104.3 ± 12.2	93.9 ± 19.3	0.049

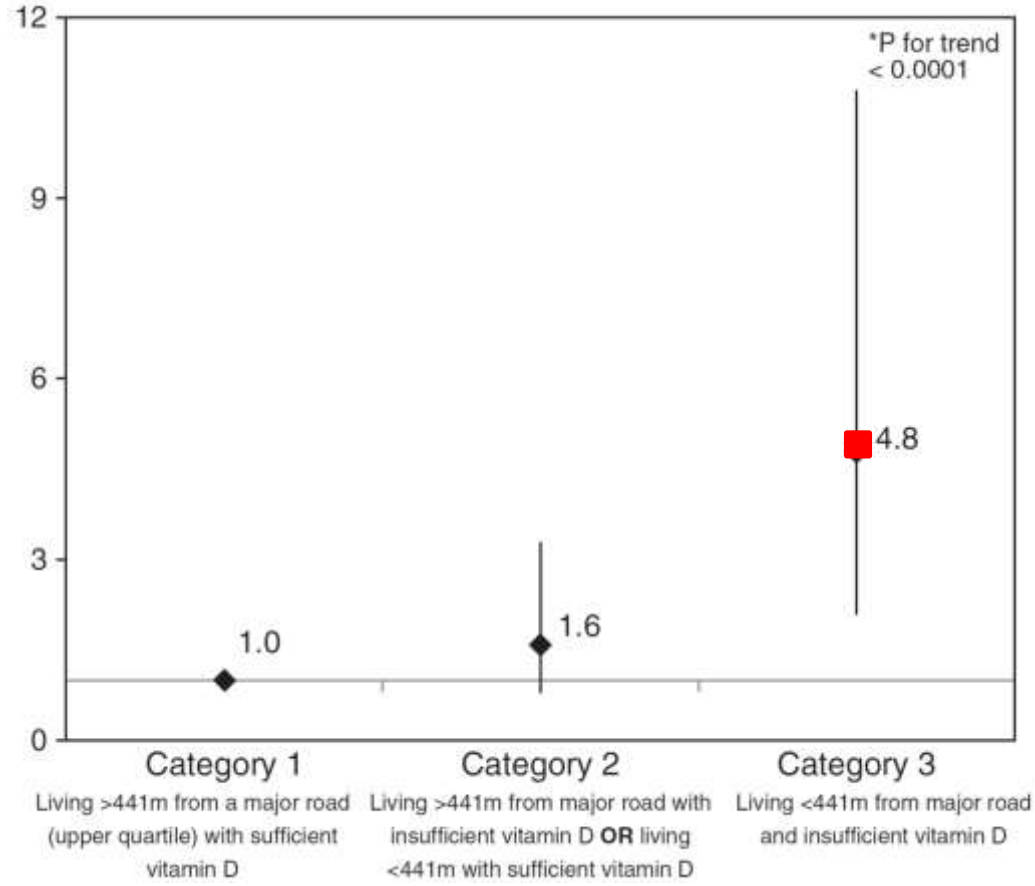
≥30 ng/ml <20 ng/ml

Proximity to a Major Road, Vitamin D Insufficiency, and Severe Asthma Exacerbations in Puerto Rican Children

Rosser F, AJRCCM 2014;190:1190

- ✓ 351 children with asthma randomly selected in Puerto Rico.
- ✓ Plasma 25-hydroxy-vitamin D.
- ✓ Residential distance from a major road

Categories of residential proximity to a major roadway (living > vs ≤ 441 m away from a major road) and vitamin D insufficiency (plasma vitamin D level <30 ng/dl) and OR for severe asthma exacerbations



25-hydroxyvitamin d3-deficiency enhances oxidative stress and corticosteroid resistance in severe asthma exacerbation. *Lan N, PLoS One. 2014 Nov 7;9(11):e111599.*

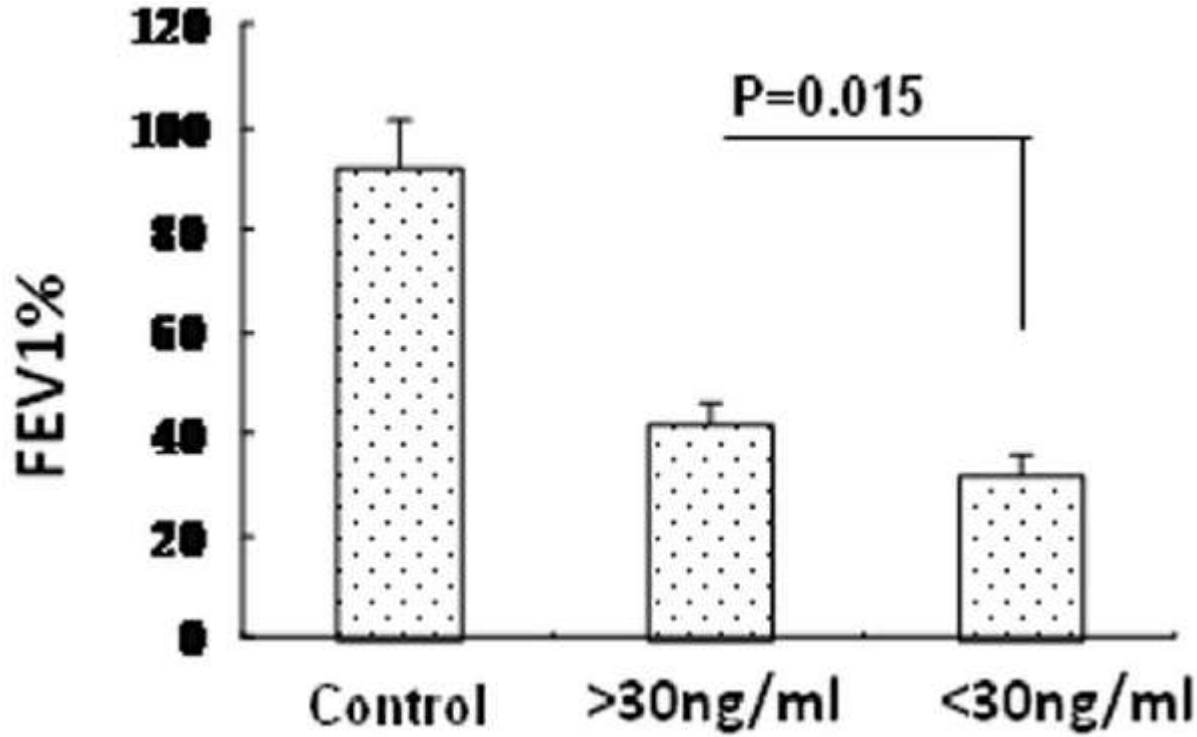
✓Severe asthma exacerbation patients with 25-hydroxyvitamin D3-deficiency (≤30 ng/mL) (n=16) or 25-hydroxyvitamin D3-sufficiency (>30 ng/mL) (n=16)

✓16 controls

✓Lung function and Superoxide Dismutase Activity in serum

✓Reactive Oxygen Species (ROS) and DNA damage in PBMC and cultured epithelial cells

Severe asthma exacerbation with V-D-deficiency showed lower FEV_1 compared to that with V-D-sufficiency.



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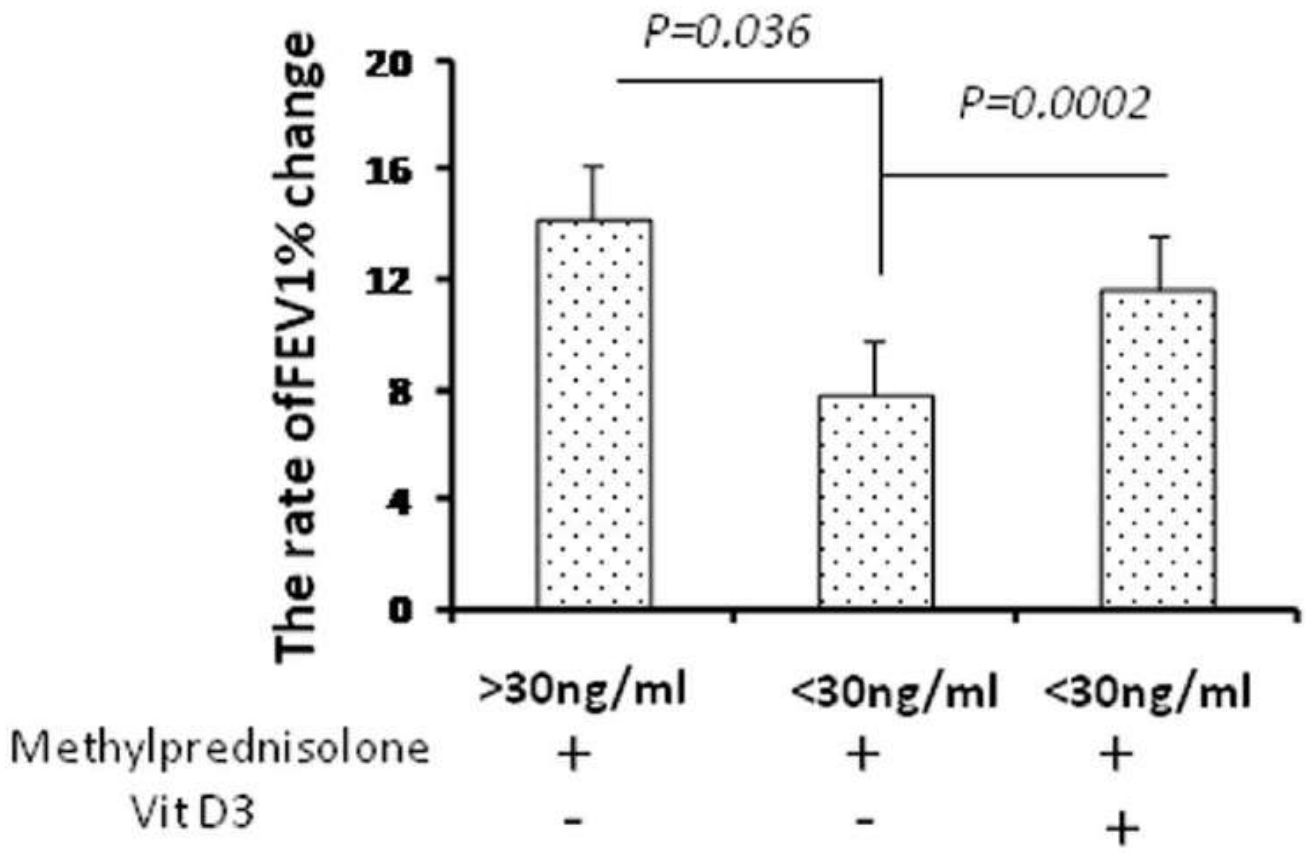


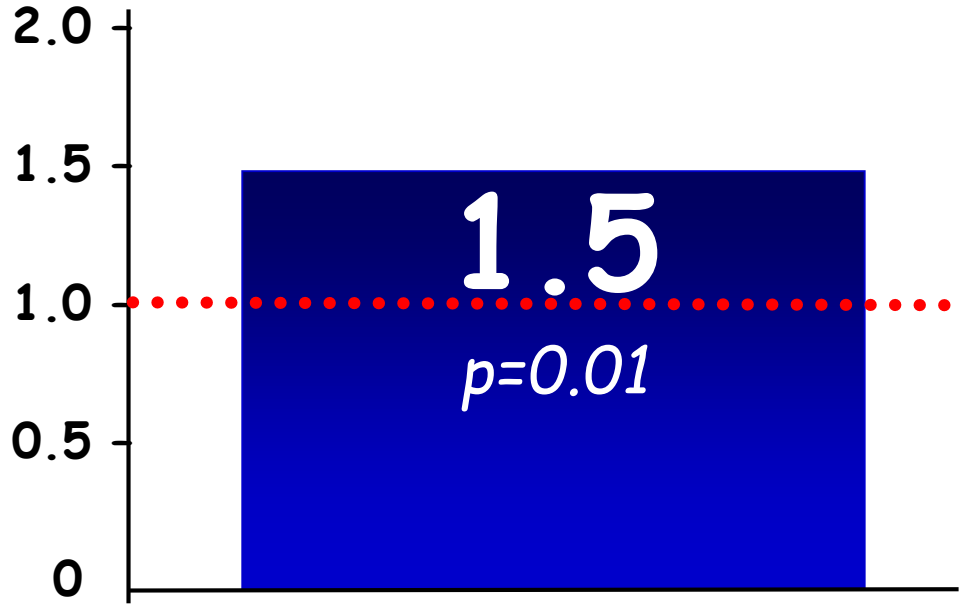
300,000 UI of vitamin D3 at day 1 and 4.

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.

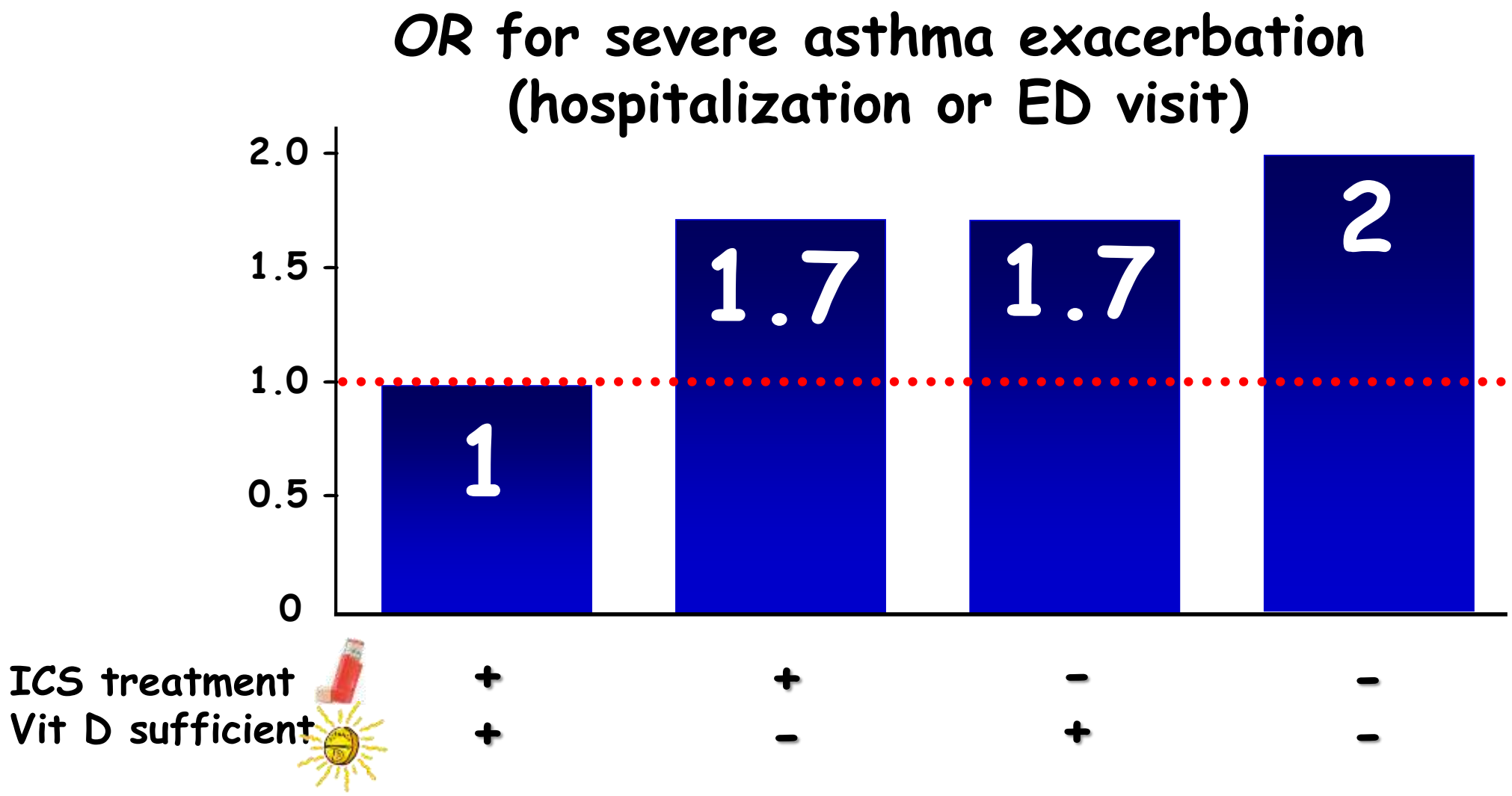
OR for any hospitalization or ED visit in the 4 years follow-up



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



Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use.

Searing DA, J All Clin Immunol. 2010;125:995–1000.

- the use of:
  - **ICS** *(P =0.0475)*,
  - **oral steroids** *(P =0.02)*,
  - **total steroid dose** *(P =0.001)*, and
  - **LABA** *(P =0.0007)*

all showed significant association with **lower Vit D levels.**

Univariate analysis of serum Vitamin D levels and medication use

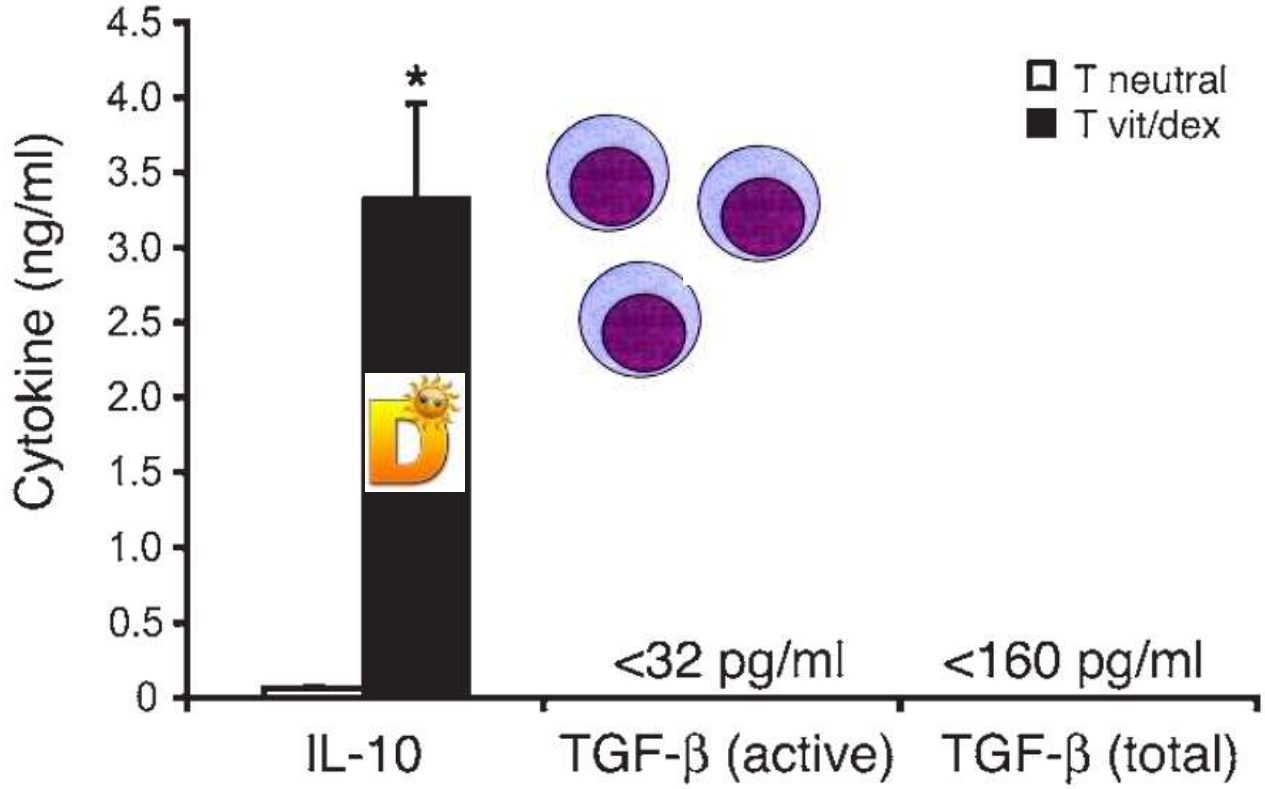
Medication used, sample size (n = 100)	VitD level,† median (IQR)	*P* value*
ICS (n = 60)	ICS: 29 (21-36) No ICS: 35 (26-42)	.0475
Oral CS (n = 14)	Oral CS: 25 (18-30) No oral CS: 32 (25-40)	.02
TCS (n = 69)	TCS: 31 (23-40) No TCS: 31 (24-38)	.98
LTRA (n = 42)	LTRA: 29 (25-37) No LTRA: 32 (23-41)	.50
LABA (n = 29)	LABA: 25 (19-31) No LABA: 34 (27-42)	.0007
MVI (n = 6)	MVI: 40 (27-53) No MVI: 31 (23-39)	.12
Total steroid dose (mg)‡ (n = 64)	ρ = −0.32§	.001

Reversing the defective induction of IL-10–secreting regulatory T cells in glucocorticoid-resistant asthma patients. *Xystrakis E, J Clin Invest 2006;116:146–155.*

✓Patients with severe asthma failling to demonstrate clinical improvement upon glucocorticoid therapy (steroid resistant = SR)

✓Dexamethasone does not enhance secretion of IL-10 by their CD4+ T cells

adding vitamin D to cell cultures increases glucocorticoid-induced secretion of IL-10 by Tregs



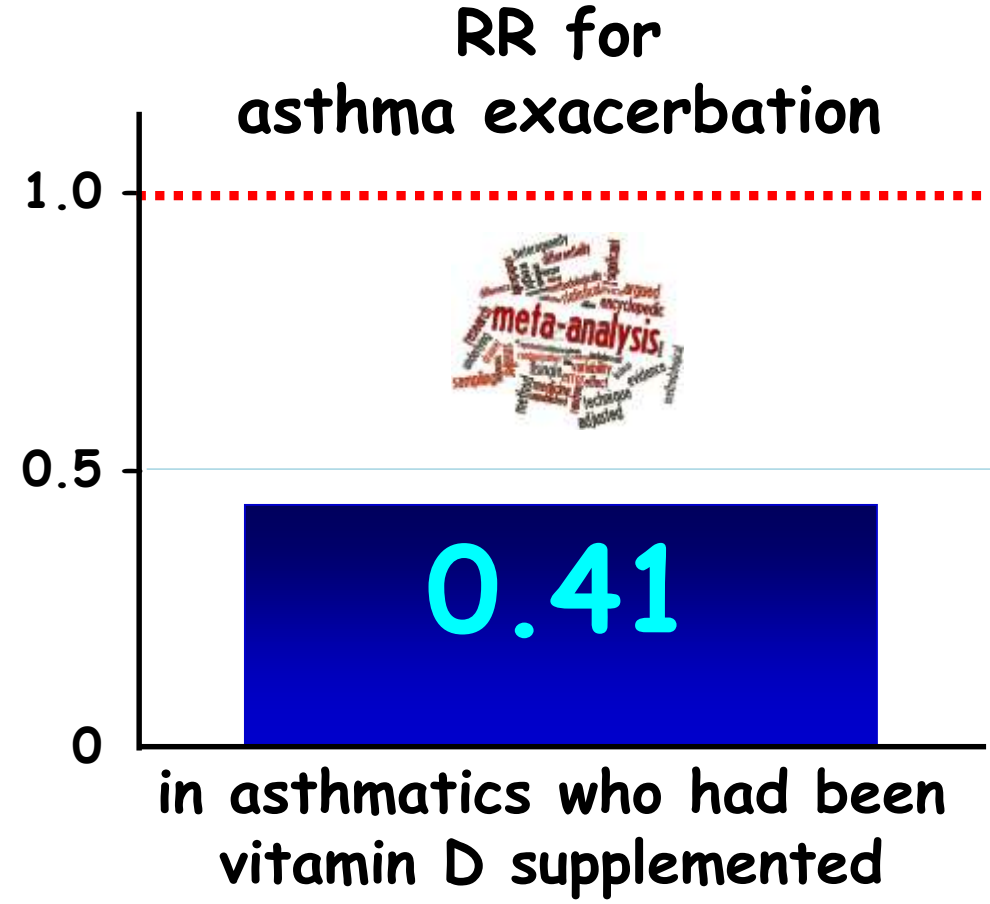
Efficacy of high-dose vitamin D in pediatric asthma: a systematic review and meta-analysis.

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

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

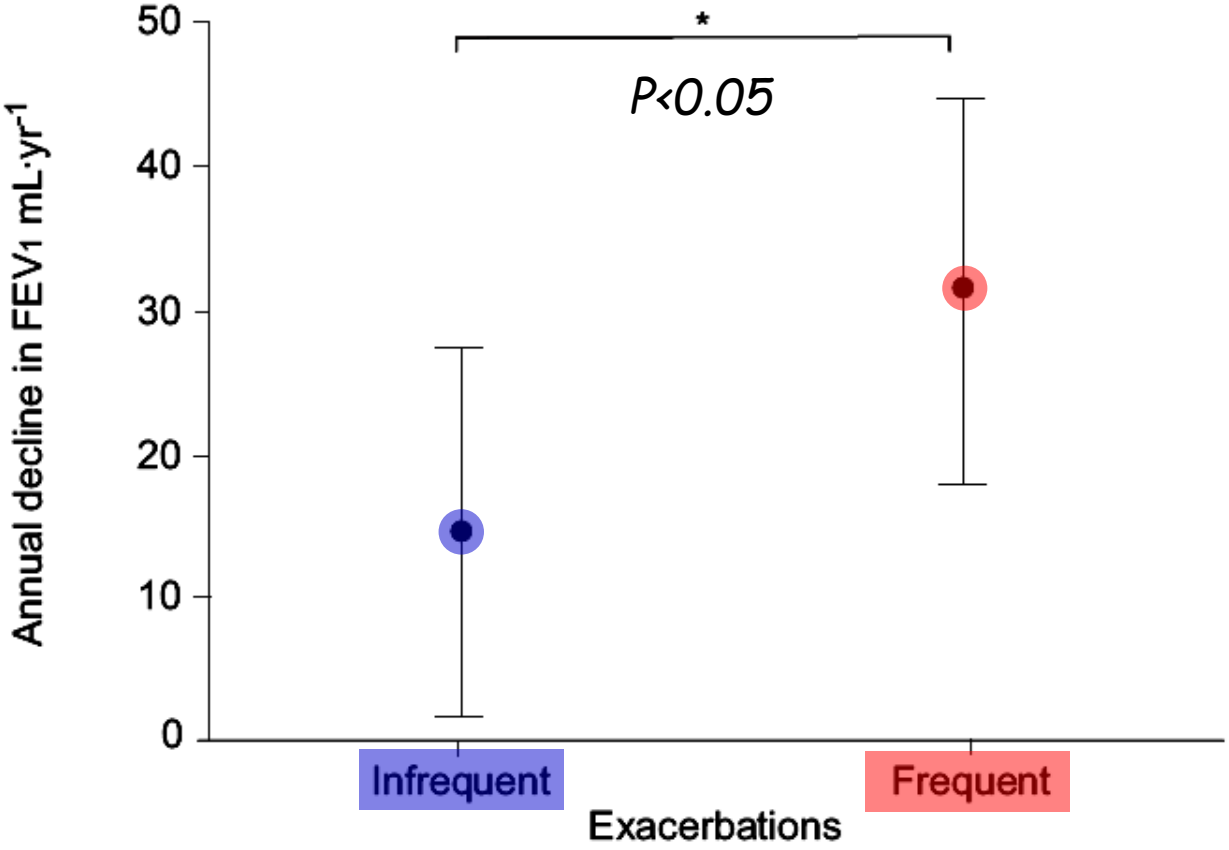
✓The median trial size was 48 participants (range 17-430)

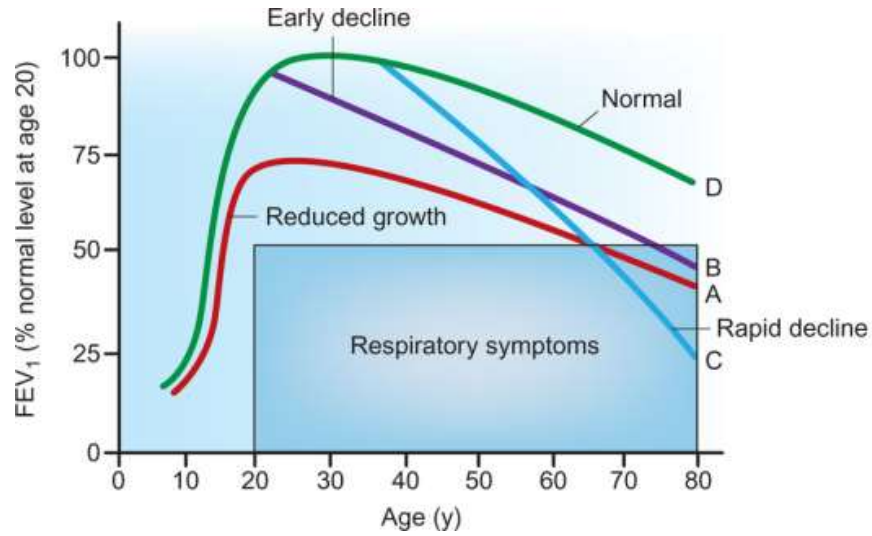
✓The average daily dose of cholecalciferol ranged from 500 to 2000 IU/day.



Severe exacerbations predict excess lung function decline in asthma. *Bai TR, Eur Respir J. 2007;30(3):452-6.*

Estimated annual decline in FEV_1 in patients with infrequent or frequent asthma exacerbations

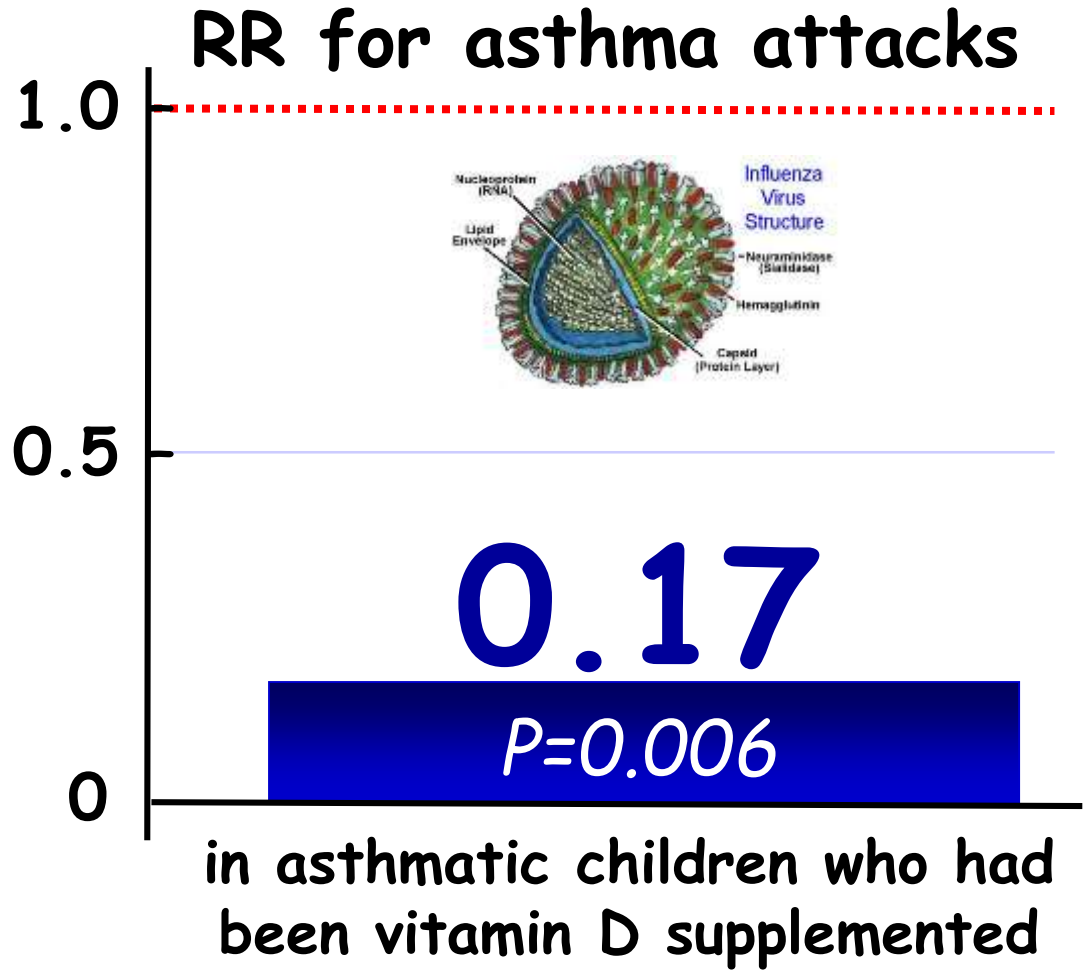




Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren.

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

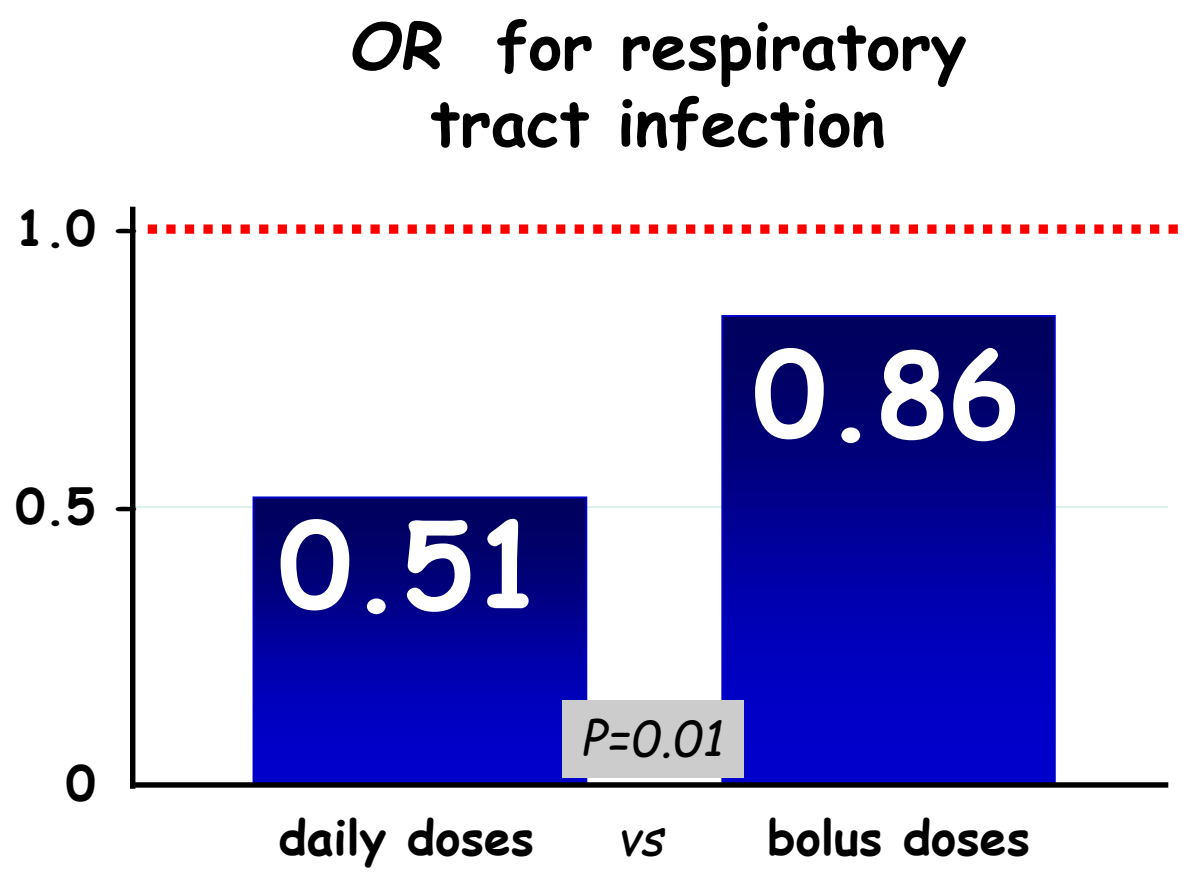
- ✓Vitamin D(3) supplements (1200 IU/d) (n= 167) or placebo (n= 167) in schoolchildren
- ✓From December 2008 through March 2009
- ✓incidence of influenza A, diagnosed with influenza antigen testing with a nasopharyngeal swab specimen.



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

Bergman P, PLoS One 2013;8:e65835

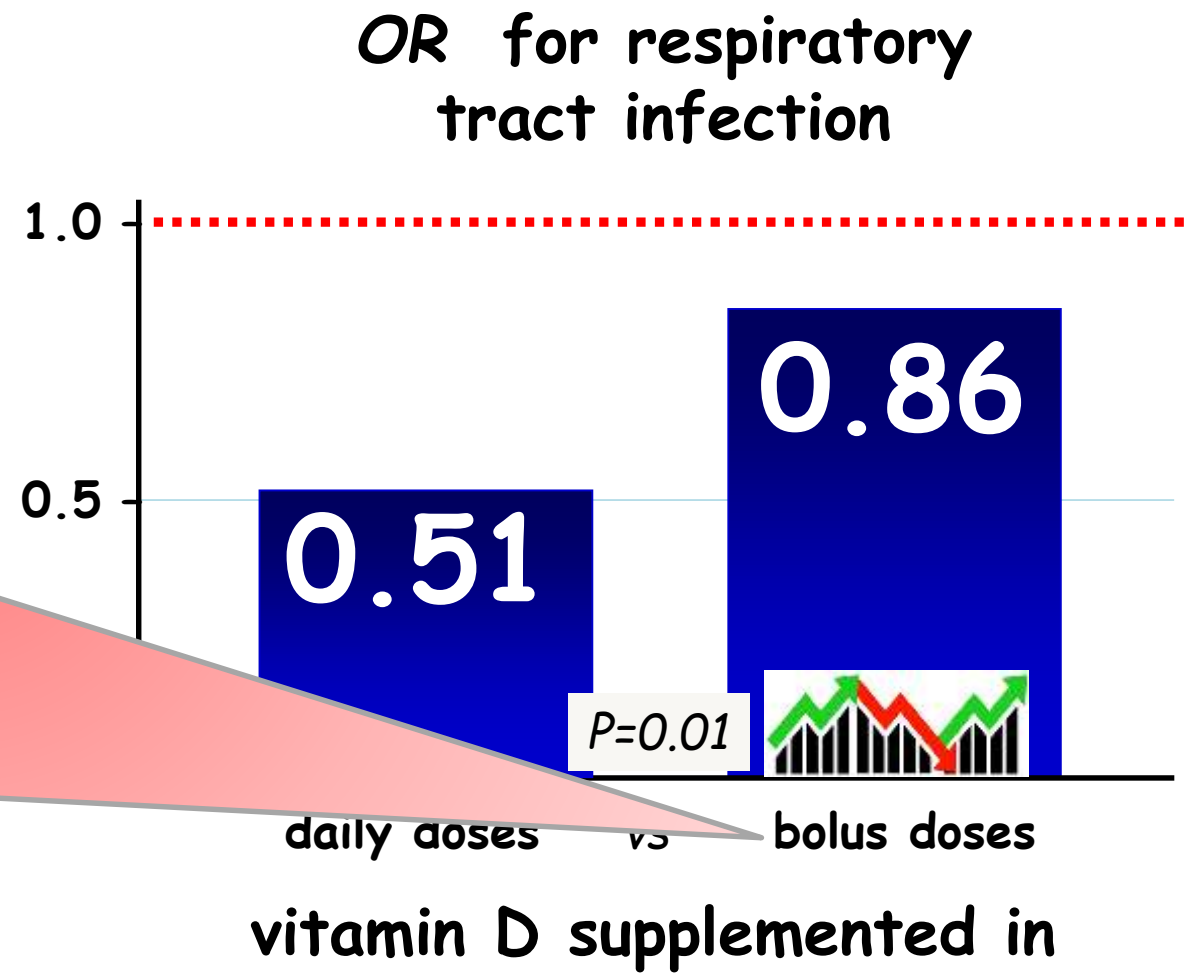
- ✓meta-analysis of 11 placebo-controlled studies
- ✓5660 patients included



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

Bergman P, PLoS One 2013;8:e65835

Intermittent bolus dosing with long lag times (greater than 3–4 weeks) leads to wide swings in circulating levels of 25 OHD, which in turn leads to dips in tissue levels of 1,25 dihydroxy D, leading to a relative excess of the catabolic enzyme 24 hydroxylase.

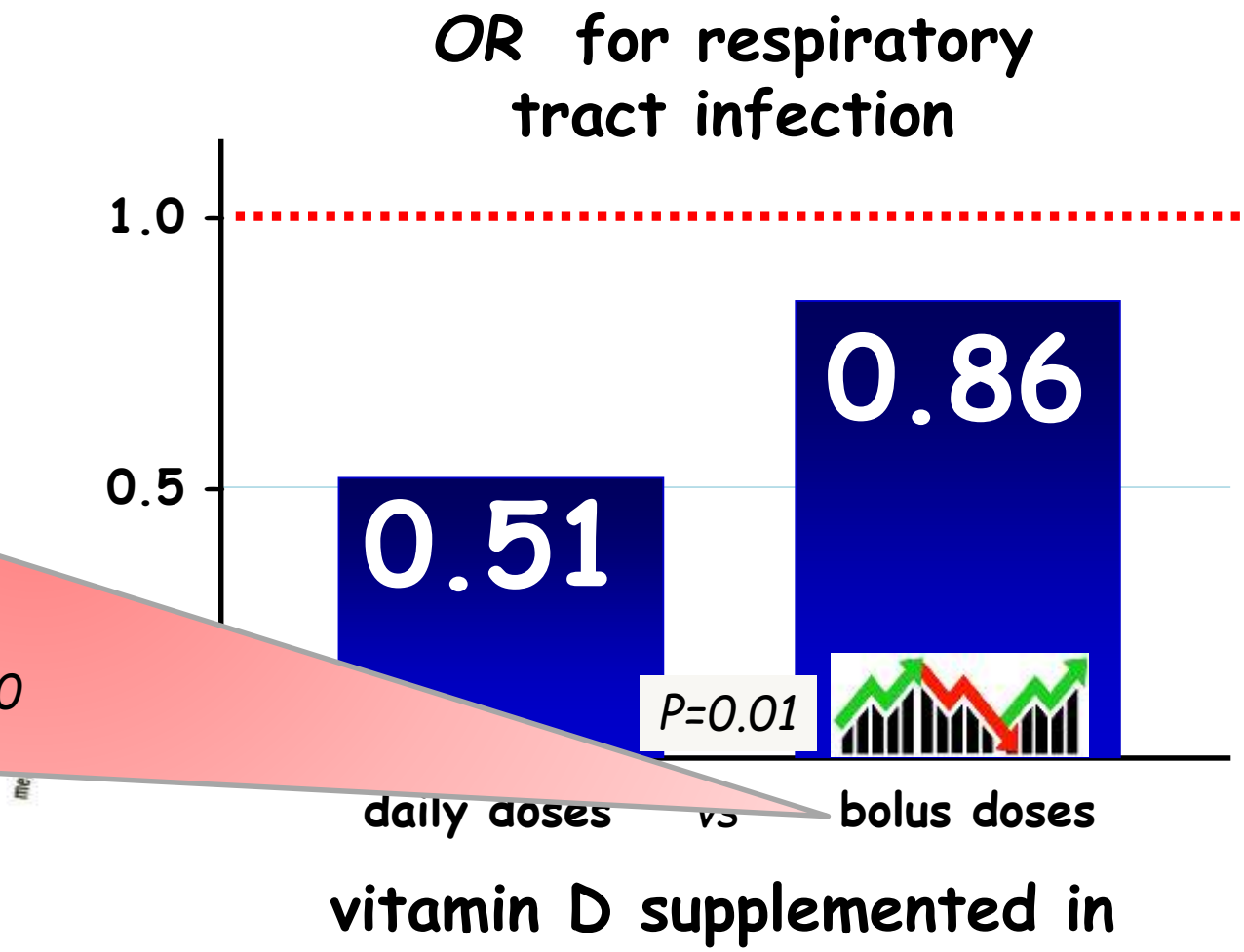


Vitamin D and respiratory tract infections: A systematic review and meta-analysis of randomized controlled trials.

Bergman P, PLoS One 2013;8:e65835

This mechanism has also been suggested to be operating in elevating the risk for some cancers due to wide fluctuations in circulating vitamin D levels.

Weiss S.Thorax 2015;70:919-920



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

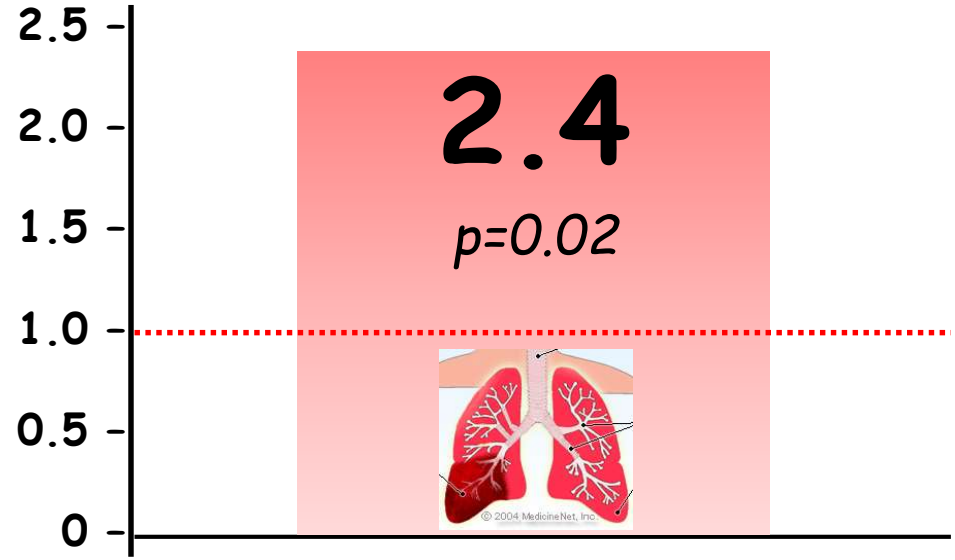
López AV, Pediatr Pulmonol 2016;51:1080-1087

- ✓ 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



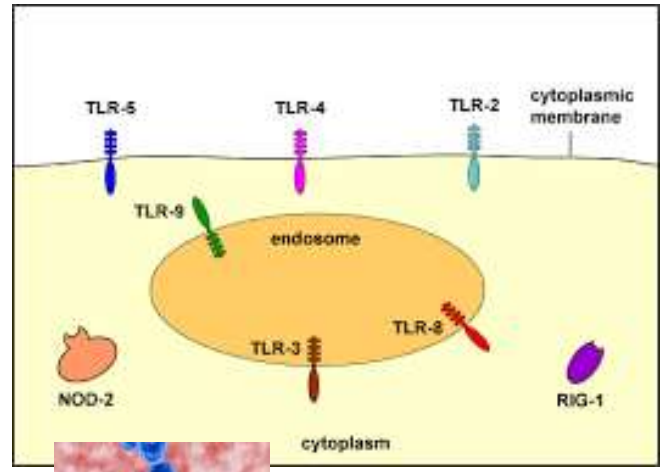
In cases
***vs* controls**

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

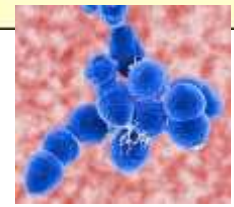
Subramanian K, J Innate Immun. 2017 [Epub ahead of print]

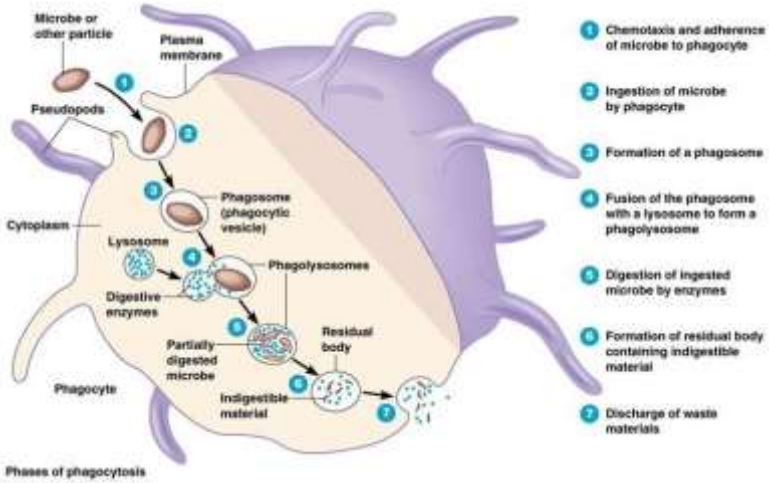
vitamin D

- 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.

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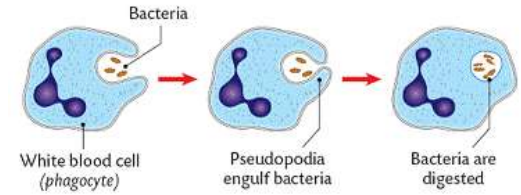
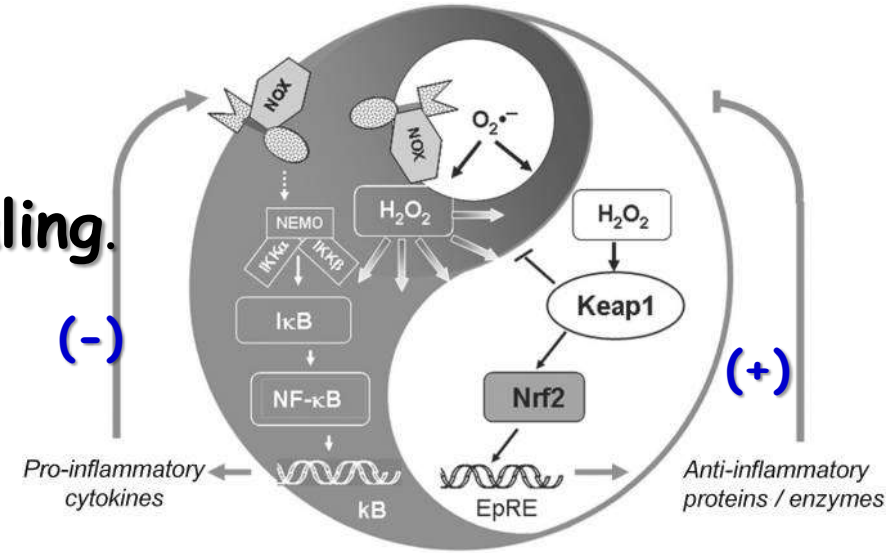


- Moreover, **vitamin D lowered inflammatory cytokine production by** infected neutrophils via IL-4 production and the induction of suppressor of cytokine signaling (SOCS) proteins SOCS-1 and SOCS-3, leading to the **suppression of NF-κB signaling**.

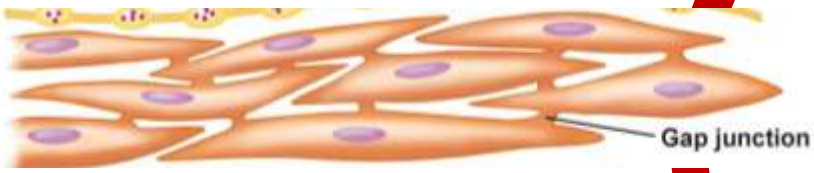


- Thus, vitamin D enhances neutrophil killing of S. pneumoniae while dampening excessive inflammatory responses and apoptosis, suggesting that vitamin D could be used alongside antibiotics when treating pneumococcal infections.

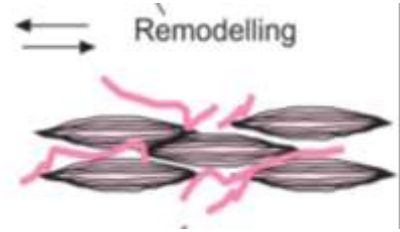
Vitamin D Attenuates Cytokine-Induced Remodeling in Human Fetal Airway Smooth Muscle Cells.

Britt RD Jr, J Cell Physiol. 2015; 230(6):1189-98

exposed to TNFα or TGFβ for up to 72 h.



human fetal airway smooth muscle (ASM) cells



- Proliferation of fetal ASM cells
- Matrix metalloproteinase MMP-9 expression
- Collagen III expression and deposition

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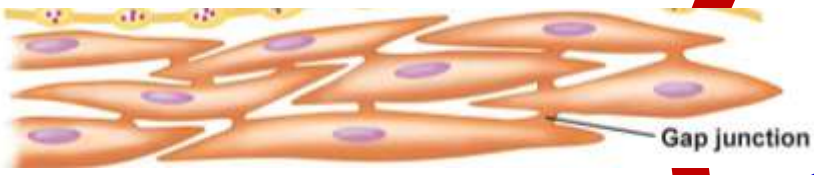
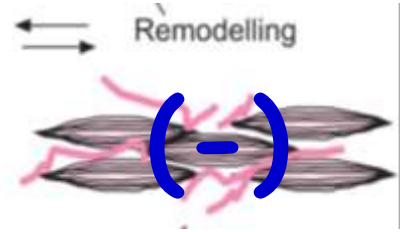


pre-treatment with calcitriol

(-)

human fetal airway smooth muscle (ASM) cells



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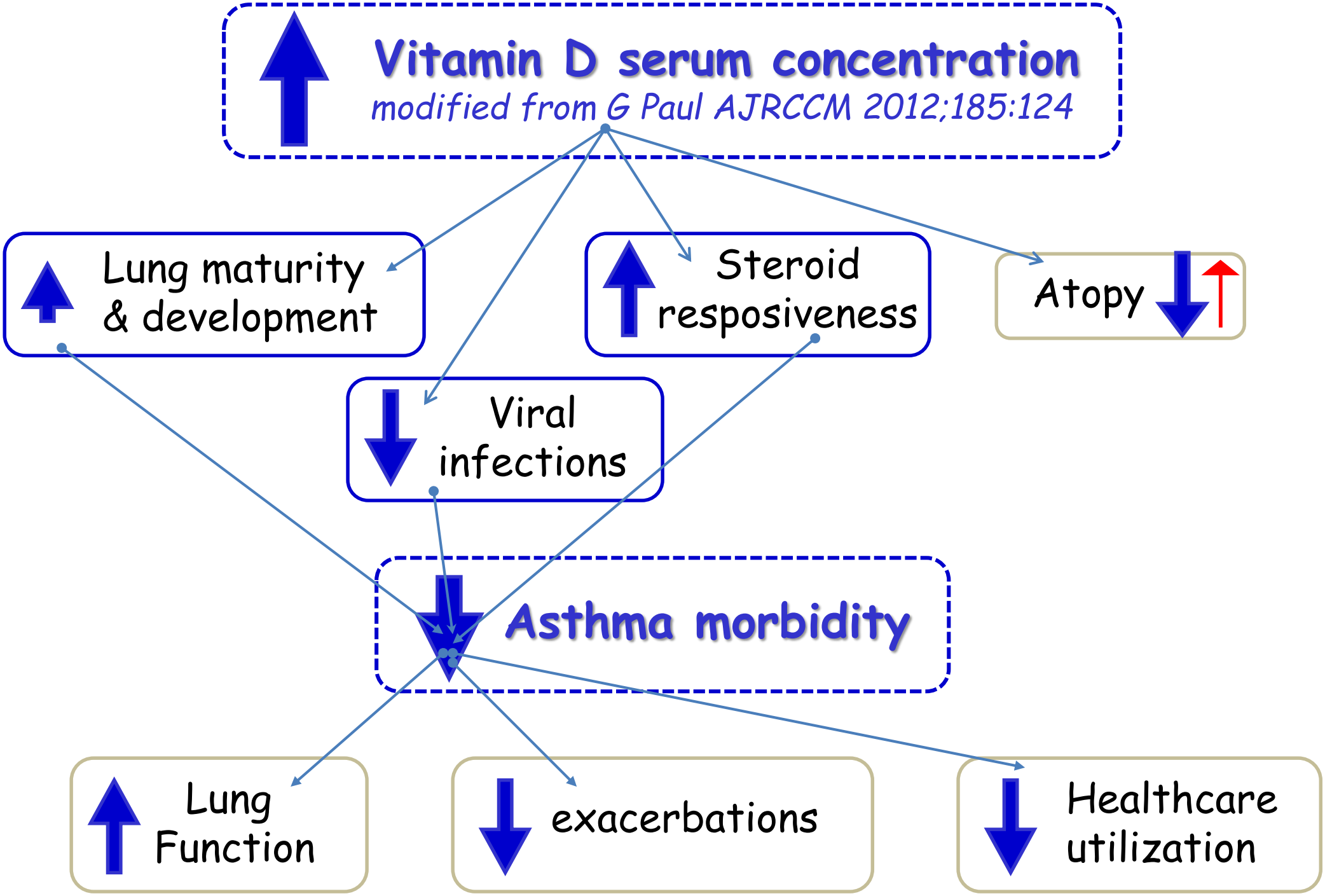

Vitamin D serum concentration
modified from G Paul AJRCCM 2012;185:124
Lung maturity & development
Steroid resposiveness
Atopy
Viral infections
Asthma morbidity
Lung Function
exacerbations
Healthcare utilization

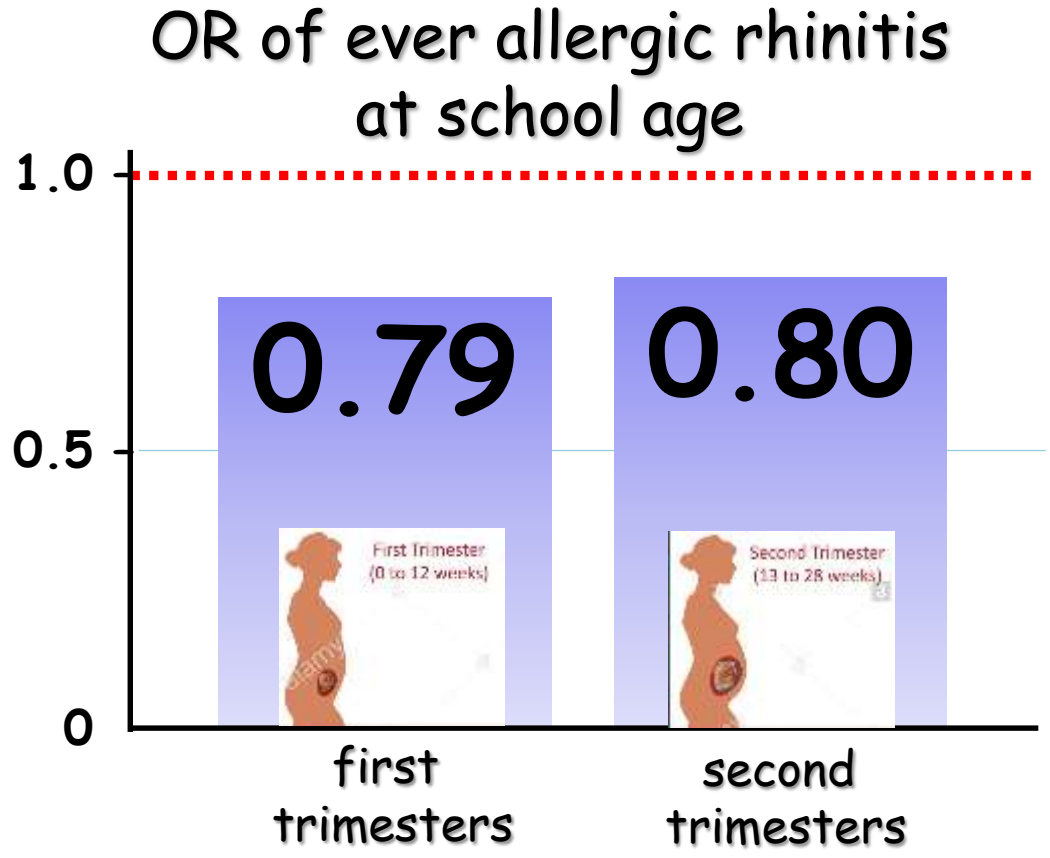
Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

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

- ✓ Introduction
- ✓ Immunomodulation related to allergy
- ✓ Fetal development
- ✓ 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

Prenatal, perinatal, and childhood vitamin D exposure and their association with childhood allergic rhinitis and allergic sensitization *Bunyavanich S, JACI 2016;137:1063.*

- ✓ 1248 mother-child pairs from a US prebirth cohort unselected for any disease;
- ✓ Vitamin D exposure assessed by measures of maternal intake during the first and second trimesters of pregnancy and serum 25[OH]D levels during pregnancy, cord blood, and children at school age (median age, 7.7 yrs).



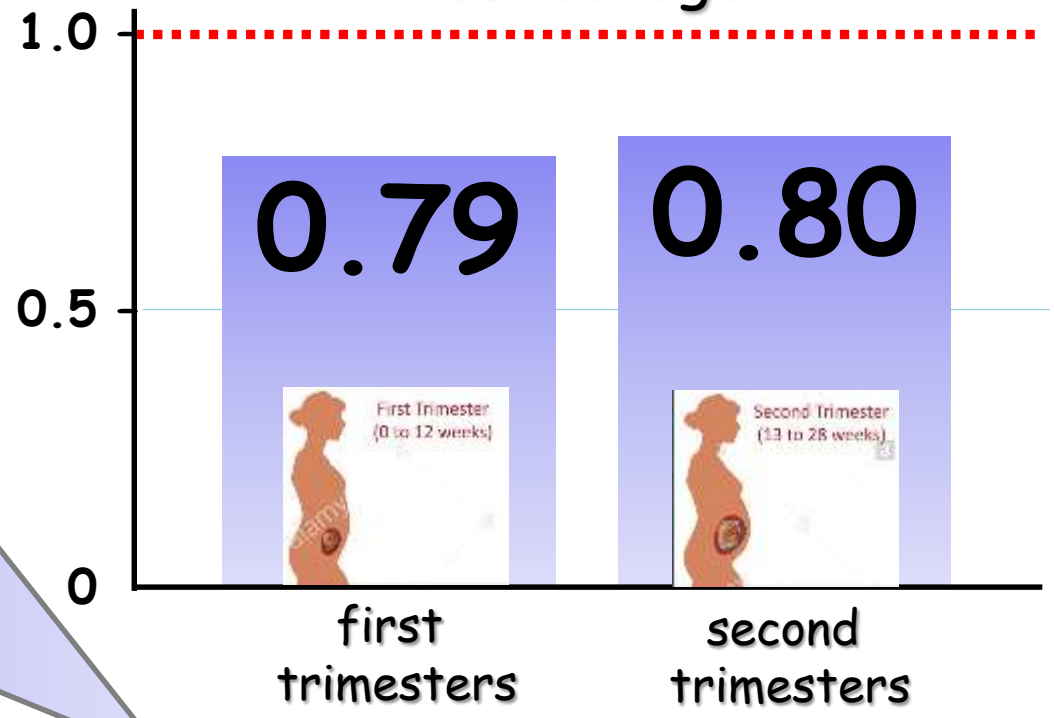
Each 100 IU/d of food-based vitamin D intake during:

Prenatal, perinatal, and childhood vitamin D exposure and their association with childhood allergic rhinitis and allergic sensitization *Bunyavanich S, JACI 2016;137:1063.*

✓

equivalent to the amount of vitamin D in an 8-ounce = **224 mL serving of milk**

OR of ever allergic rhinitis at school age



Each 100 IU/d of food-based vitamin D intake during:

Viosterol of high potency in seasonal hay fever and related conditions.

Rappaport BZ, JAMA 1933;101:105-9.

The treatment of hay fever and asthma with viosterol of high potency.

Rappaport BZ, J Allergy 1934;5:541-53.

Historically, **Rappaport** and colleagues investigated the modifying effect of vitamin D on allergic conditions as **early as the 1930s**

Relief of symptoms in a majority of allergic patients treated with viosterol (a vitamin D preparation produced by the irradiation of ergosterol) compared to controls

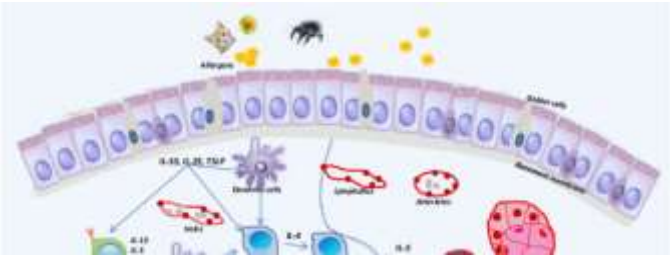
a finding subsequently supported by several studies:

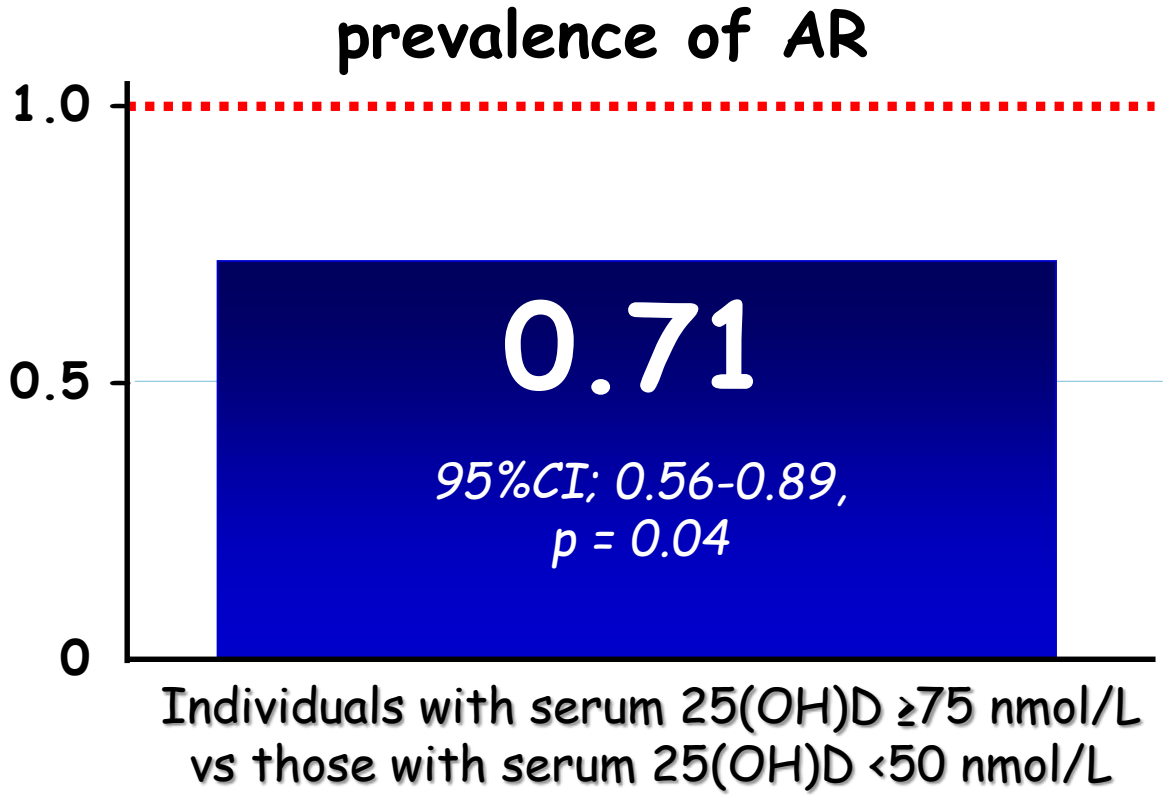
- *Jakso G. Borgy es Venerol Szemle **1950**; 4:223-5.*
- *Canon P. Acta OtorhinolaryngolBelg **1951**; 5:495-508.*
- *Utz G, MMW **1976**;118:1395-8.*
- *Reeve J, Br Med J **1980**;280:1340-4.*

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

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

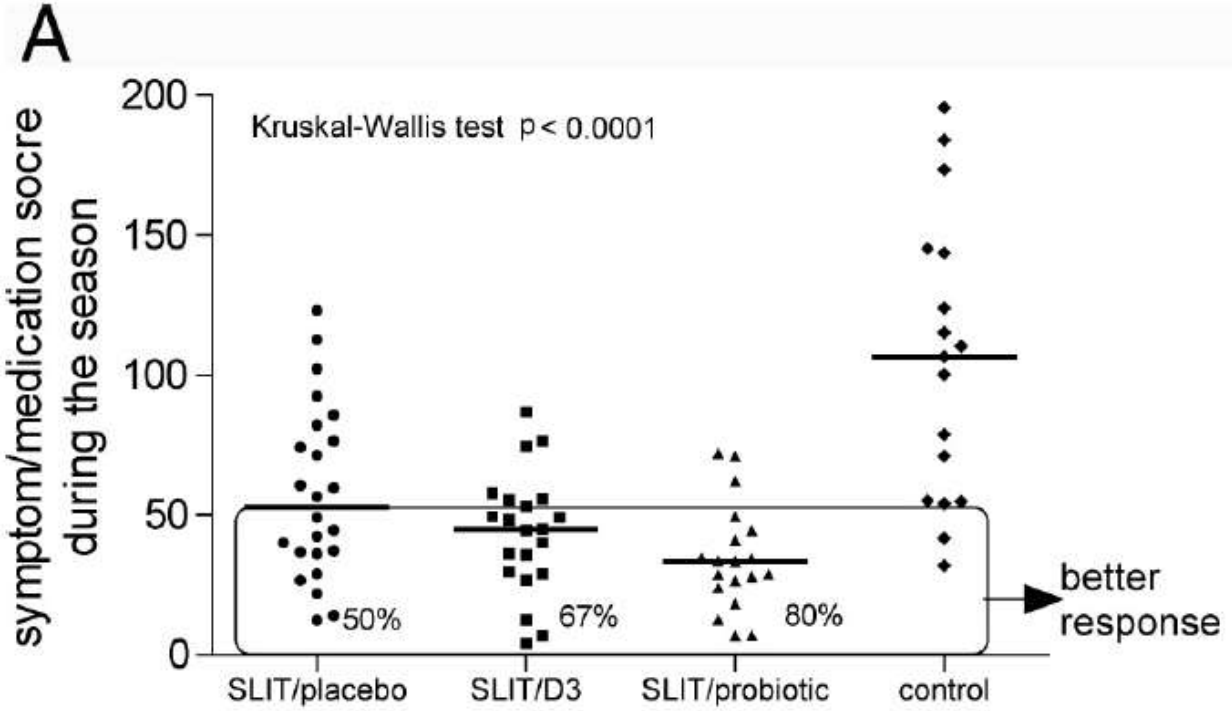
✓21 observational studies





Effect of Lactobacillus rhamnosus GG and vitamin D supplementation on the immunologic effectiveness of grass-specific sublingual immunotherapy in children with allergy. *Jerzynska J, Allergy Asthma Proc. 2016;37(4):324-34.*

- ✓100 children, ages 5-12 years, sensitive to grass pollen, with allergic rhinitis
- ✓5-grass SLIT 300 IR tablets with either vitamin D 1000 IU daily supplementation, probiotic, or placebo for 5 months
- ✓Control group



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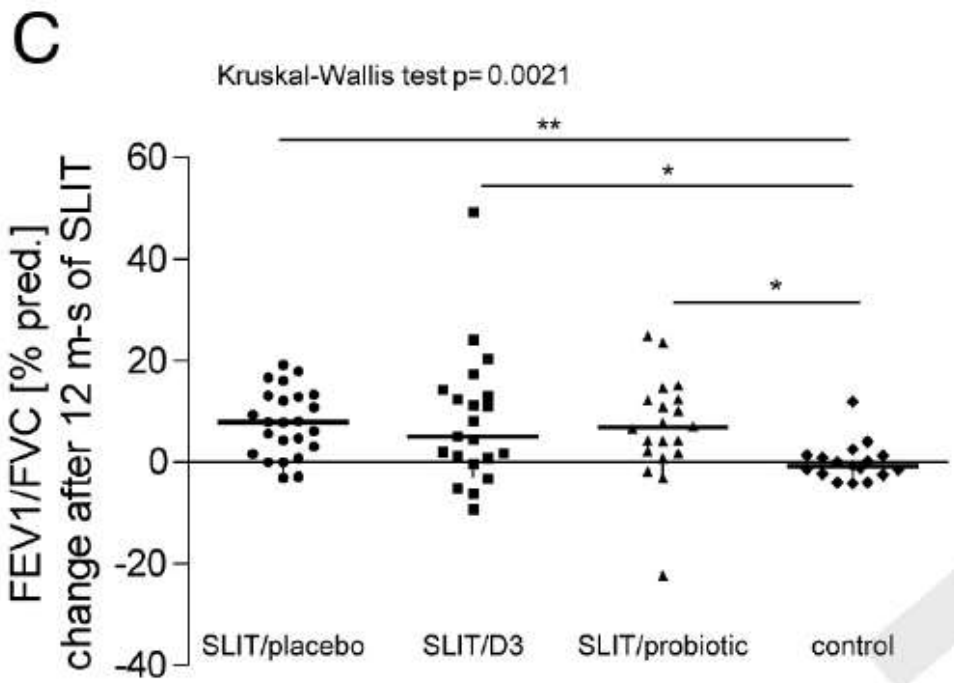

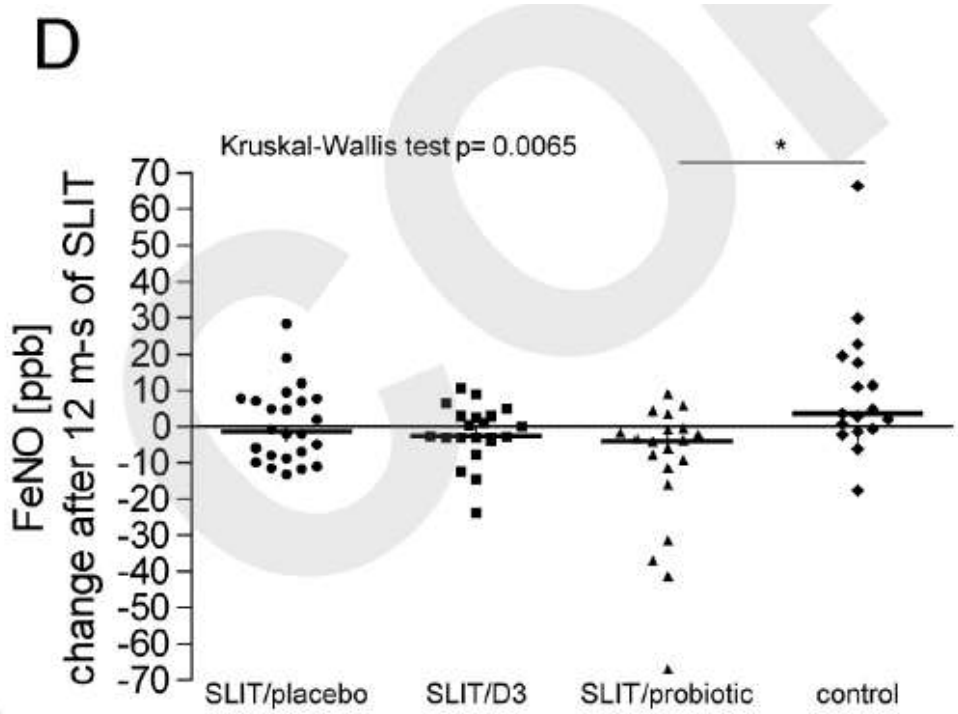

** p<0.05 ** p<0.01 *** p<0.001*

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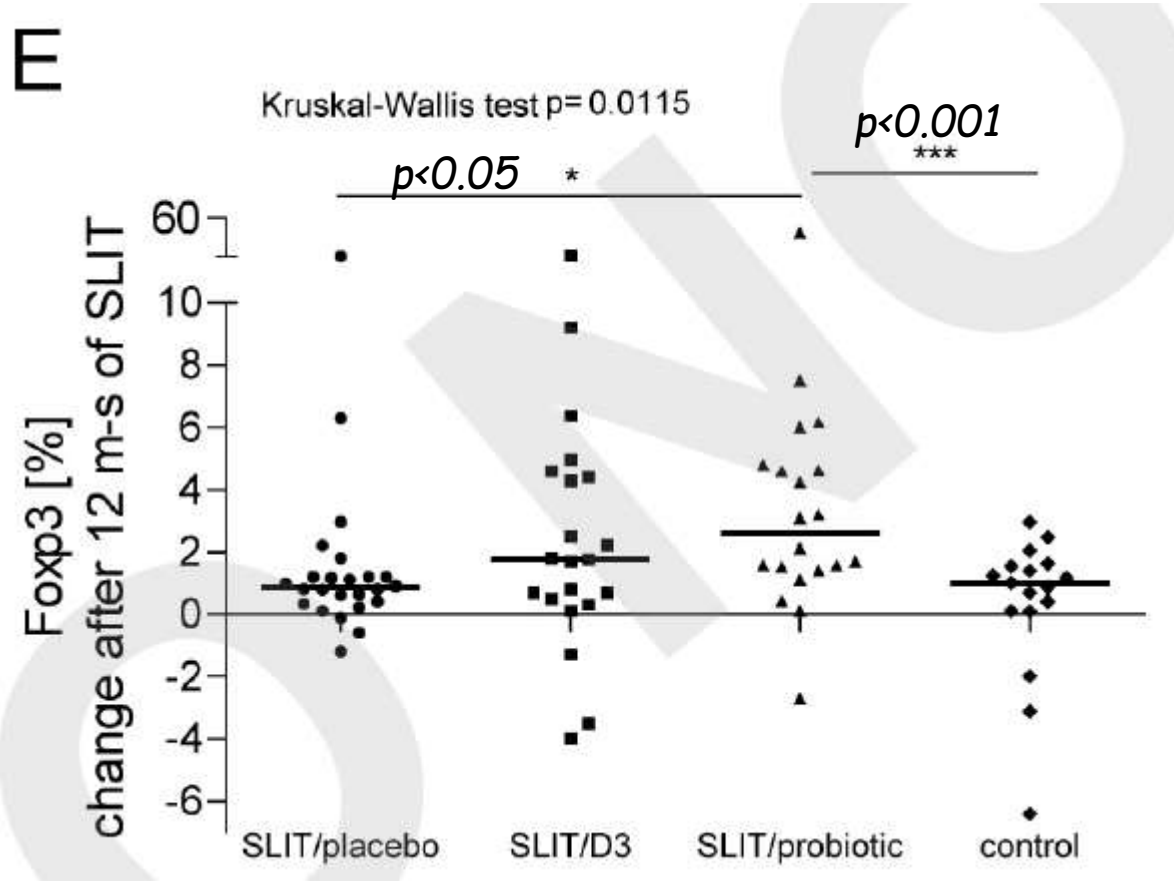
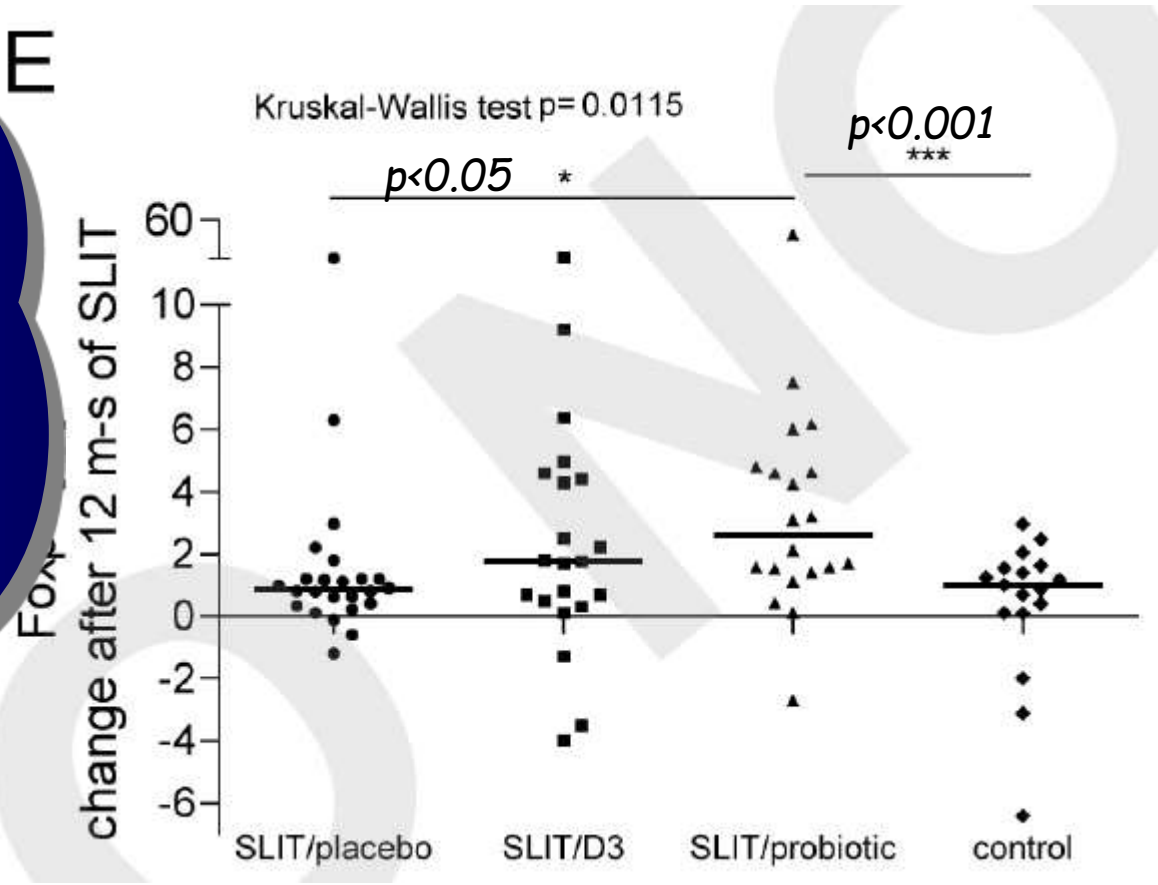


Effect of Lactobacillus rhamnosus GG and vitamin D supplementation on the immunologic effectiveness of grass-specific sublingual immunotherapy in children with allergy. *Jerzynska J, Allergy Asthma Proc. 2016;37(4):324-34.*

adding probiotic or vitamin D to SLIT improved clinical and immunologic effectiveness of SLIT without increasing its allergenicity, thereby improving the risk-benefit profile.



Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

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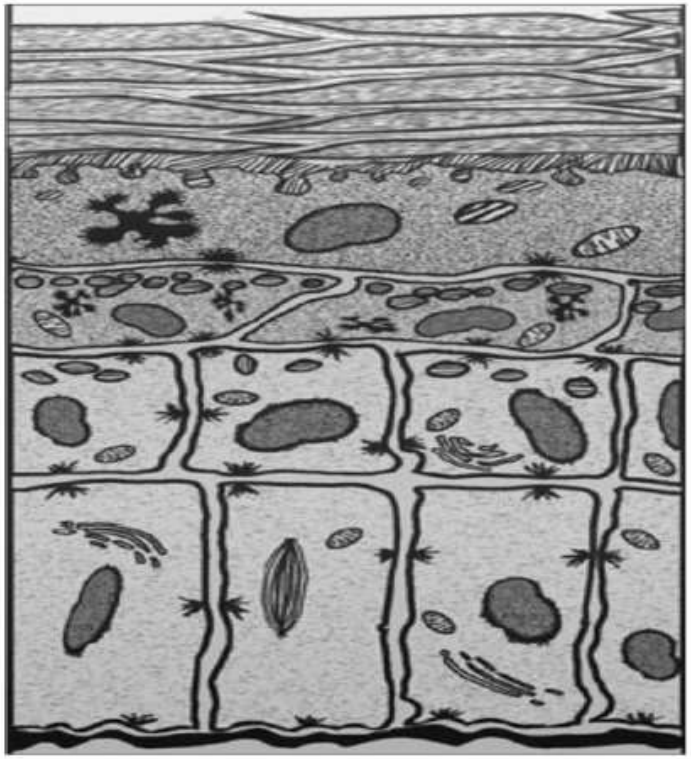
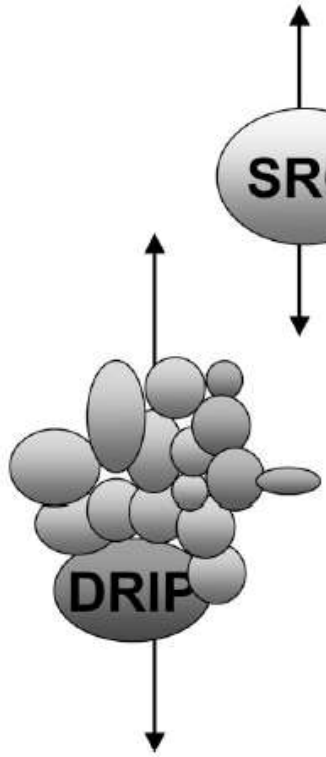
- ✓ Prevention and modification of food allergy anaphylaxis, urticaria
- ✓ Autoimmunity
- ✓ Other Diseases
- ✓ Conclusions

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



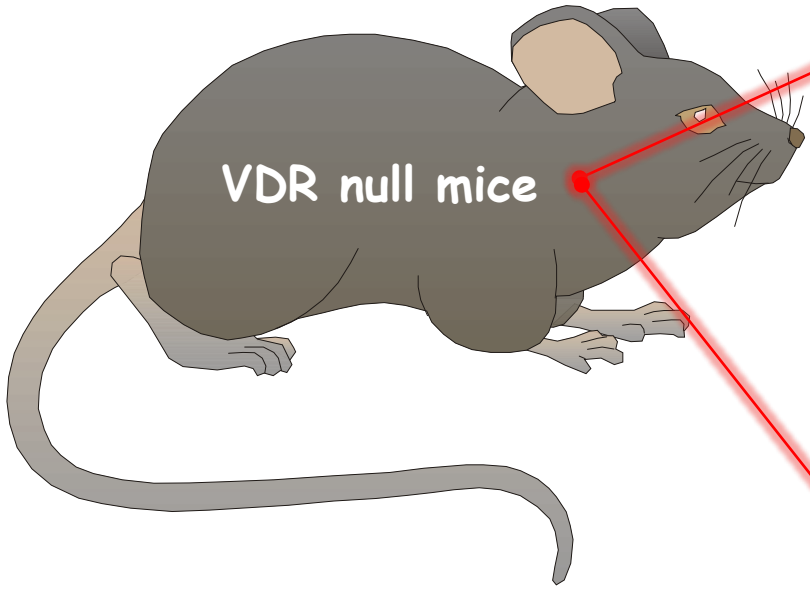


Coactivators	VDR Function	Target genes
SRC	Barrier formation	ABCA12, UGCG, ELOVL4
	Innate Immunity	Cathelicidin, CD14
	Epidermal Differentiation	K1, K10, FLG, LOR
	Hair Differentiation	Hair keratins
DRIP	Proliferation	Cyclin D1, Gli 1
	Wnt signaling	

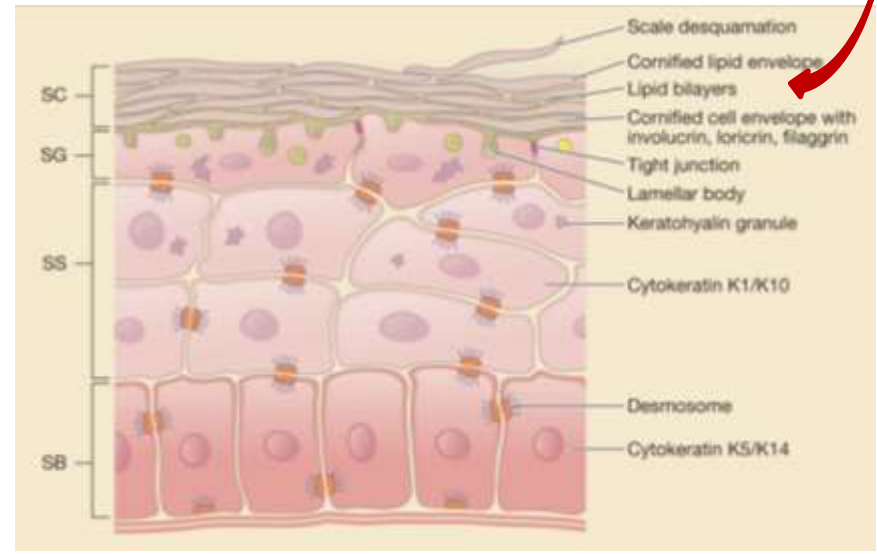
Bikle DD. ***Vitamin D metabolism and function in the skin.*** *Mol Cell Endocrinol. 2011;347(1-2):80-9.*

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*.



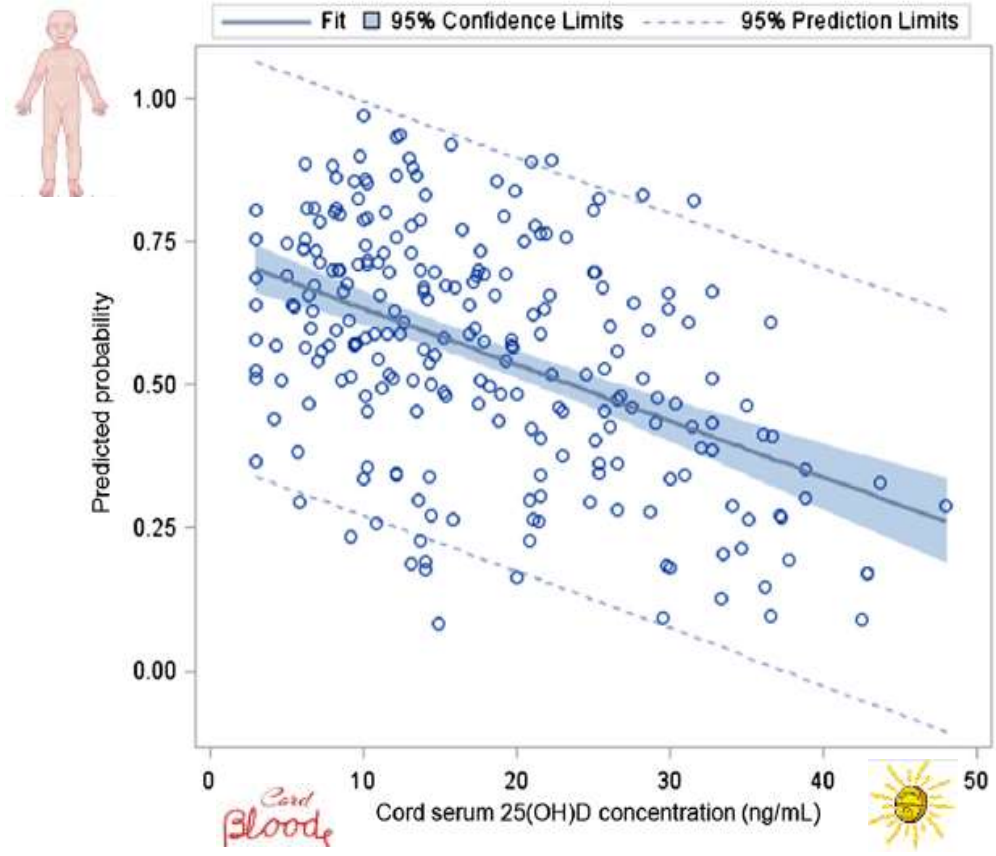
Reduced Skin Barrier Function

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

Baiz N, JACI 2014;133:147

- ✓ 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



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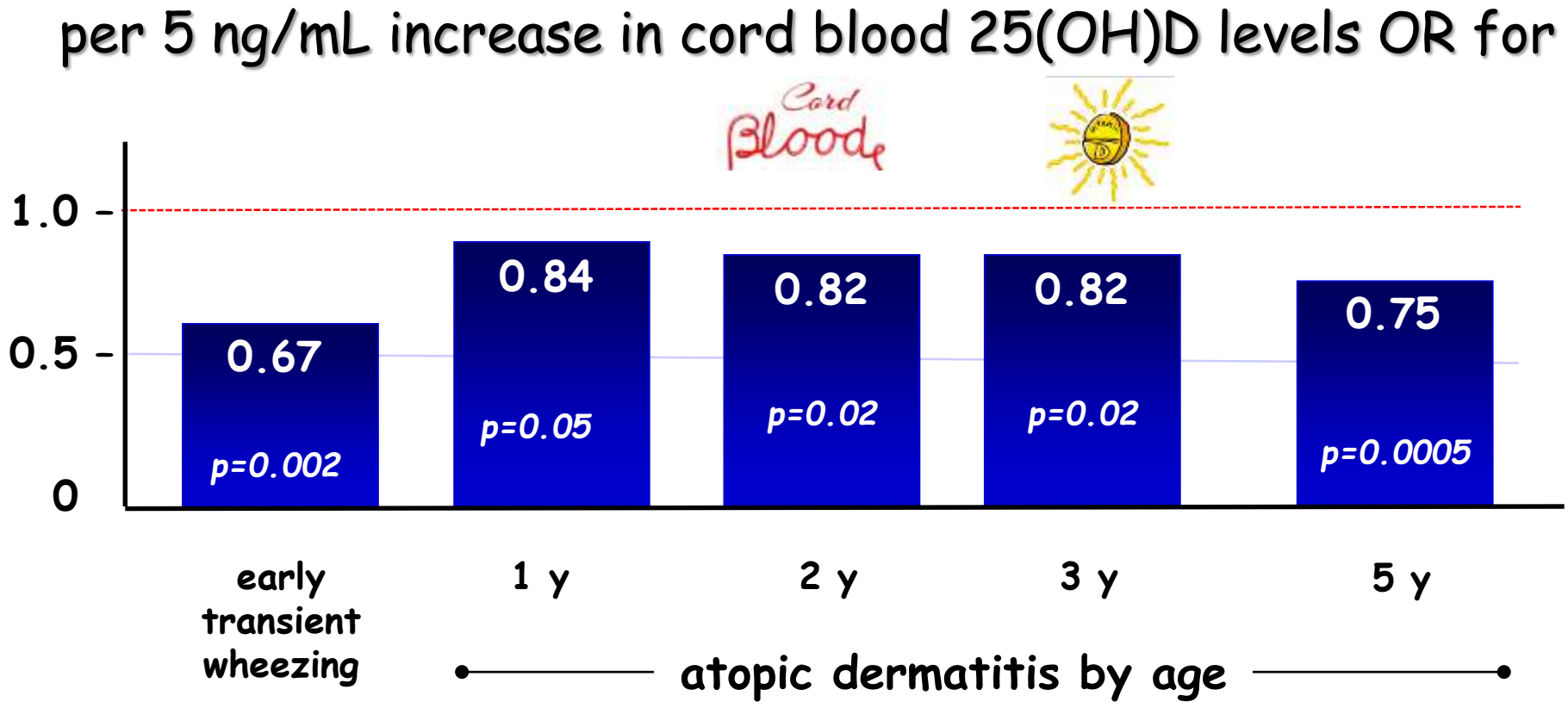
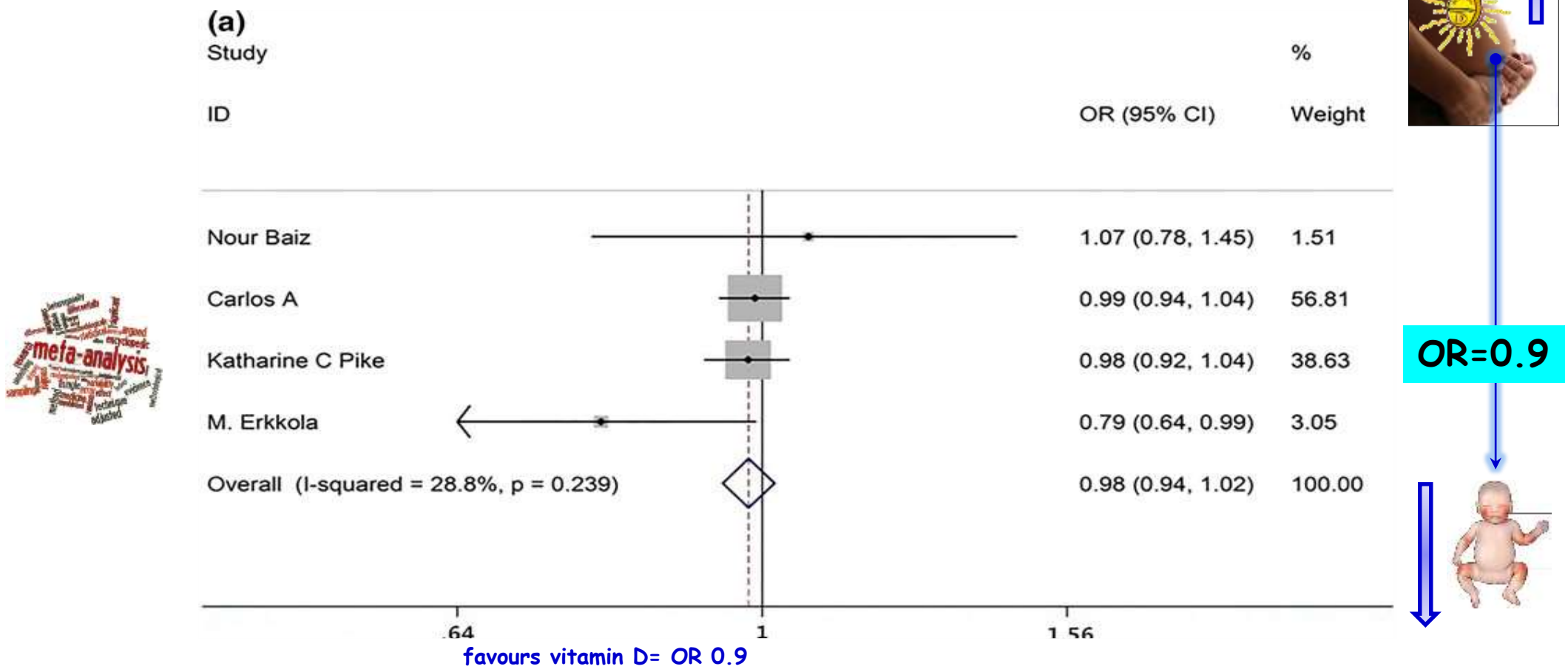
Baiz N, JACI 2014;133:147



Maternal vitamin D status and childhood asthma, wheeze and eczema: a sistematic review and meta-analysis

Wei Z, PAI 2016;27:612-619

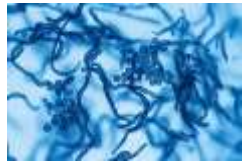
Forest plot of the association between maternal vitamin D status and childhood eczema



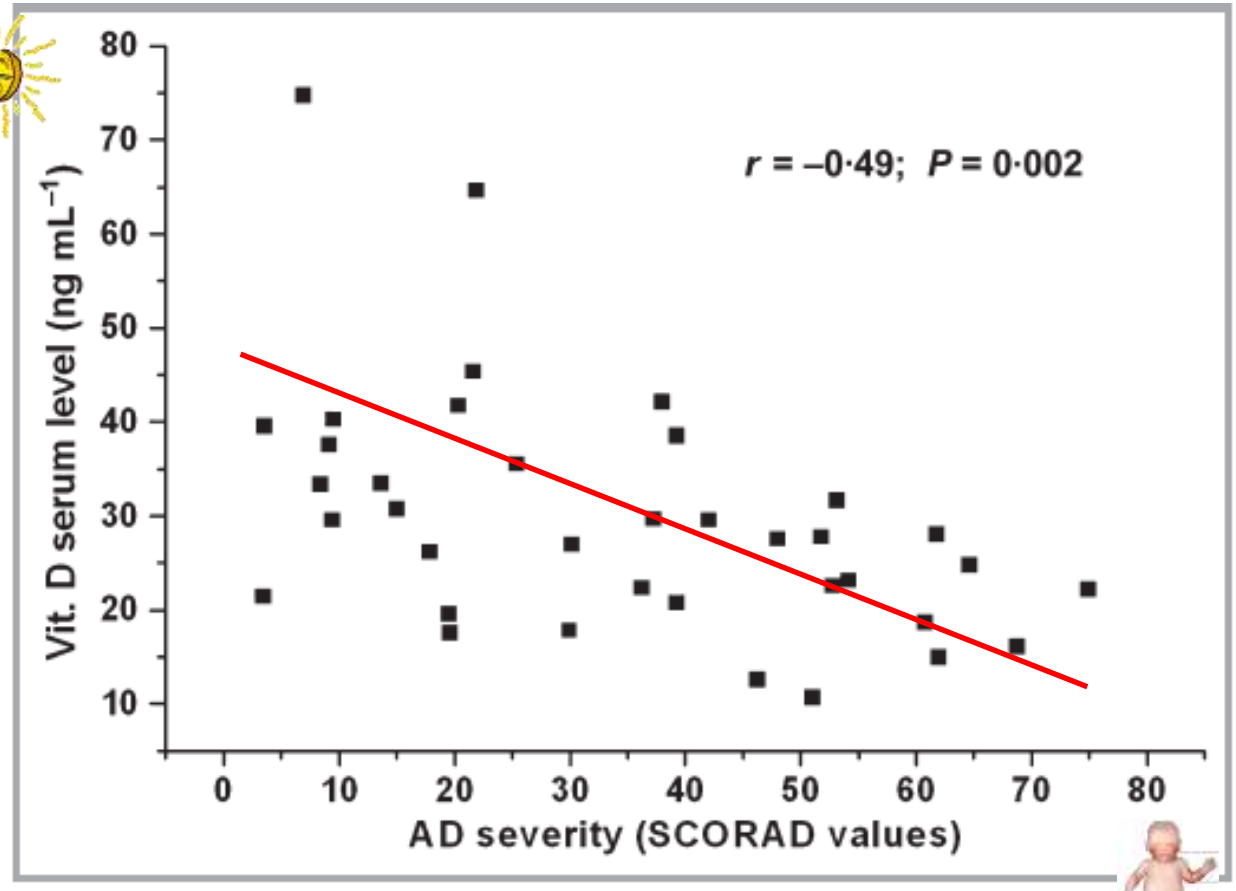
Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children.

Peroni DG, 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.

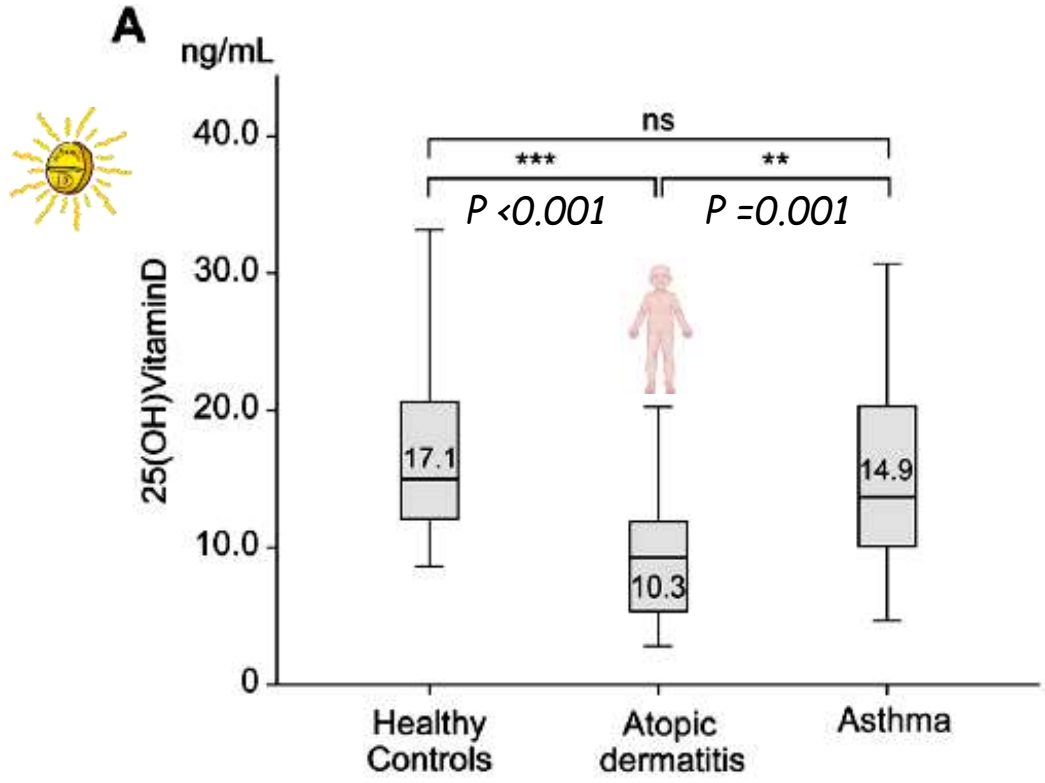


Lower vitamin D status is closely correlated with eczema of the head and neck.

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

- ✓ 82 patients with AD, 38 asthmatic patients, and 49 healthy control subjects (HCs).
- ✓ 25-hydroxyvitamin D.

Mean serum 25-hydroxyvitamin D *(25[OH]VitaminD)* concentrations

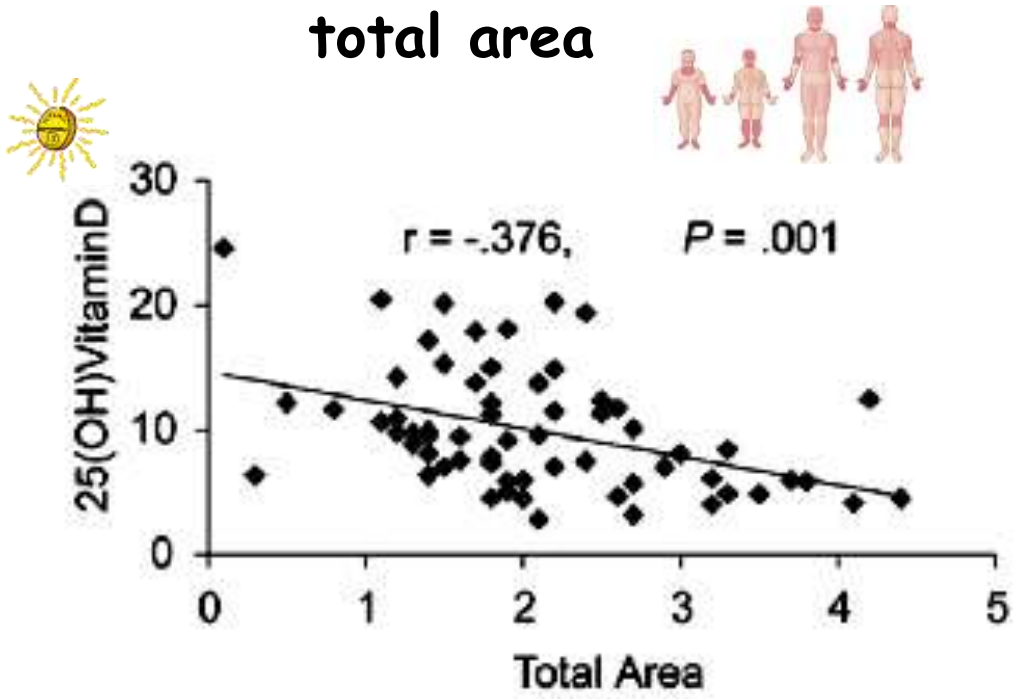


Lower vitamin D status is closely correlated with eczema of the head and neck.

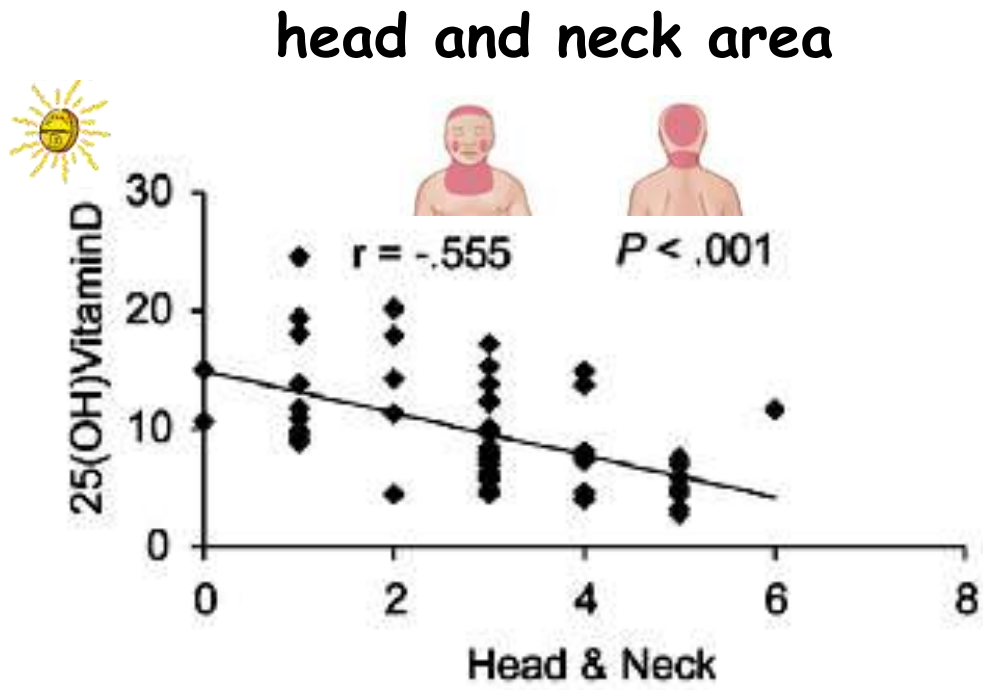
Noh S, J Allergy Clin Immunol 2014;133:1767-69

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

total area



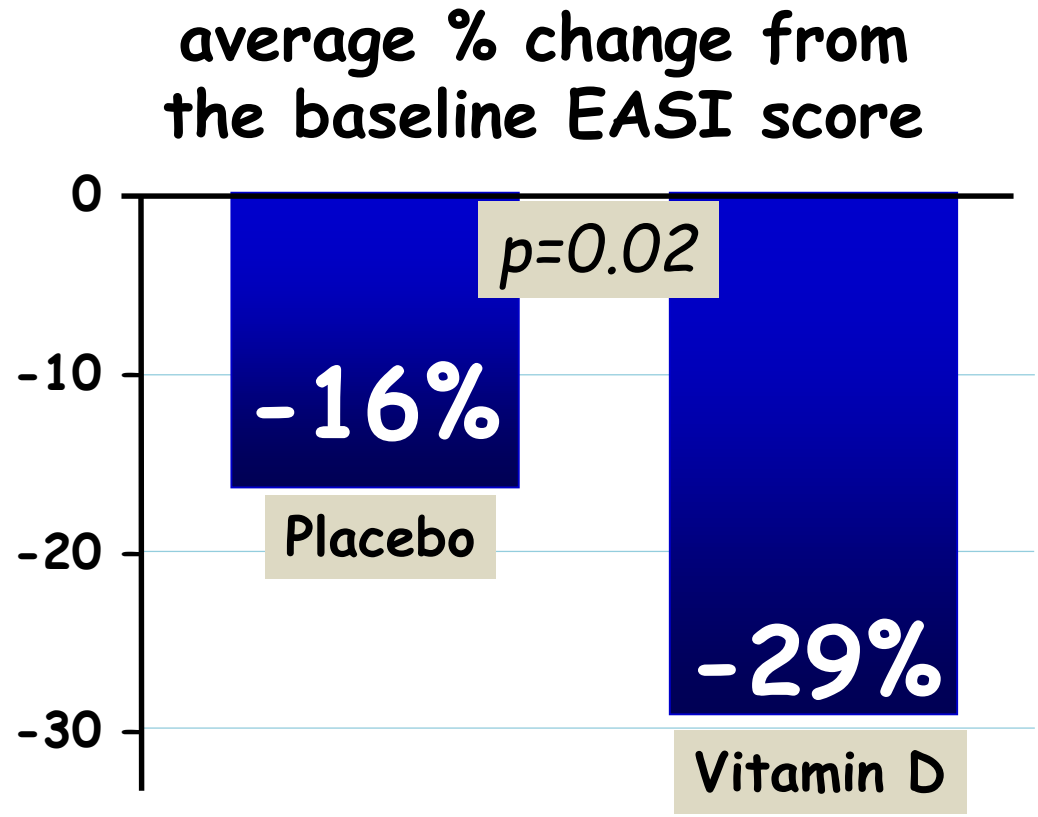
head and neck area



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.



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

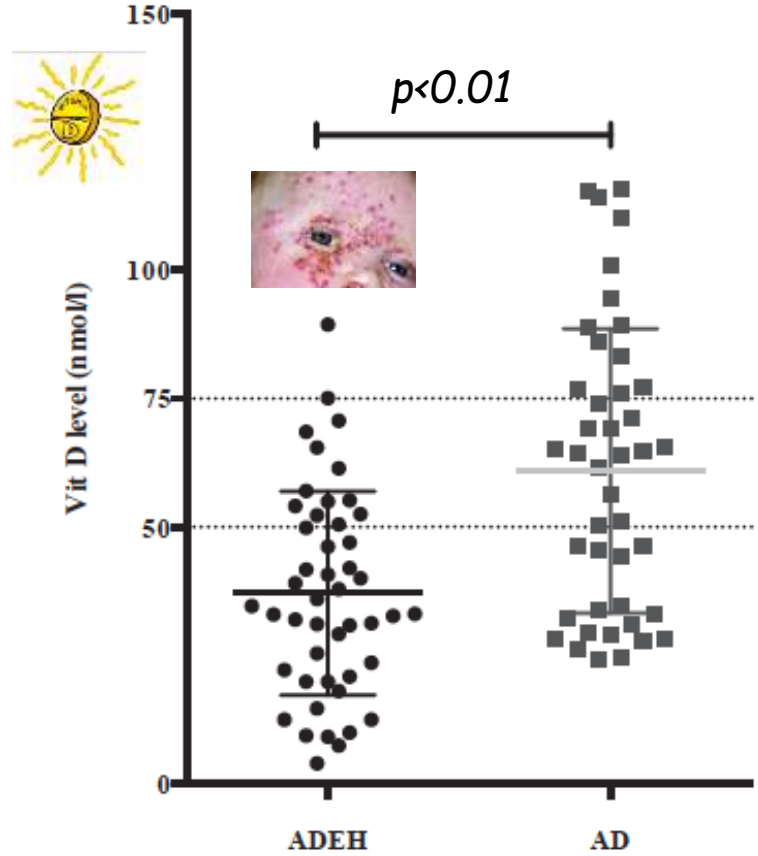
Albenali LH , JACI 2016;138:1715.

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).



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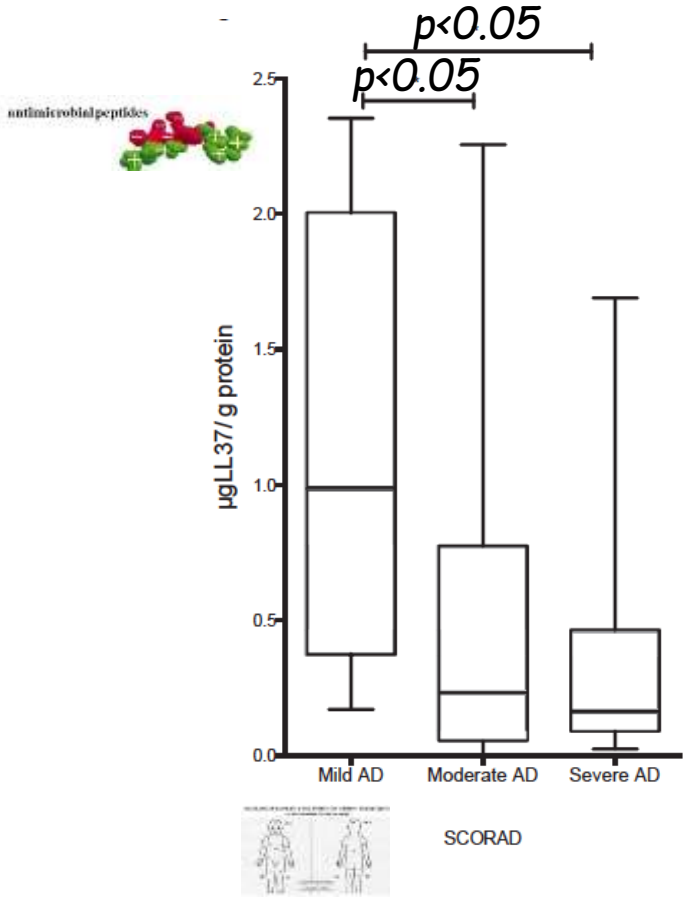
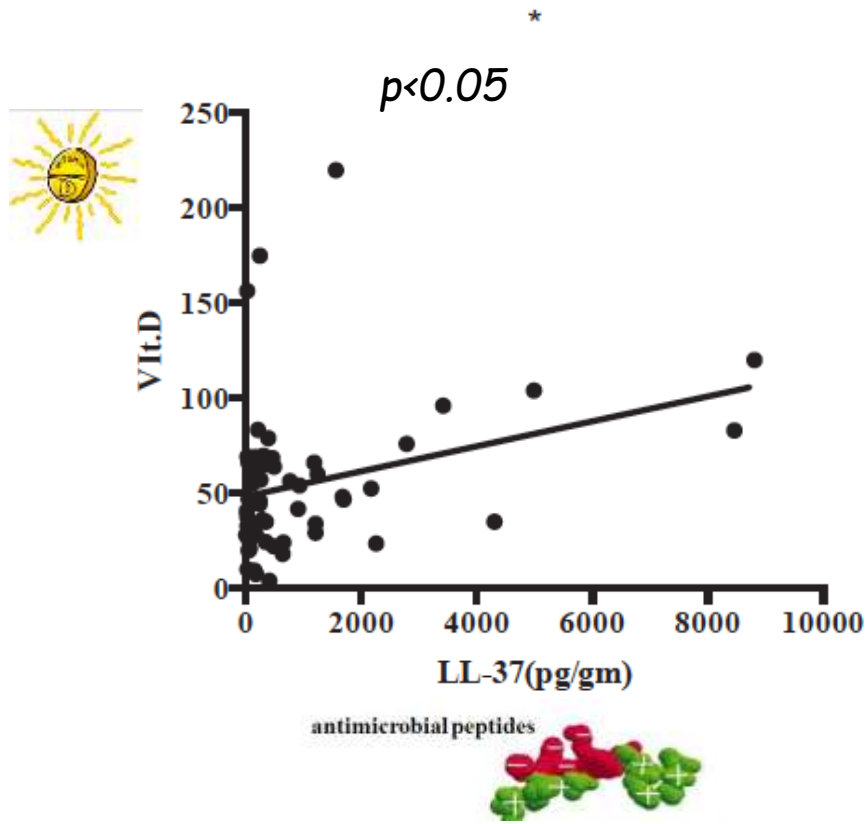
Albenali LH , JACI 2016;138:1715.

Baseline LL-37 levels stratified according to SCORAD



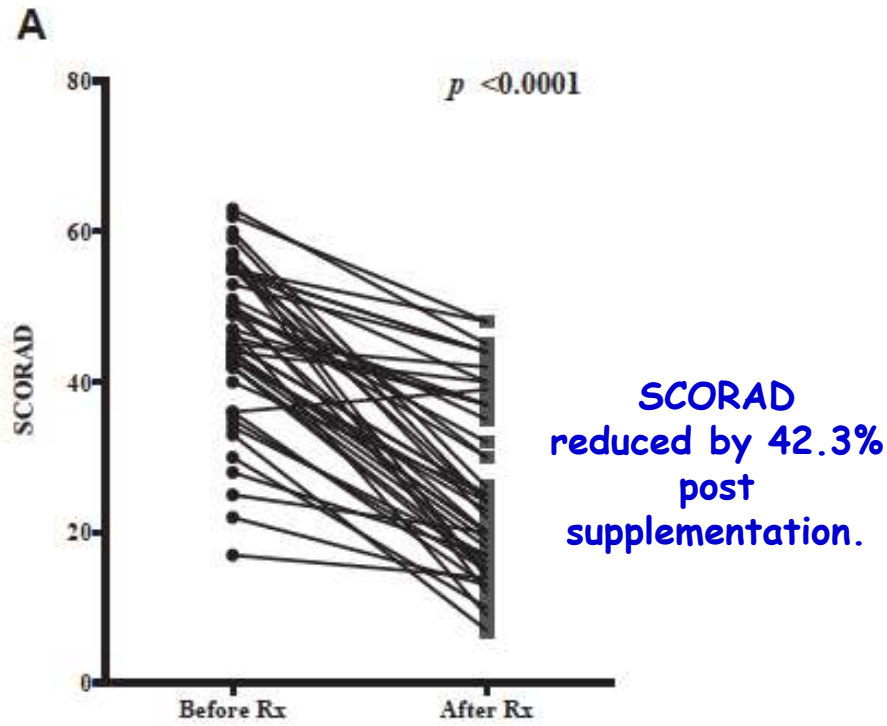
VD and LL-37 correlation.



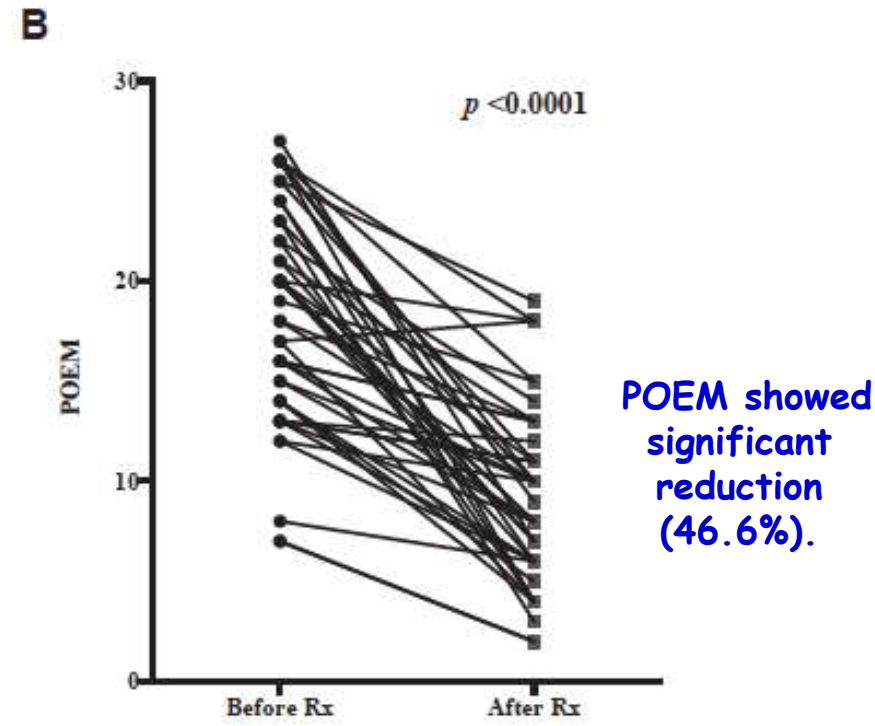
Vitamin D and antimicrobial peptide levels in patients with atopic dermatitis and atopic dermatitis complicated by eczema herpeticum: A pilot study.

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

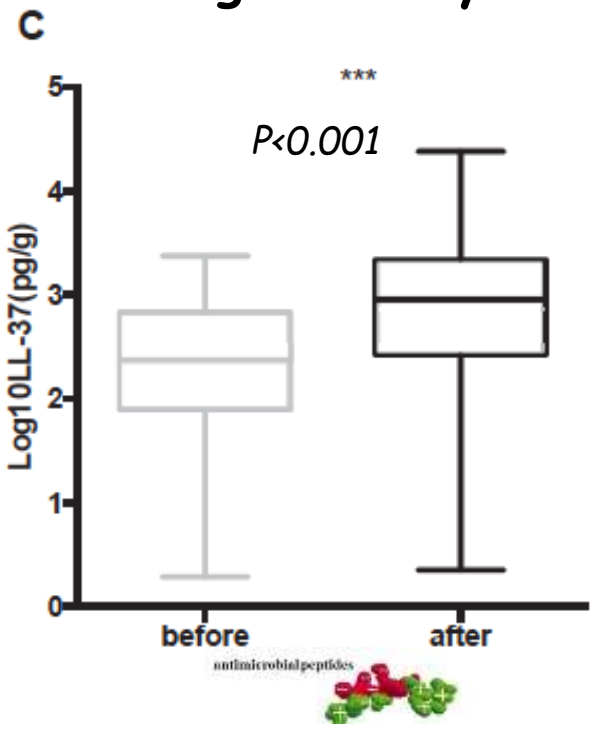
POEM: Patient Oriented Eczema Measure

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

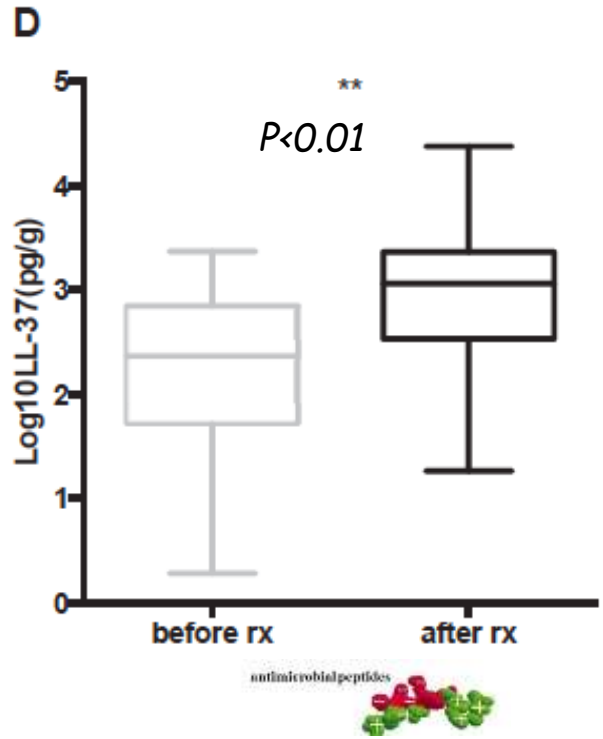
Albenali LH , JACI 2016;138:1715.

Postsupplementation analysis (n=47).

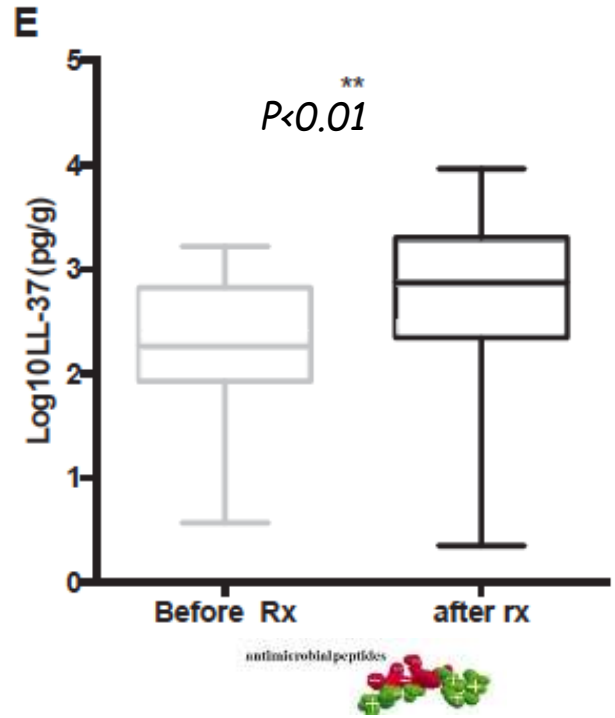
LL-37 levels increased significantly



Lesional LL-37 levels increased



Non-Lesional LL-37 levels increased

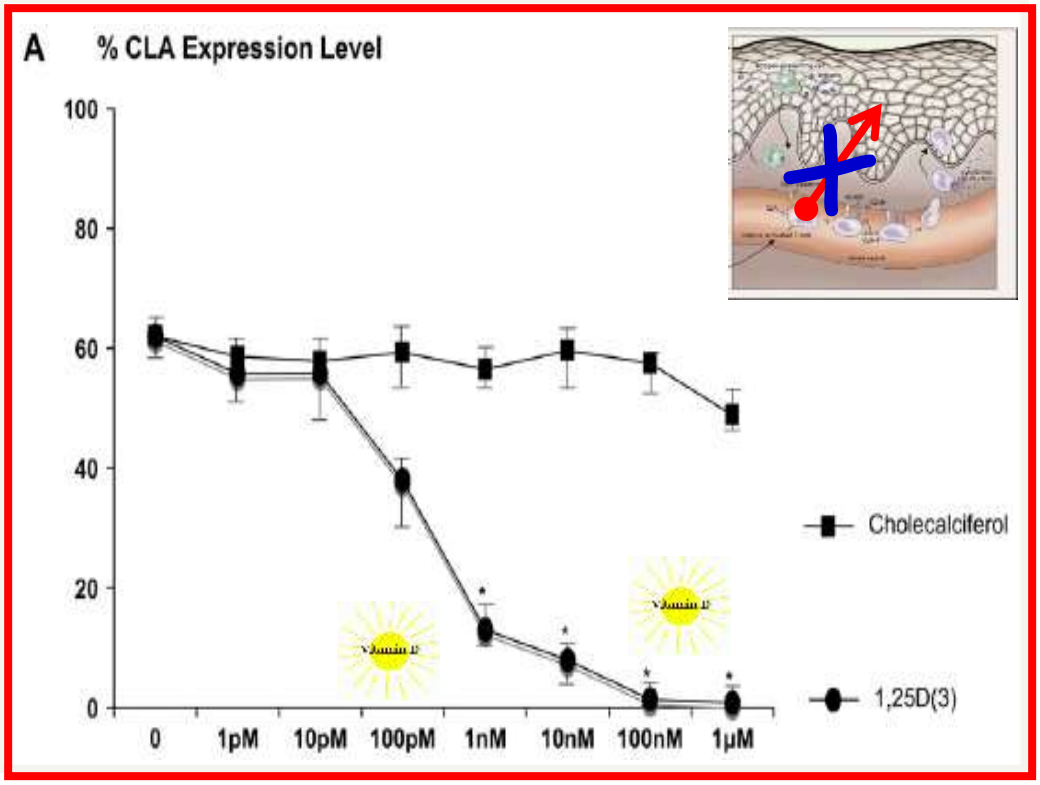


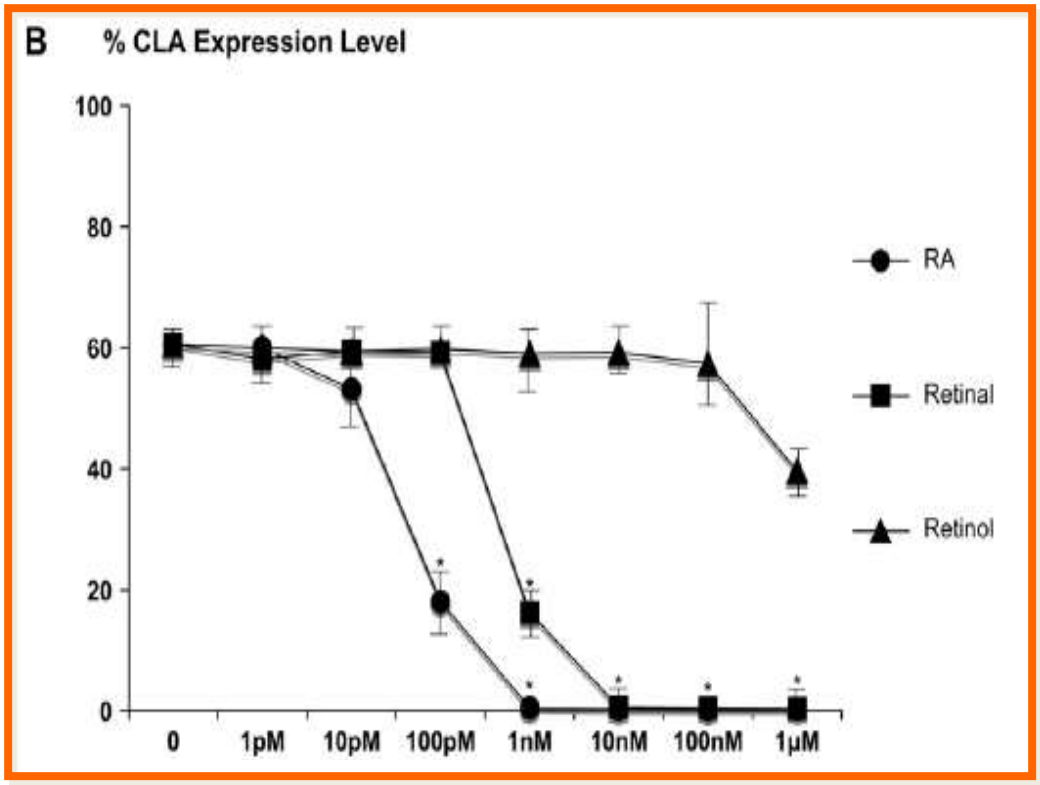
LL-37 levels were quantified from superficial samples of stratum corneum

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*

Probiotics and Atopic Dermatitis: An Overview.

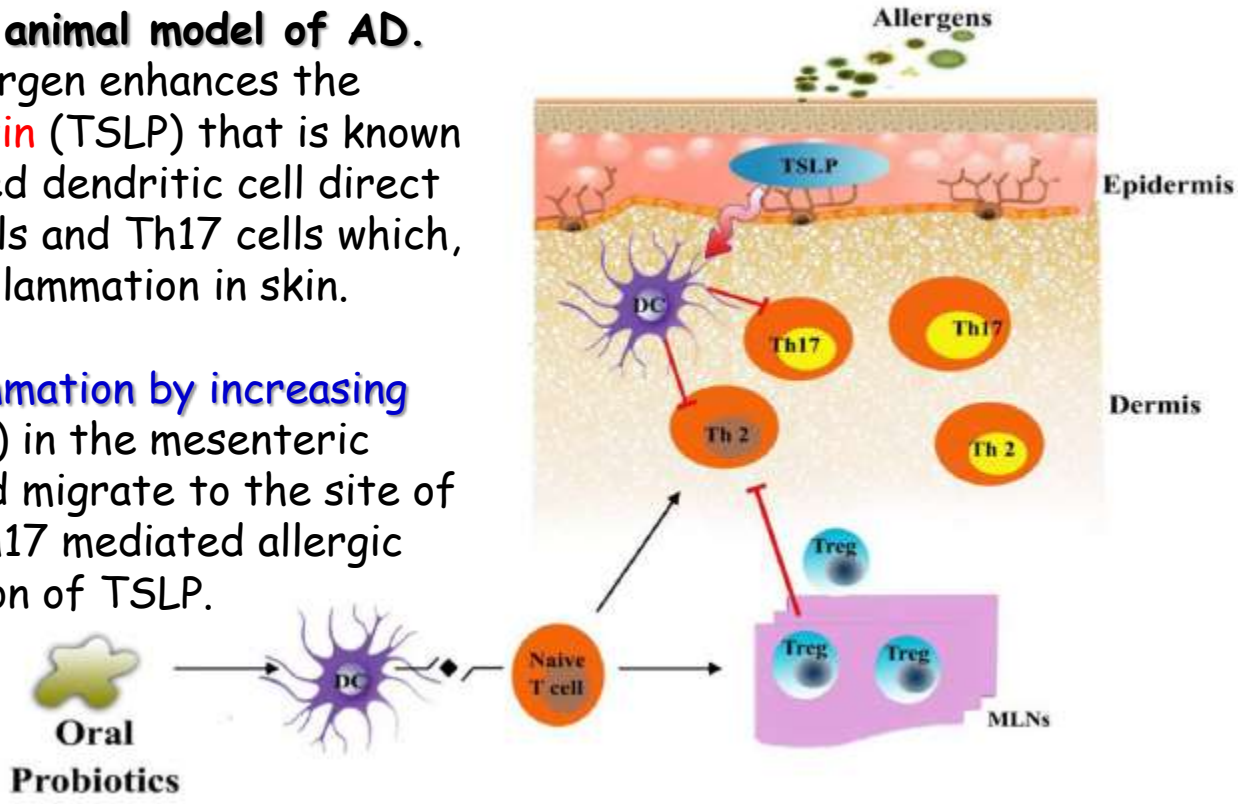
Rather IA, Front Microbiol. 2016 Apr 12;7:507.

- The effects of probiotics in the prevention and treatment of AD remain elusive.

- However, evidence from different research groups show that **probiotics could have positive effect on AD treatment**, if any, that depend on multiple factors, such as specific probiotic strains, time of administration (onset time), duration of exposure, and dosage.

Proposed mechanism of probiotics in an animal model of AD. Exposure of atopic skin to a potential allergen enhances the expression of thymic stromal lymphopoietin (TSLP) that is known to activate dendritic cells (DC). Stimulated dendritic cell direct differentiation of naïveT-cell intoTh2 cells and Th17 cells which, are known as the mediators of allergic inflammation in skin.

Probiotics could inhibit the allergic inflammation by increasing the population of regulatoryTcells (Tregs) in the mesenteric lymphnodes of patients. TheseTregs could migrate to the site of inflammation and suppress theTh2 and Th17 mediated allergic response or directly reduce the expression of TSLP.



Reduced Th22 cell proportion and prevention of atopic dermatitis in infants following maternal probiotic supplementation.

Rø ADB. Clin Exp Allergy. 2017 [Epub ahead of print]

✓415 pregnant women randomized to ingest a combination of Lactobacillus rhamnosus GG (LGG), Bifidobacterium animalis subsp. lactis Bb-12 (Bb-12) and Lactobacillus acidophilus La-5 (La-5) or placebo,

✓their offspring assessed for AD during the first 2 years of life.

✓Peripheral blood collected at 3 months of age for regulatory T cells (n=140) and Th subsets (n=77) including Th1, Th2, Th9, Th17 and Th22.

- The proportion of Th22 cells (≈Th17) was reduced in children in the probiotic group compared to the placebo group (median 0.038% vs 0.064%, *P=.009*).

- The difference between the probiotic and placebo groups was also observed in the children who did not develop AD during the 2-year follow-up.

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- The proportion of Th22 cells was increased in children who developed AD compared to the children who did not develop AD (0.090% vs 0.044%, P<.001).

the preventive effect of probiotics on AD is partially mediated through the reduction in Th22 cells.

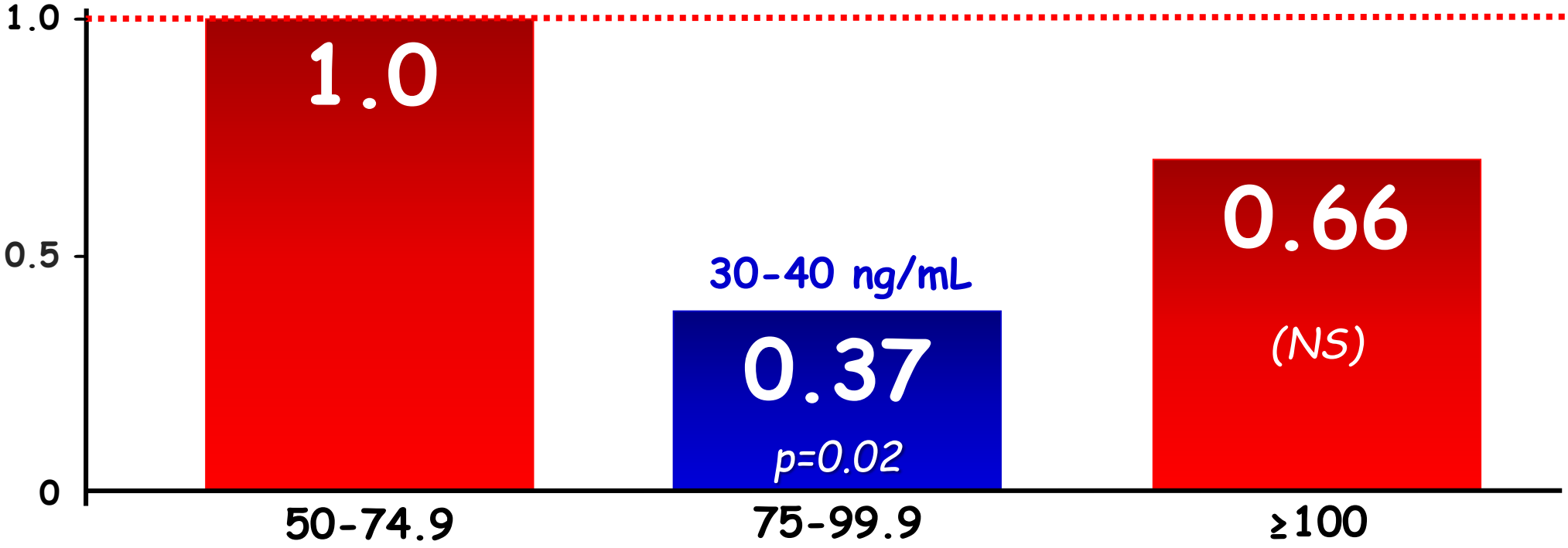
Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

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

- ✓ Introduction
- ✓ Immunomodulation related to allergy
- ✓ Fetal development
- ✓ 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

Neonatal vitamin D status and childhood peanut allergy: a pilot study. *Mullins, Ann Allergy Asthma Immunol 2012;109:324*

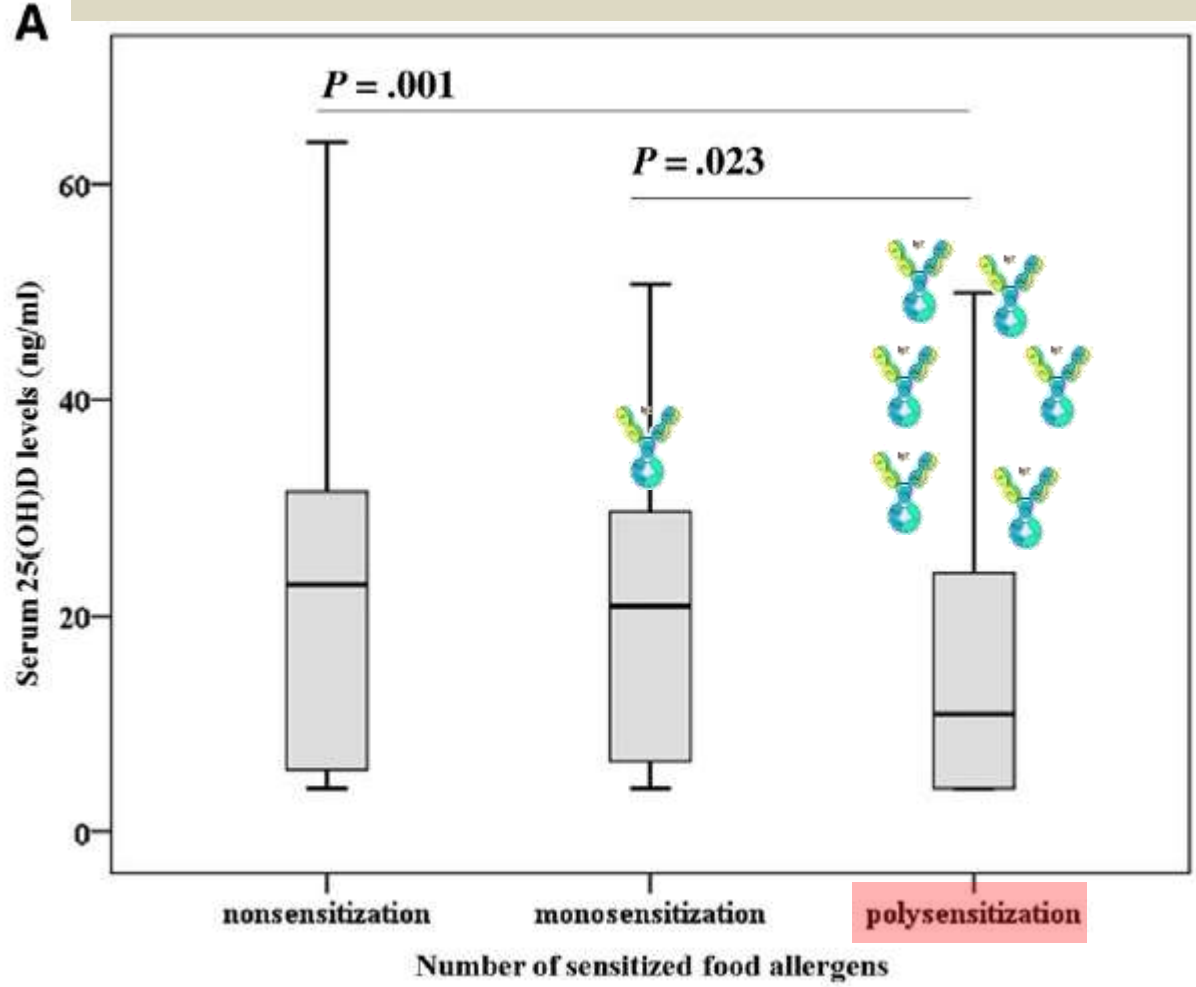
OR for peanut allergy in children ≤72 mo.



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)

Median serum vitamin D levels in the groups classified by the number of sensitized food allergens



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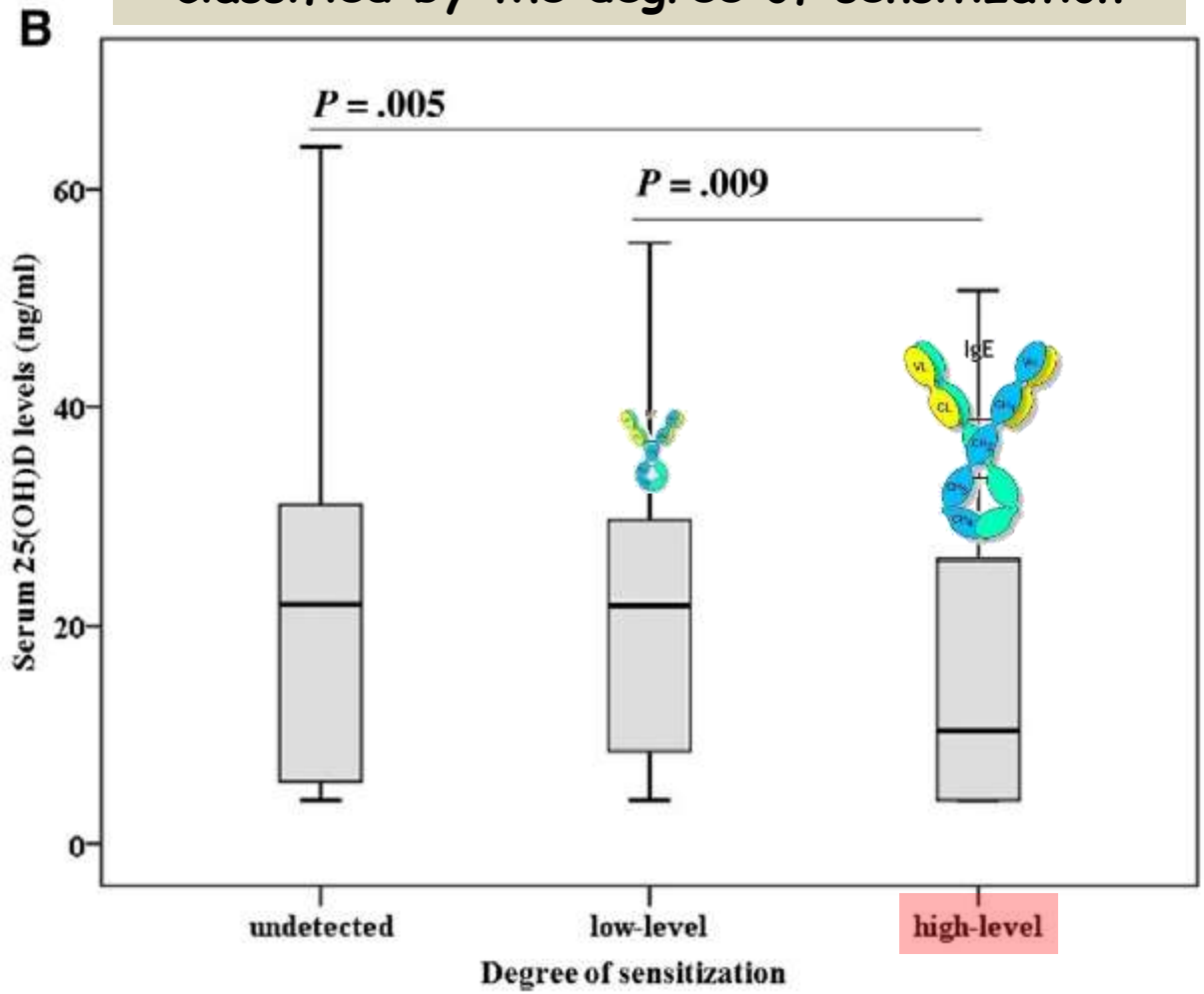
Median serum vitamin D levels in the groups classified by the degree of sensitization



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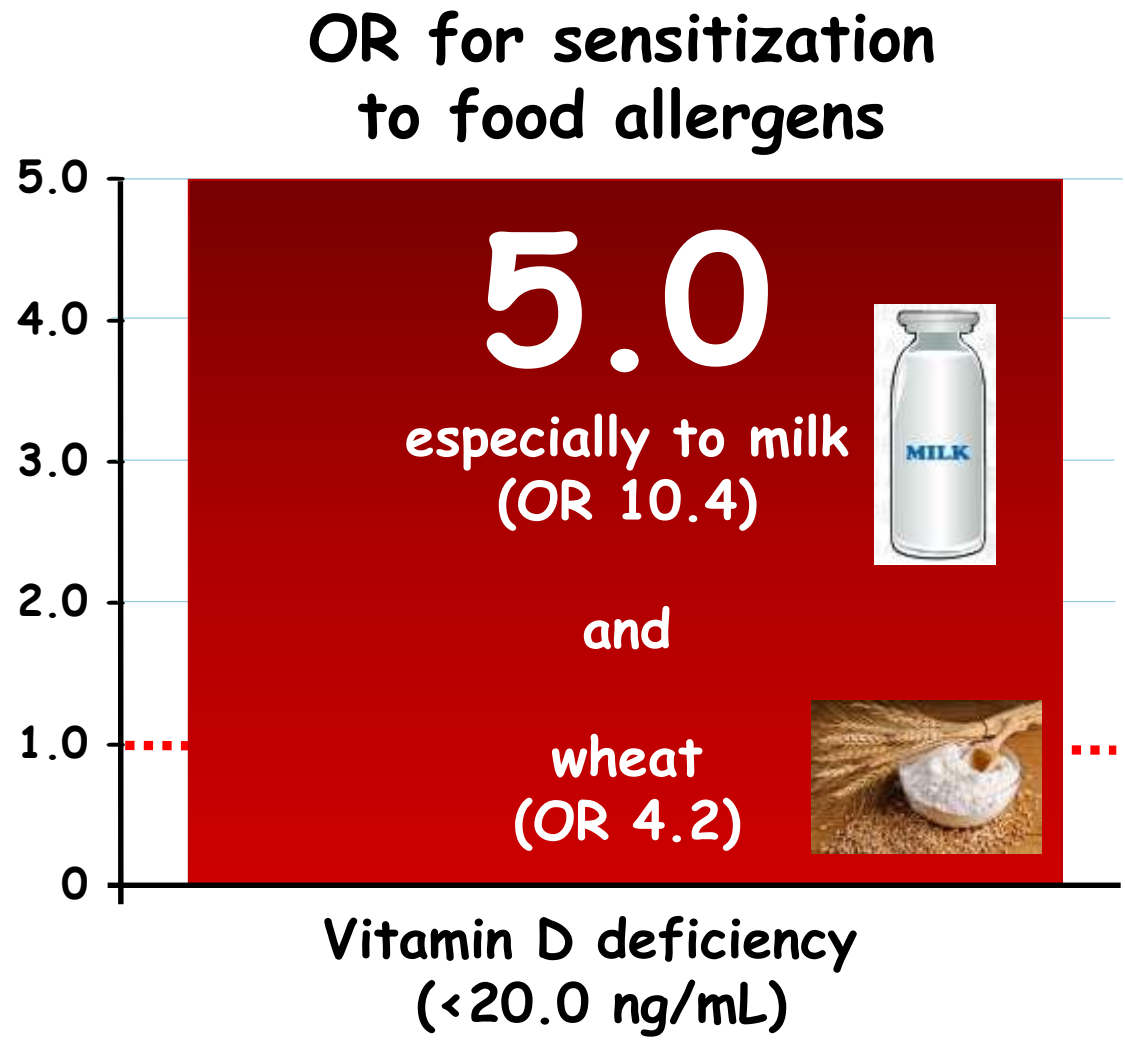
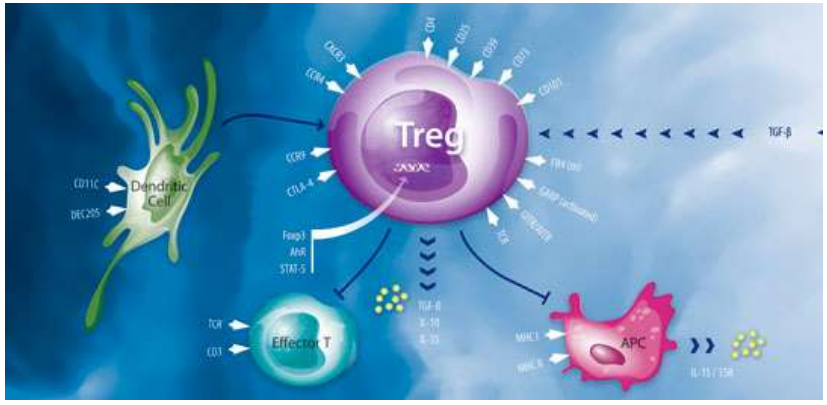
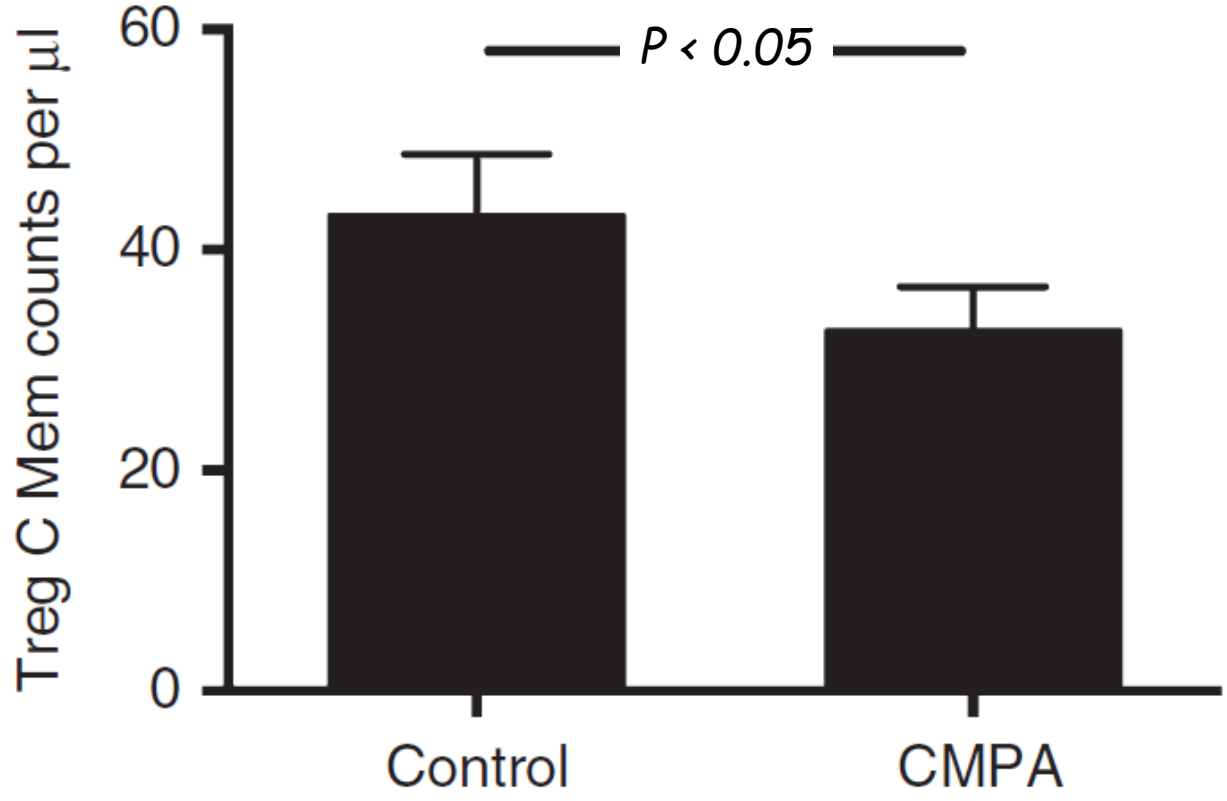


The establishment of cow's milk protein allergy in infants is related with a deficit of regulatory T cells (Treg) and vitamin D. *Perezabad L, Pediatr Res. 2017 [Epub ahead of print]*

✓Treg and cytokine-secreting cells in blood samples from 28 infants younger than 9 mo obtained 1-4 d after the first adverse reaction to milk.





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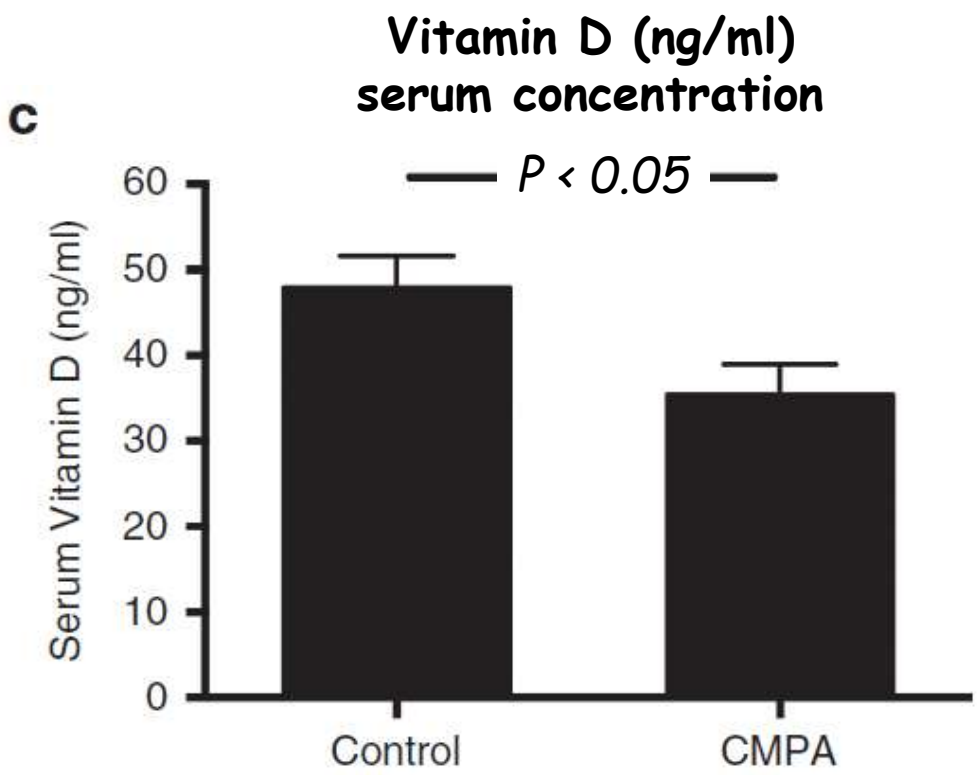

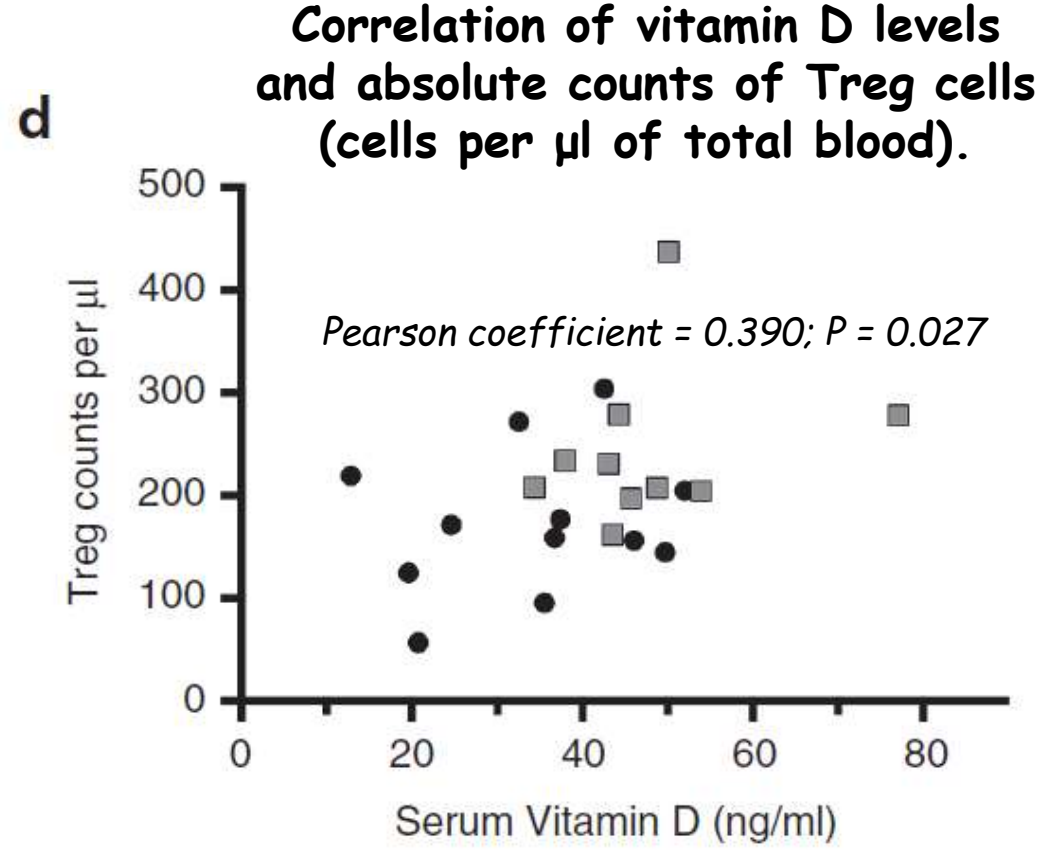

Control: gray squares;
CMPA: black dots.

The establishment of cow's milk protein allergy in infants is related with a deficit of regulatory T cells (Treg) and vitamin D. *Perezabad L, Pediatr Res. 2017 [Epub ahead of print]*

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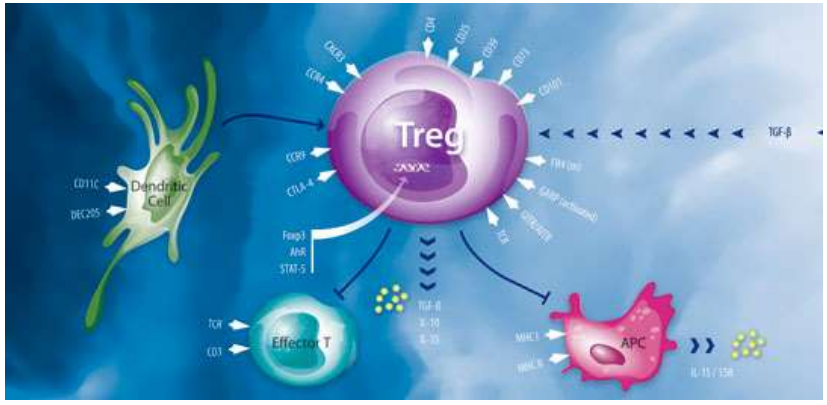
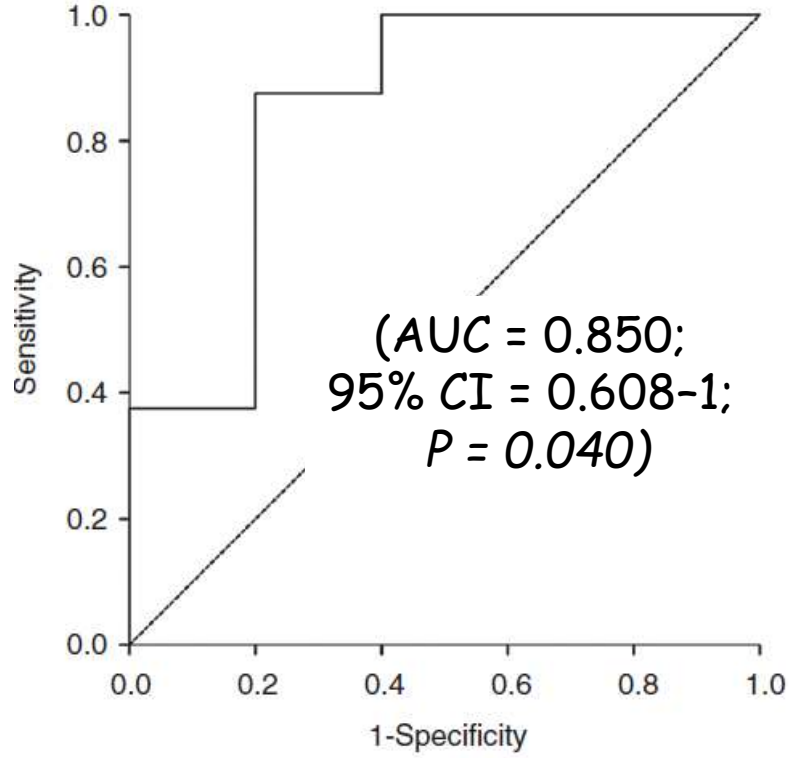
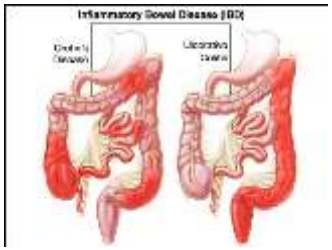


basal levels of vitamin D < 40 ng/ml predicted with a sensitivity of 87.5% and a specificity of 80% those patients that remained allergic after 1 y

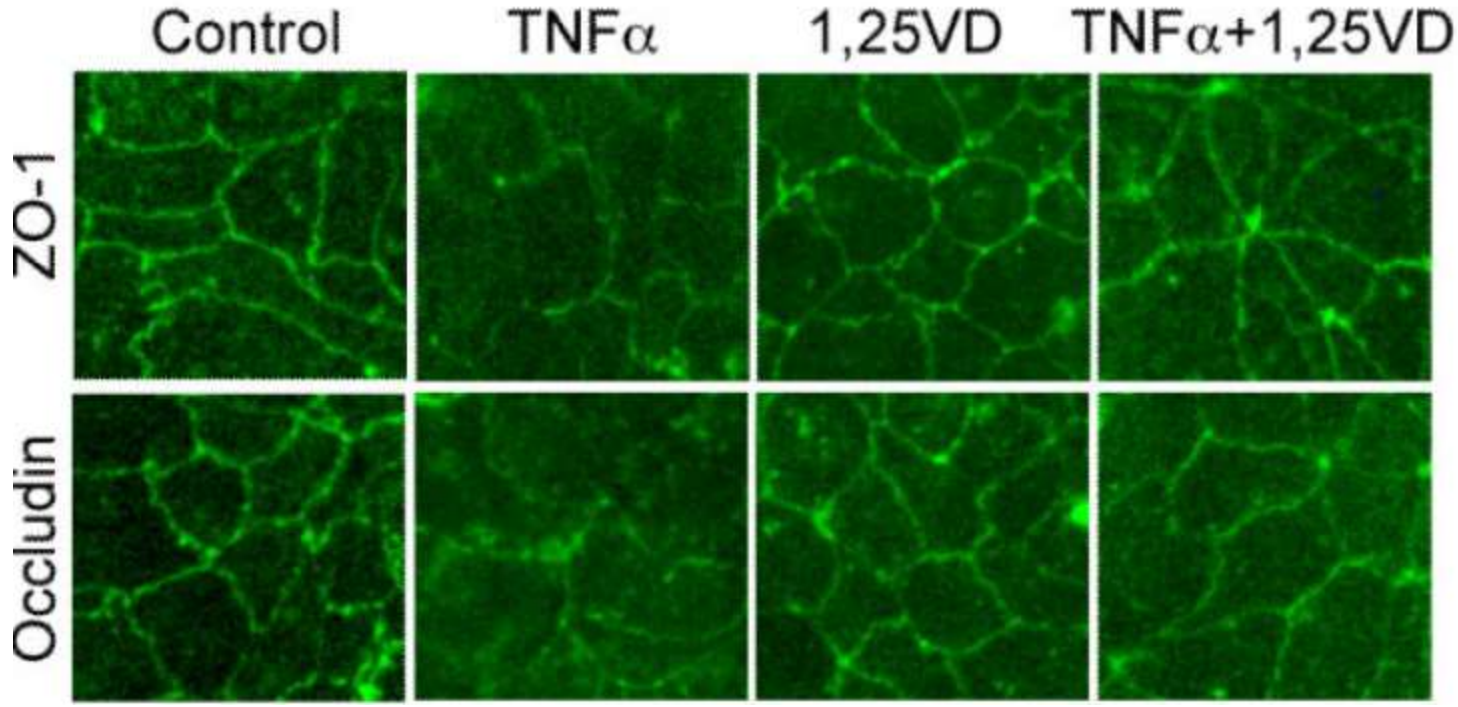


1,25-Dihydroxyvitamin D Protects Intestinal Epithelial Barrier by Regulating the Myosin Light Chain Kinase Signaling Pathway. *Du J. Inflamm Bowel Dis. 2015;21:2495-506.*



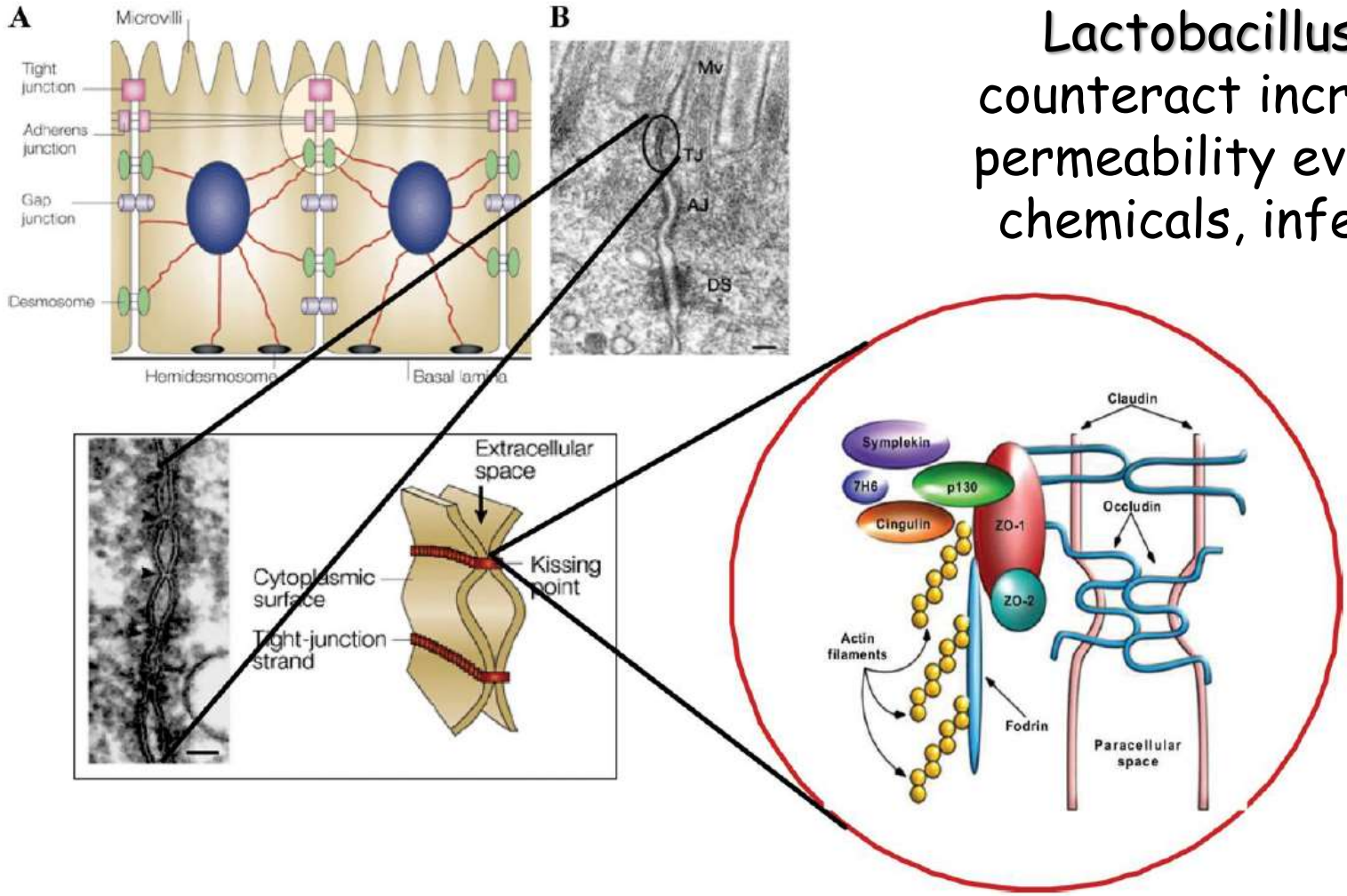
✓barrier permeability using monolayers of Caco-2 cells treated with TNFa with or without 1,25(OH)2D3.

Caco-2 monolayer immunostained with antibodies against ZO-1 or occludin as indicated.



Lactobacillus rhamnosus alleviates intestinal barrier dysfunction in part by increasing expression of zonula occludens-1 and myosin light-chain kinase in vivo.

Miyauchi E, J Dairy Sci. 2009;92(6):2400-8.



Lactobacillus rhamnosus can counteract increased paracellular permeability evoked by cytokines, chemicals, infections, or stress.

(A) Macroscopic arrangement and (B) microscopic composition of intercellular tight junctions;

Food allergy and probiotics

- In food challenge-proven cow's milk allergy, treatment with Lactobacillus rhamnosus in combination with extensively hydrolyzed casein formula increased rates of milk allergy resolution compared to a control group receiving hydrolyzed formula alone.

Berni Canani R, J Allergy Clin Immunol. 2012; 129:580–2. 2, e1–5.
Berni Canani R,. J Pediatr. 2013; 163:771–7.
Hol J, J Allergy Clin Immunol. 2008; 121:1448–54.

- Notably, treatment with Lactobacillus rhamnosus correlated with increased levels of fecal butyrate. *Berni Canani R, ISME J. 2015*

- Co-administration of peanut oral immunotherapy (OIT) with Lactobacillus rhamnosus for 18 months resulted in nonresponsiveness in 82% of treated individuals at 2-5 weeks after cessation of OIT, vs. 3% of those receiving placebo. *Tang ML, J Allergy Clin Immunol. 2015; 135:737–44. e8.*

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

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

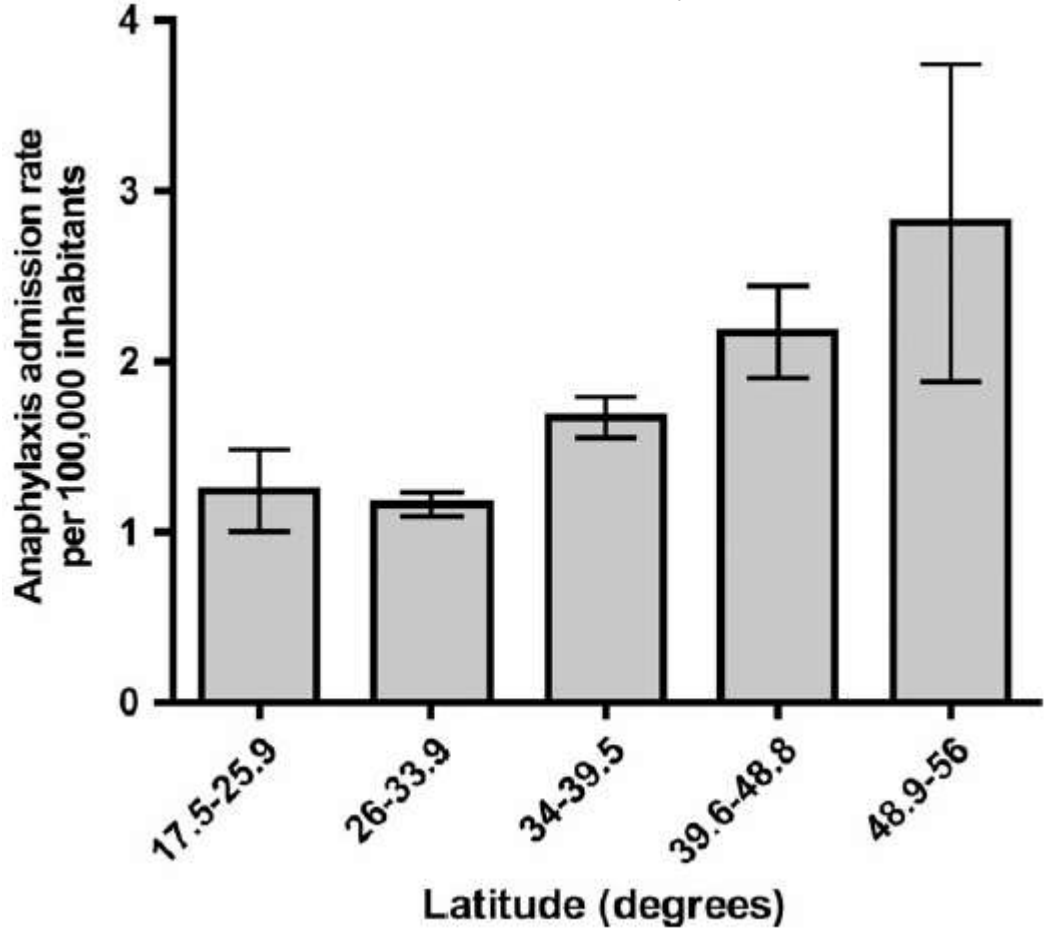
✓2316 anaphylaxis admissions

✓Median age of patients 41 yr;

- 17.5 S

- 56.0 S

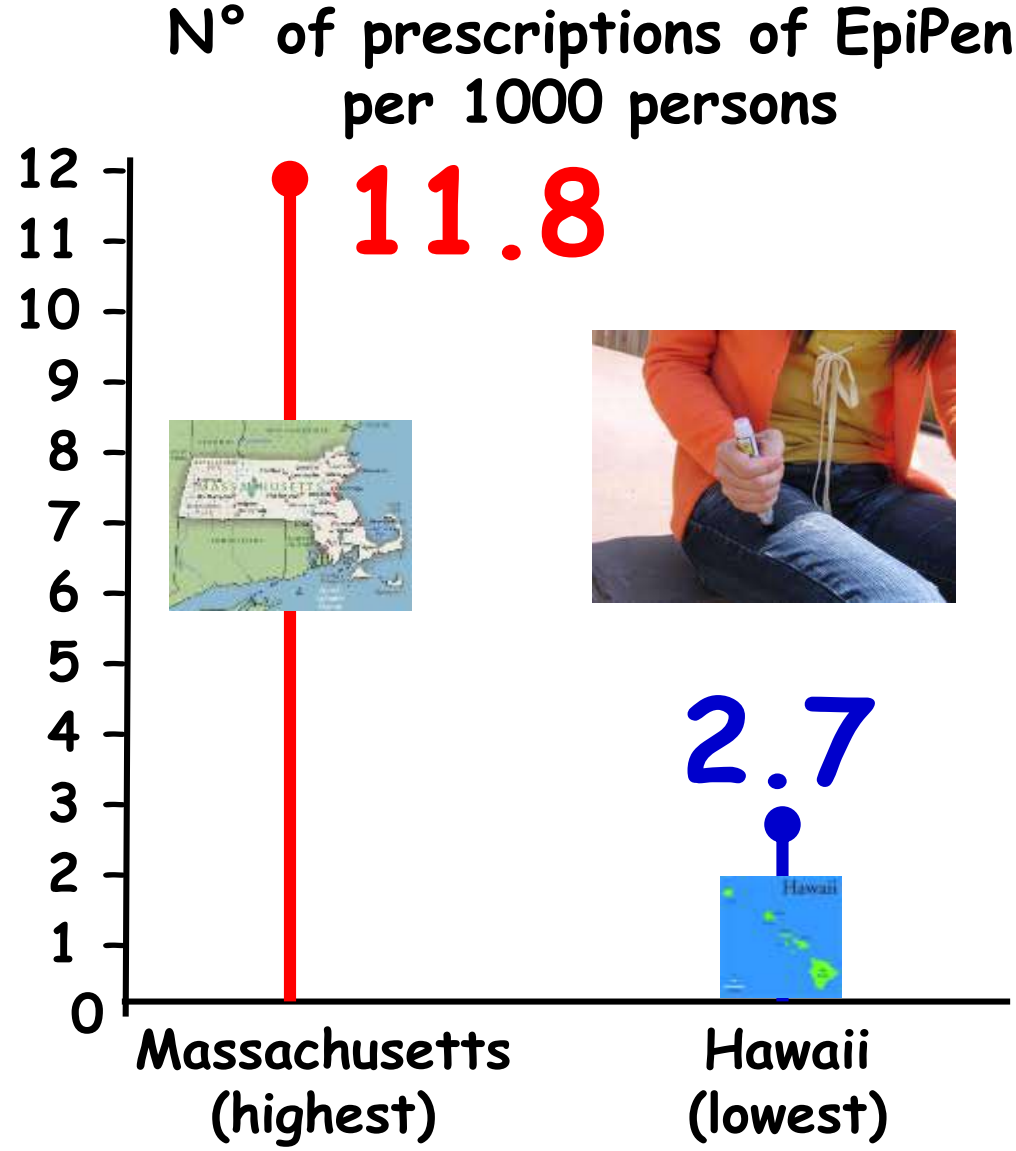
Latitudinal distribution of anaphylaxis admissions in Chile, 2001–2010.



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.

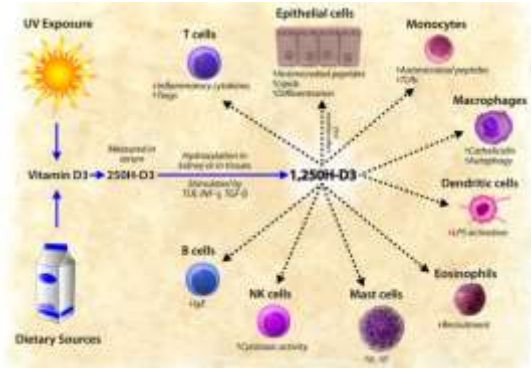
Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

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

- ✓ Introduction
- ✓ Immunomodulation related to allergy
- ✓ Fetal development
- ✓ 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 in Autoimmunity: Molecular Mechanisms and Therapeutic Potential.

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



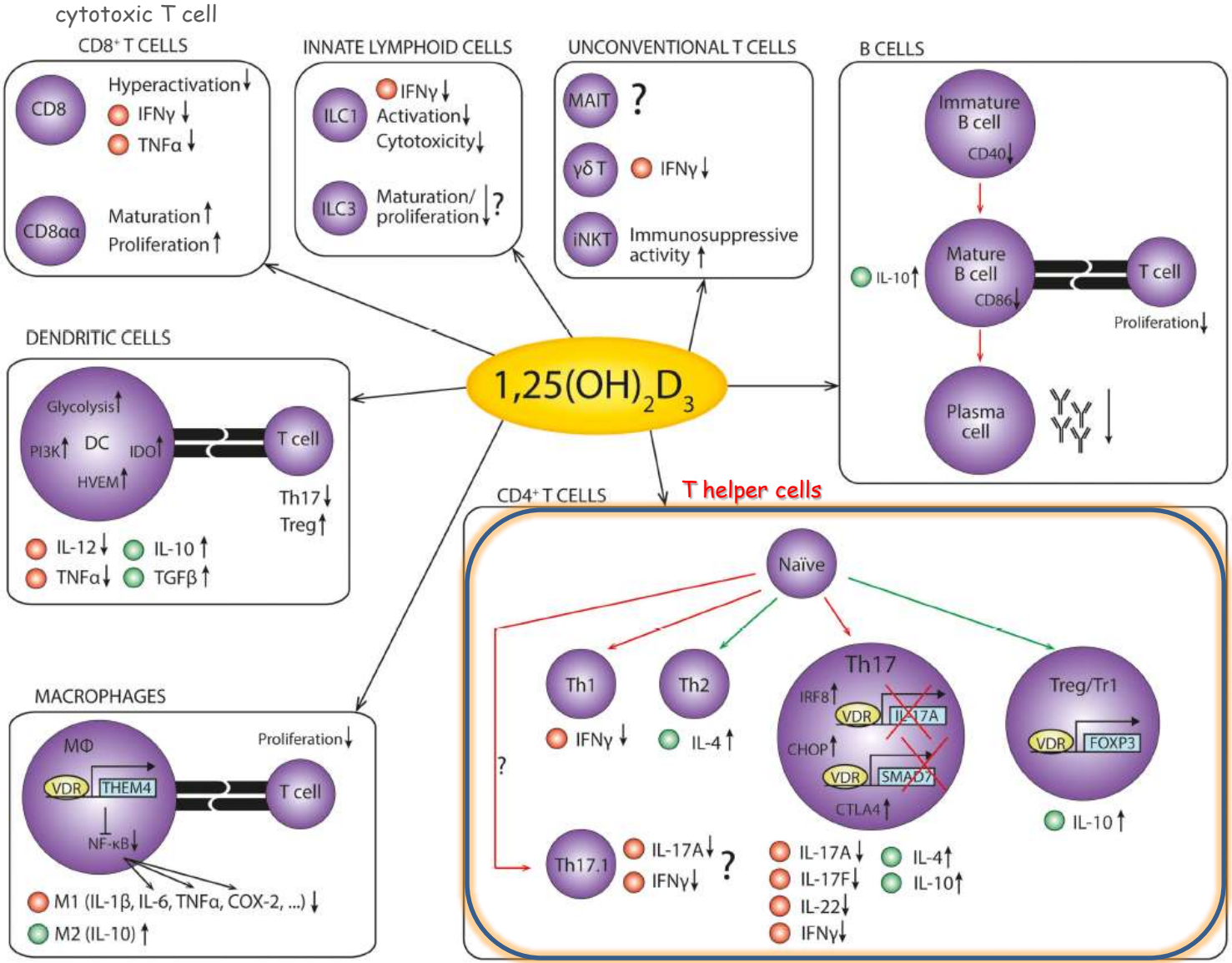
- An important extra-skeletal effect of vitamin D is the modulation of the immune system.

- 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, and systemic lupus erythematosus**.

Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential.

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



The anti-inflammatory effects of 1,25(OH)2D3 on cells of the immune system.

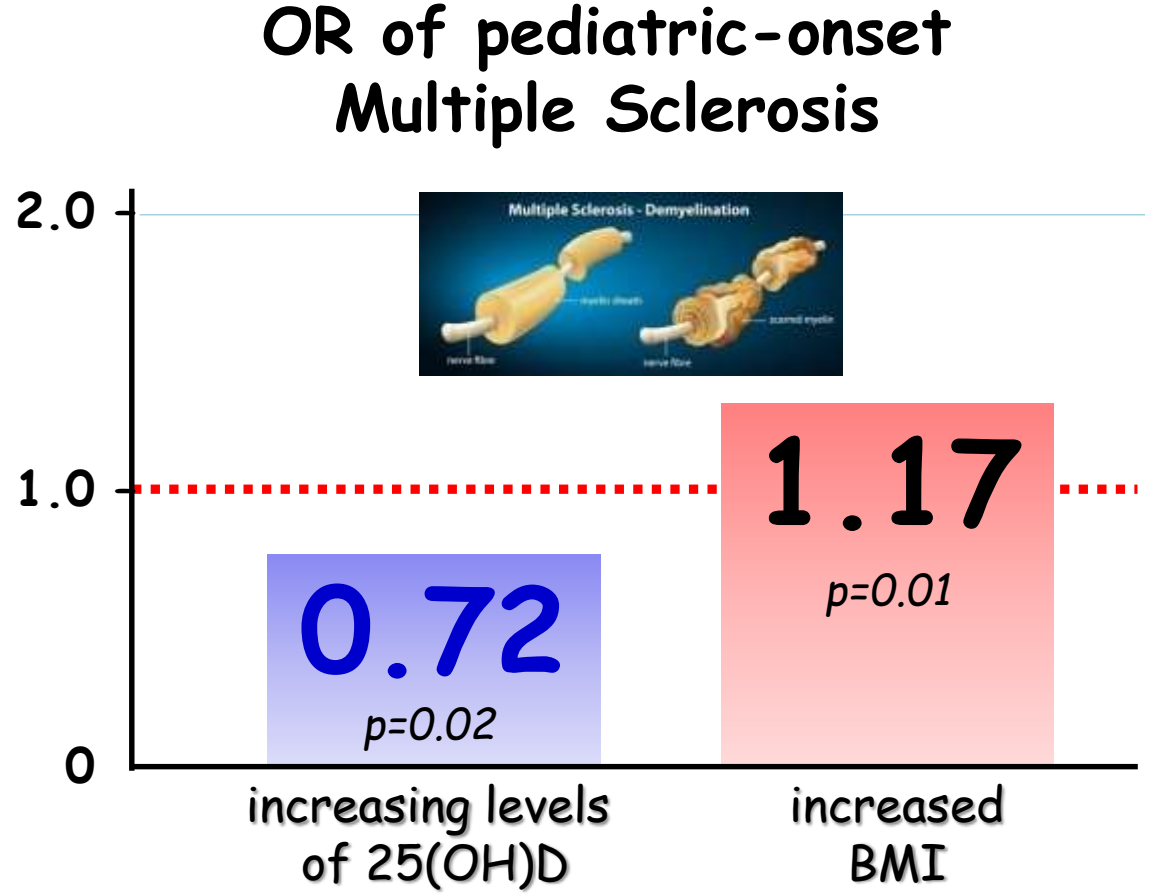
Red dots represent pro-inflammatory cytokines, while green dots represent anti-inflammatory cytokines.

Red arrows indicate decreased differentiation, and green arrows indicate increased differentiation.

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

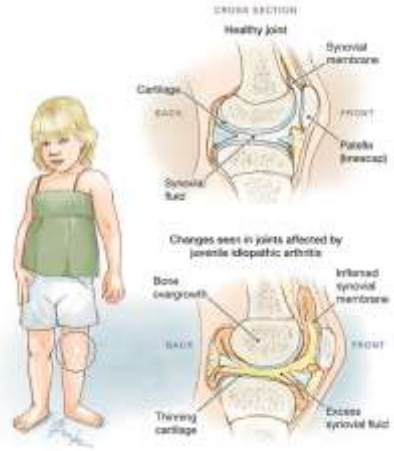
Gianfrancesco MA, Neurology. 2017 Epub ahead of print

- ✓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).



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.

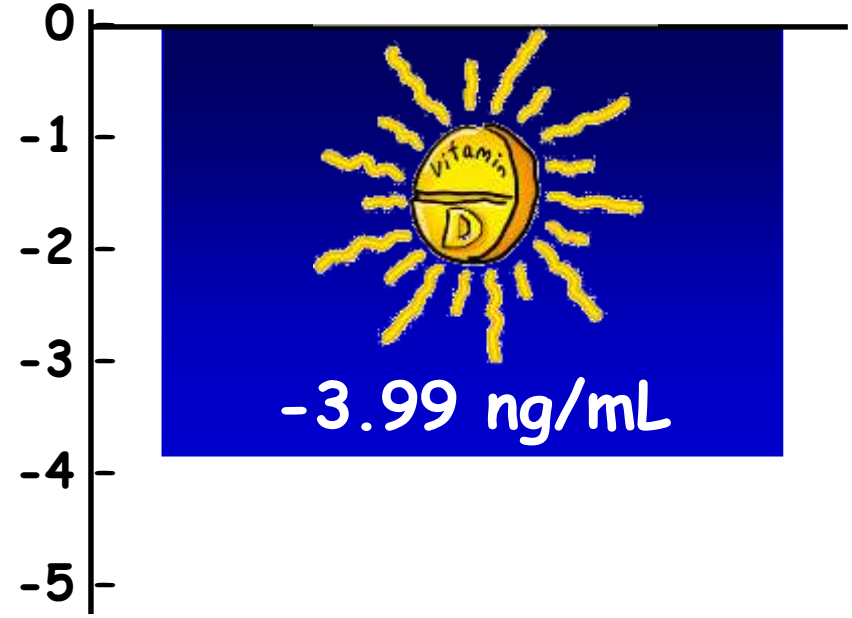
- Patients with JIA showed reduced 25(OH)D levels compared to controls *($p < 0.001$).*
- Patients with active disease and/or frequent relapses had reduced 25(OH)D levels compared to patients with no active disease and no frequent flares *($p < 0.005$).*
- JIA patients had significantly higher PTH levels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

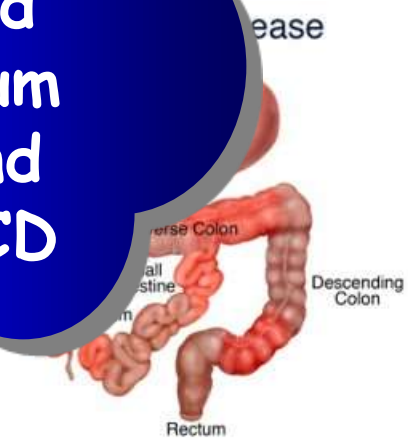
Mean levels of 25(OH)D in CD patients compared with healthy controls



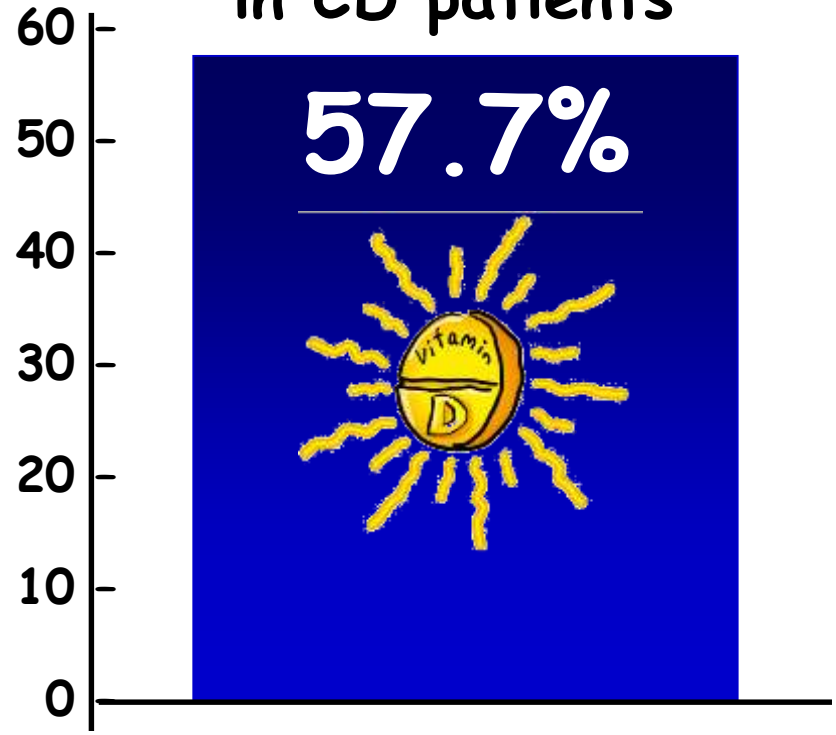
Vitamin D status in relation to Crohn's disease: Meta-analysis of observational studies

Sadeghian M, Nutrition 2016;32:505-514

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



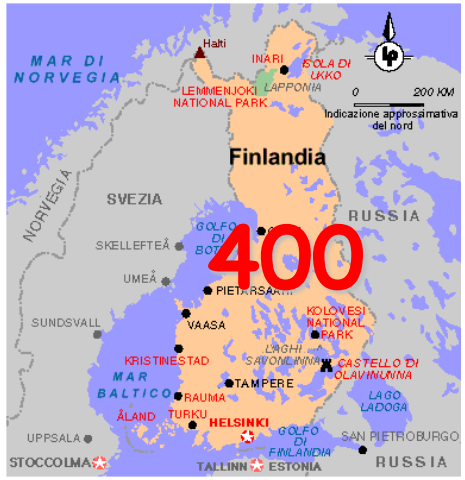
Prevalence of vitamin D deficiency in CD patients



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

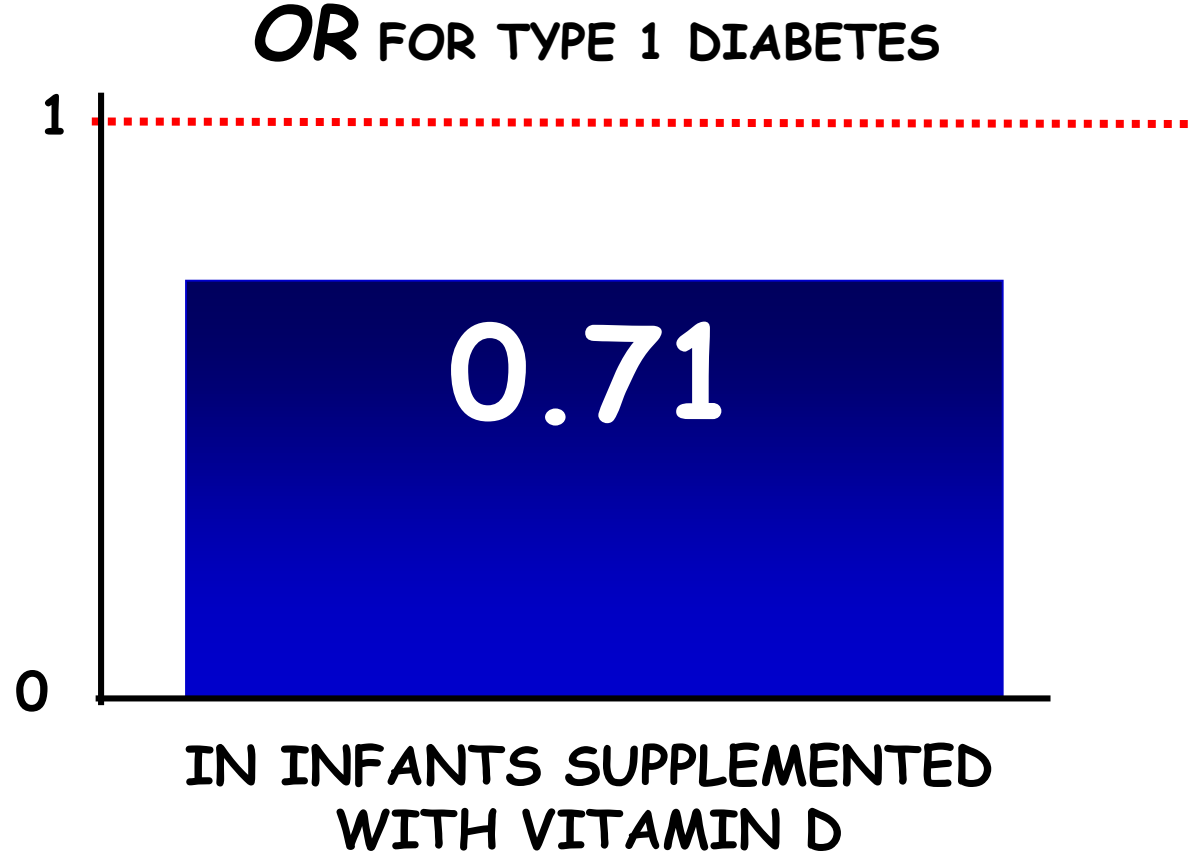
1. Type 1 diabetes is characterized by autoimmune destruction of insulin-producing β cells in the pancreas.
2. There is a marked geographic variation in incidence, with a child in Finland being about 400 times more likely than a child in Venezuela to acquire the disease.



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).

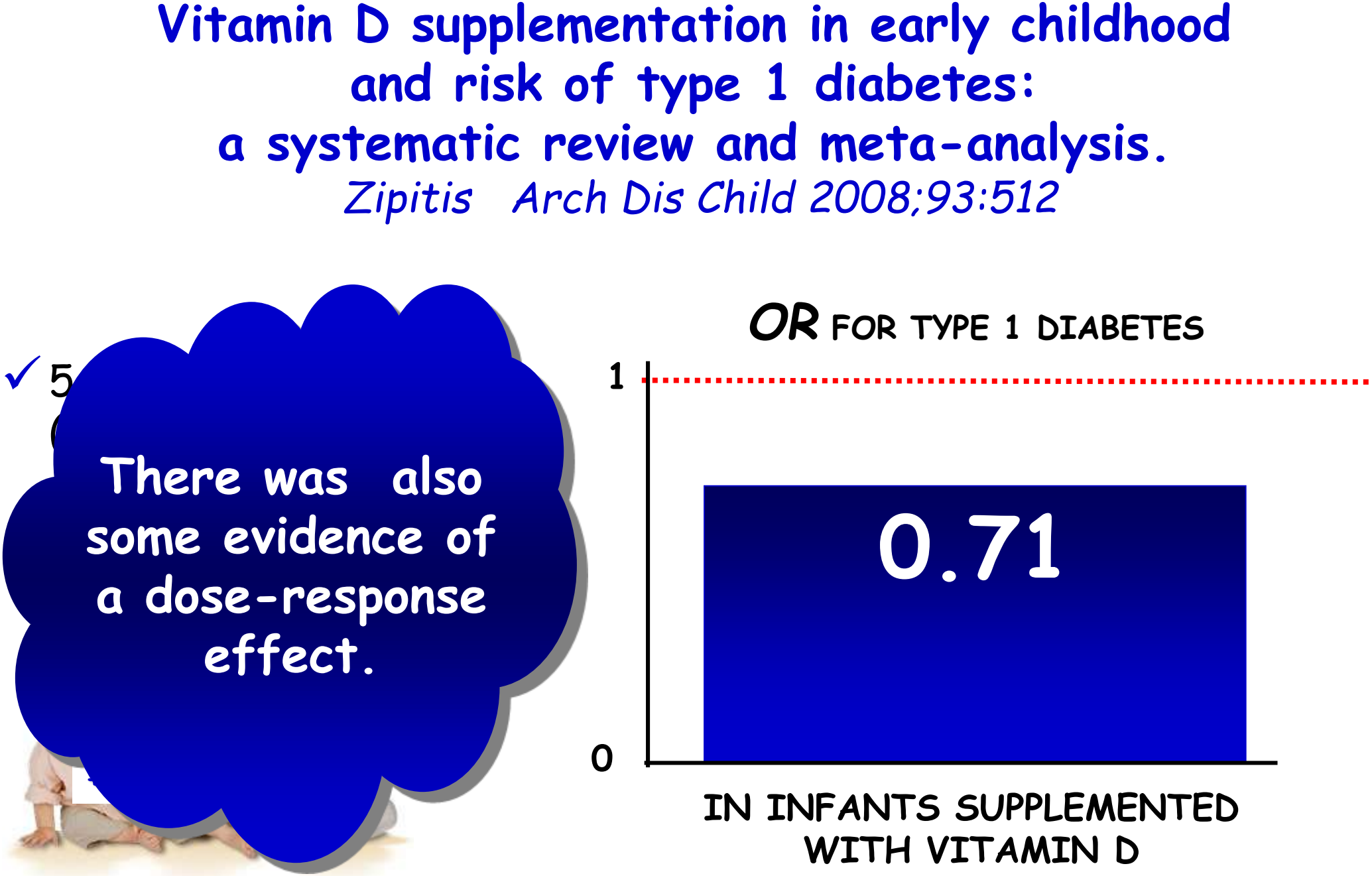


Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis.

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)

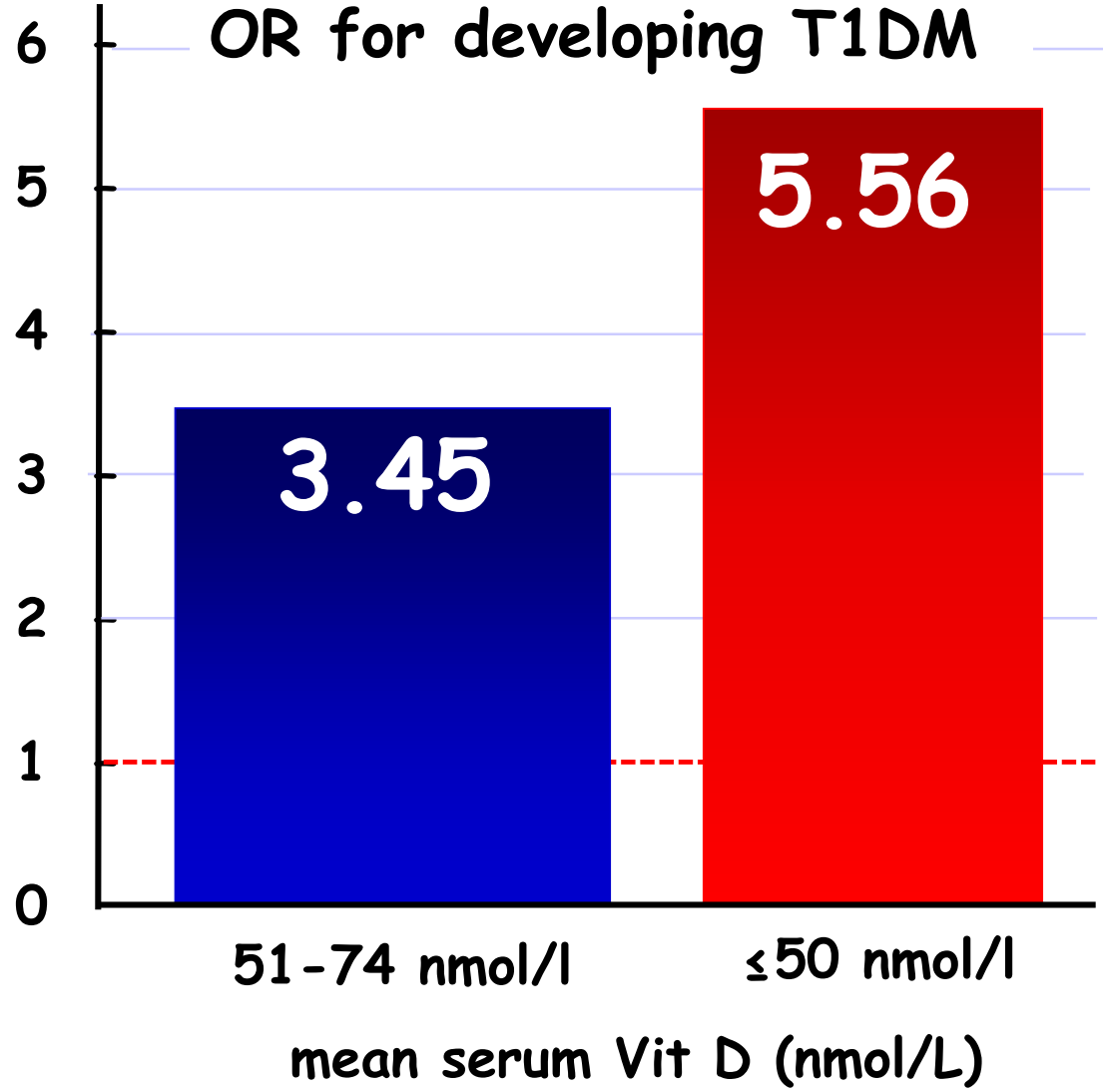
✓between May 2010 and July 2012

- 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)
- ✓between May 2010 and July 2012

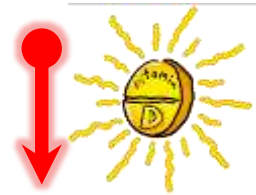


Vitamin D status in children with systemic lupus erythematosus and its association with clinical and laboratory parameters

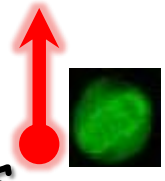
AlSaleem A, Clin Rheumatol 2015;34:81-84

- ✓ 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.



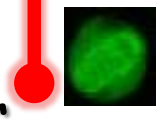
Vitamin D status in children with systemic lupus erythematosus and its association with clinical and laboratory parameters

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.

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



Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

Attilio Boner
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attilio.boner@univr.it

- ✓ Introduction
- ✓ Immunomodulation related to allergy
- ✓ Fetal development
- ✓ Prevention and modification of asthma & COPD
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- ✓ Autoimmunity
- ✓ **Other Diseases**
- ✓ Conclusions

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 [Epub ahead of print]

✓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

Vitamin D status in pediatric irritable bowel syndrome.

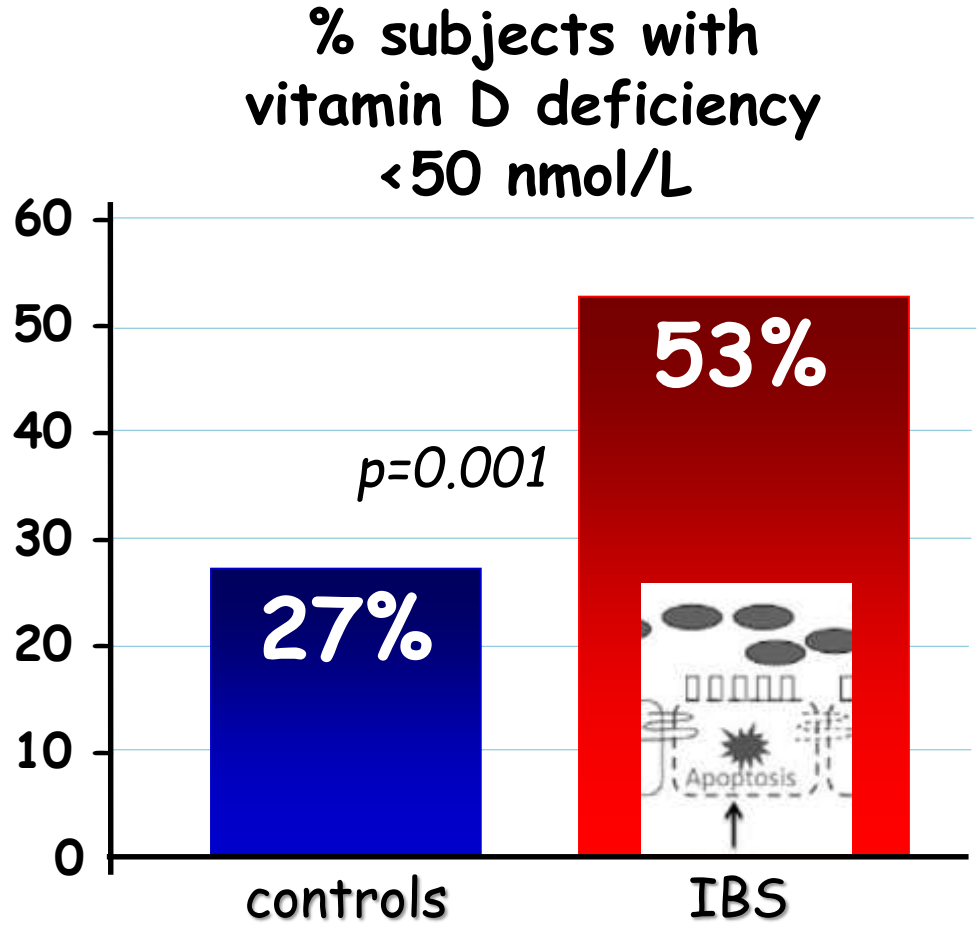
Nwosu BU, PLoS One. 2017;12(2):e0172183.

✓retrospective case-controlled study of 116 controls (age 14.6 ± 4.3 y), and 55 subjects with IBS (age 16.5 ± 3.1y).

✓Overweight defined as BMI ≥85th but <95th percentile, and obesity as BMI ≥95th percentile.

✓Vitamin D deficiency defined as 25(OH)D <50 nmol/L,

✓Major psychosomatic manifestations included in the analysis were depression, anxiety, and migraine.



Vitamin D and autism, what's new?

Cannell JJ. Rev Endocr Metab Disord. 2017. [Epub ahead of print]

An increasing amount of evidence points to the possibility that gestational and early childhood vitamin D deficiency [25(OH)D < 40 ng/ml] cause some cases of autism.

Vitamin D is metabolized into a seco-steroid (a type of steroid with a "broken" ring) hormone that regulates about 3% of the 26,000 genes in the coding human genome.

It is also a neurosteroid that is active in brain development, having effects on cellular proliferation, differentiation, calcium signaling, neurotrophic and neuroprotective actions; it also appears to have effect on neurotransmission and synaptic plasticity.

Vitamin D and autism, what's new?

Cannell JJ. Rev Endocr Metab Disord. 2017. [Epub ahead of print]

- These two open label trials were recently confirmed with a randomized controlled trial (RCT) using 300 IU/kg/day with a maximum of 5000 IU/day and resulted in effects similar to the two open label studies. *Saad K, J Child Psychol Psychiatry 2017; in press*

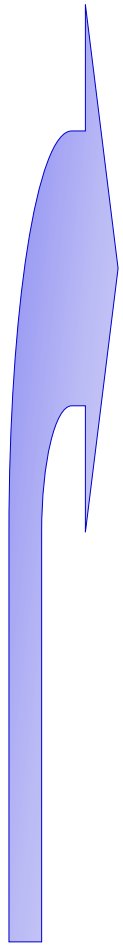
- In terms of prevention, a recent small study showed vitamin D supplementation during pregnancy (5000 IU/day) and during infancy and early childhood (1000 IU/day) significantly reduced the expected incidence of autism in mothers who already had one autistic child from 20% to 5%.

from 20% to 5%.

Randomized controlled trial of vitamin D supplementation in children with autism spectrum disorder

Saad K, J Child Psychol Psychiatry 2017; in press

- ✓ 109 children with autism spectrum disorder (ASD) (aged 3-10 years).
- ✓ Effects of vitamin D supplementation on the core symptoms of autism, were assessed by the Childhood Autism Rating Scale (CARS), Aberrant Behavior Checklist (ABC), Social Responsiveness Scale (SRS), and the Autism Treatment Evaluation Checklist (ATEC).



- The daily doses used in the therapy group was 300 IU vitamin D3/kg/day, maximun 5,000 IU/day.
- Autism symptoms of the children improved significantly, following 4-month vitamin D3 supplementation, but not in the placebo group.

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.

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

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✓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.

- 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.

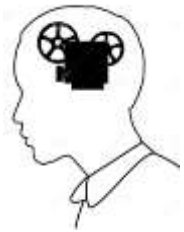
Does high dose vitamin D supplementation enhance cognition?: A randomized trial in healthy adults.

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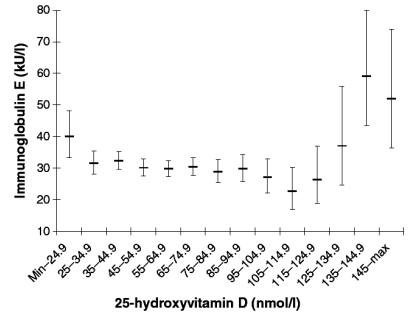
- ✓ **Conclusions**

Conclusions

- Vitamin D is a 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 improves control of allergic/autoimmune diseaes and are necessary in all persons and not only in infancy.

- Supplementation of vitamin D associated with probiotics, other nutraceuticals might be more efficacious but further study are necessary.

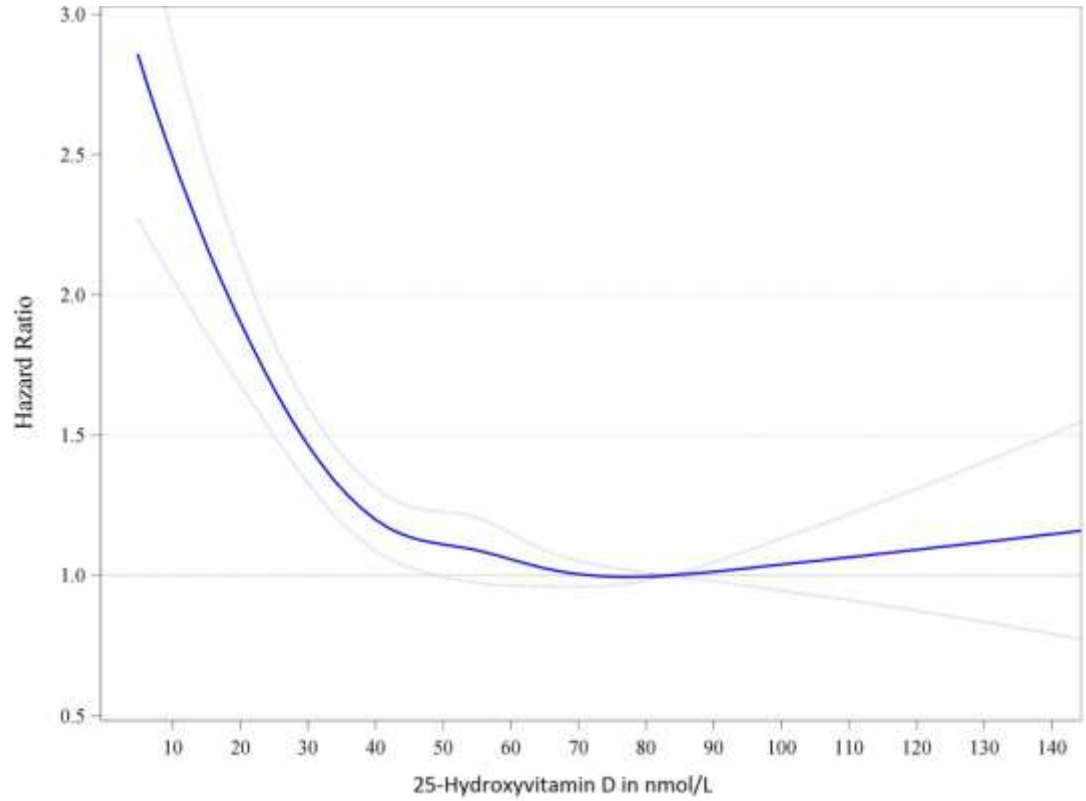
Vitamin D and mortality: Individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium.

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.



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.

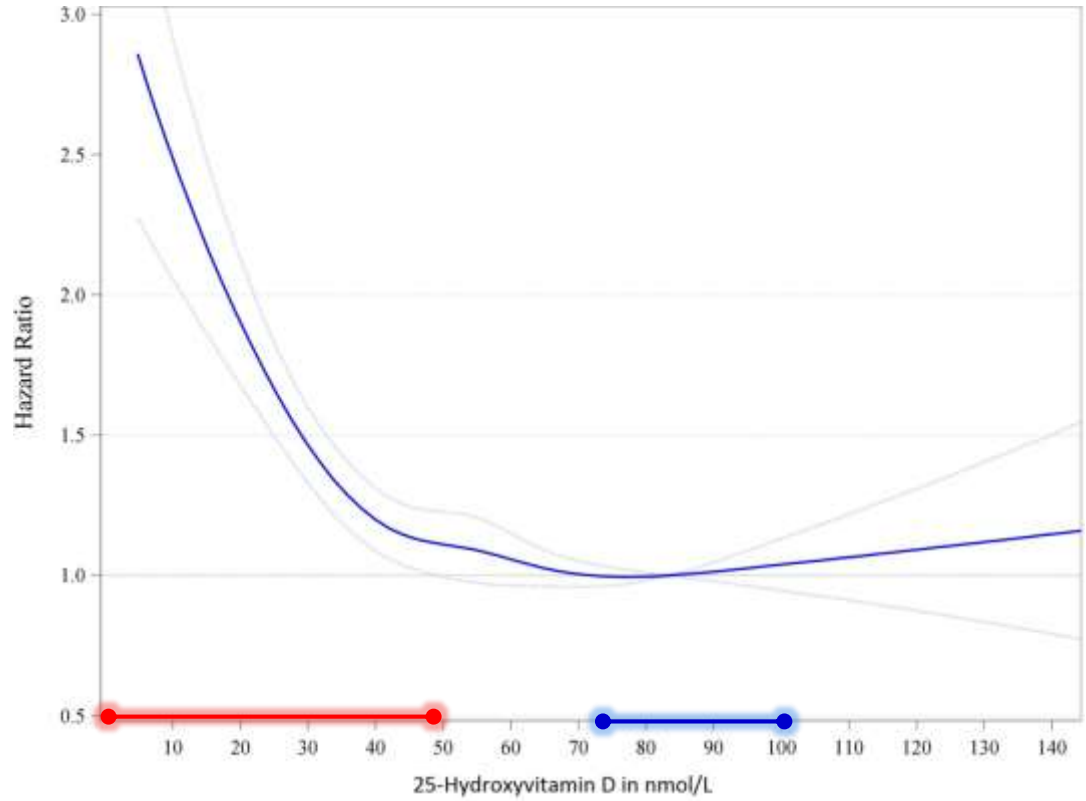
Compared to participants with 25(OH)D concentrations of 75 to 99.99 nmol/L, the adjusted Hazard Ratios for mortality were in the 25(OH)D groups with:

40 to 49.99 → 1.15 (1.00-1.29),

30 to 39.99 → 1.33 (1.16-1.51),

<30 nmol/L → 1.67 (1.44-1.89),

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



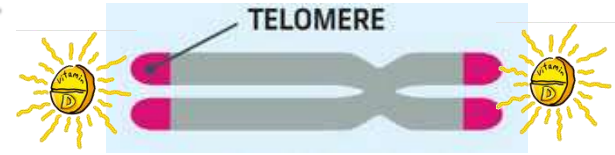
Serum 25-Hydroxyvitamin D Has a Modest Positive Association with Leukocyte Telomere Length in Middle-Aged US Adults. *Beilfuss J. J Nutr. 2017;147(4):514-520.*

✓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)*.

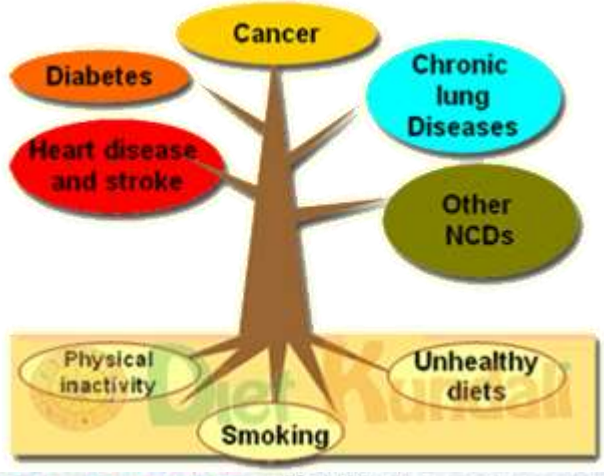


- In the same age group, 25(OH)D concentrations ≥50 nmol/L were associated with a 0.13- ± 0.04-kbp longer LTL than those for 25(OH)D concentrations <50 nmol/L *(P = 0.01)*.

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

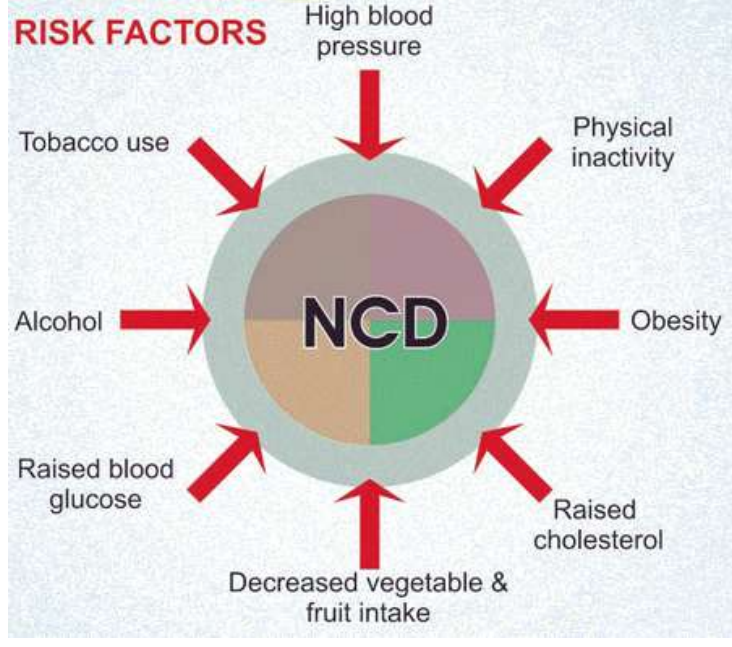
O'Keefe EL, Prog Cardiovasc Dis. 2016;58(5):505-13.

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



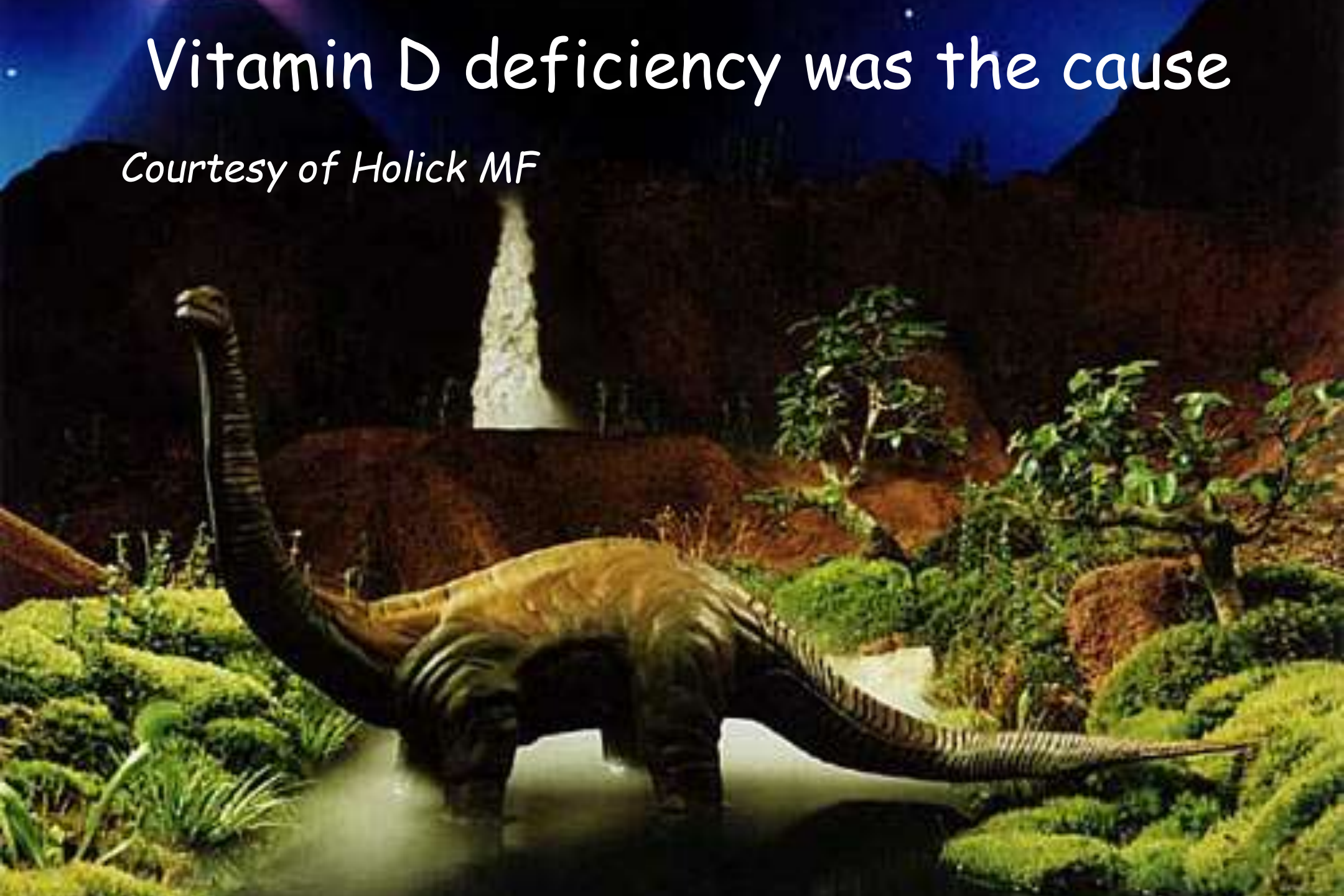
❑The alarming outbreak of cardiovascular disease are due to negative lifestyle factors such as:

- 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



Thank you
for your
attention to
the story
my granpa
told you

and Vitamin D
600 IU/day