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
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 1a-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 1a-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 D₃ during winter.
Global Consensus Recommendations on Prevention and Management of Nutritional Rickets


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, divide by 2.496.
25-hydroxyvitamin D serum level in children of different ethnicity living in Italy.

1374 pediatric subjects of different ethnicity

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

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

Caucasians: 44.2%
Africans: 65.2%
North Africans: 69.2%
Indians: 54.0%
Others: 44.8%

P<0.001
25-hydroxyvitamin D serum level in children of different ethnicity living in Italy.

1374 pediatric subjects of different ethnicity

Prevalence of 25(OH)D deficiency (≤ 20 ng/ml) and insufficiency (21-29 ng/ml)

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

21.0 ng/mL (IQR = 14.0-29.6 ng/ml)
25-hydroxyvitamin D serum level in children of different ethnicity living in Italy.

- 1374 pediatric subjects of different ethnicity
- Prevalence of 25(OH)D deficiency (≤ 20 ng/ml) and insufficiency (21-29 ng/ml)
Regular breakfast consumption is associated with higher blood vitamin status in adolescents: the HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) Study.


- 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 concentrations, compared with skippers ($P<0.05$), 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 ($P<0.05$).

1058 (52.8 % females) European adolescents (aged 12.5-17.5 years) from ten cities.

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.

- 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.


<table>
<thead>
<tr>
<th>Life-stage group (age and gender)</th>
<th>Calcium</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 yr (M+F)</td>
<td>RDA (mg/d)</td>
<td>UL (mg/d)</td>
</tr>
<tr>
<td>4–8 yr (M+F)</td>
<td>700</td>
<td>2500</td>
</tr>
<tr>
<td>9–13 yr (M+F)</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>14–18 yr (M+F)</td>
<td>1300</td>
<td>3000</td>
</tr>
<tr>
<td>19–30 yr (M+F)</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>31–50 yr (M+F)</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>51–70 yr (M)</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>51–70 yr (F)</td>
<td>1200</td>
<td>2000</td>
</tr>
<tr>
<td>71+ yr (M+F)</td>
<td>1200</td>
<td>2000</td>
</tr>
<tr>
<td>Pregnant or lactating (F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–18 yr</td>
<td>1300</td>
<td>3000</td>
</tr>
<tr>
<td>19–50 yr</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6 months (M+F)</td>
<td>200&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1000</td>
</tr>
<tr>
<td>6–12 months (M+F)</td>
<td>260&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1500</td>
</tr>
</tbody>
</table>

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

100 IU = 2.5 µg

For bone health.

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

- 140 mothers with exclusively breastfed infants, and 44 who used both breast and formula milk
- Maternal preferences for vitamin D supplementation

**OR for vitamin D supplementation**

8.3

(95% CI, 3.8-18)
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.
The great majority of breastfeeding mothers (88.4%) preferred supplementing themselves rather than their infants with vitamin D. If the 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).

<table>
<thead>
<tr>
<th>Themes</th>
<th>Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of knowledge about supplementation</td>
<td>“I didn’t know I should”</td>
</tr>
<tr>
<td>Assumption that fortified milk provides infant with needed vitamin D</td>
<td>“Too young – will start soon”</td>
</tr>
<tr>
<td>Assumption that breast milk provides infant with needed nutrition</td>
<td>“Never even knew vitamin D supplementation was needed”</td>
</tr>
<tr>
<td>Inconvenience/Dislike</td>
<td>“I gave vitamin D supplement when she was breast milk-fed, provider told us to discontinue when formula started”</td>
</tr>
<tr>
<td></td>
<td>“My baby went to exclusive soy formula at 2 months old, which has vitamin D supplement”</td>
</tr>
<tr>
<td></td>
<td>“Baby formula has all that is needed and recommended”</td>
</tr>
<tr>
<td></td>
<td>“Stopped giving it when I stopped nursing and started to give formula”</td>
</tr>
<tr>
<td></td>
<td>“Find it hard to believe the whole population is so deficient in Vitamin D, especially in breast milk”</td>
</tr>
<tr>
<td></td>
<td>“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”</td>
</tr>
<tr>
<td></td>
<td>“It causes her to spit up”</td>
</tr>
<tr>
<td></td>
<td>“I forget to because she doesn’t take it well and doesn’t seem to like the taste”</td>
</tr>
</tbody>
</table>
1370 healthy children 1 to 6 years of age

Healthy maintenance physician’s visit in Toronto, Ontario, Canada

Nonfasting total 25-hydroxyvitamin D

Nonfasting PTH

Parathyroid Hormone as Functional Indicator of Vitamin D Sufficiency in Children
Maguire JL, JAMA Ped 2014;168;383-384

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

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

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

- Introduction
- Immunomodulation related to allergy
- Foetal development
- Prevention and modification of asthma & COPD
- Prevention and modification of allergic rhinitis, atopic dermatitis
- Prevention and modification of food allergy, anaphylaxis, urticaria
- Autoimmunity
- Other diseases
- Conclusions
Vitamin D and immunomodulation related to allergy

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.


Vitamin D has immunomodulatory effects on allergen induced inflammatory pathways

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

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]

In DCs a negative correlation was identified between the data of serum calcitriol (1,25-dihydroxyvitamin D₃) and TIM4 (CD80, CD86) which provide costimulatory signals necessary for T cell activation and survival.

- 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).

- 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.

* Treg regulatory cells % of CD4+ cells

* Vitamin D serum levels ng/ml
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.
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

B cells with CD23 (IgE receptor) expression

B cells with CD21 (IgE receptor) expression

Children with asthma

Control children

Children with asthma

Control children

\( P < 0.05 \)
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

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

Correlation of 25(OH)D₃ and B cells with CD21 (IgE receptor) expression
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.

**% 18 months old children with sIgE for Der-f1**

- **Placebo/Placebo**: 18% (p=0.009 for trend)
- **1000 IU/400 IU**: 10%
- **2000 IU/800 IU**: 2%
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.

Optimal vitamin D level: 30-50 ng/mL
Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

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✓ Prevention and modification of allergic rhinitis
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✓ 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.

Vitamin D in pregnancy and foetal development

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

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

Mirzakhani H. Clin Exp All 2015;45:114

- 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:

- Low birthweight: 0.40
- Small-for-gestational age: 0.67
- Preterm delivery (<37 weeks): 0.77
Vitamin D and risk of preterm birth: Up-to-date meta-analysis of randomized controlled trials and observational studies.

24 articles (6 RCT and 18 observational studies)
Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

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- Other Diseases
- Conclusions
Vitamin D and lung development

- **Vitamin D influence fetal lung development.**

- Experimental evidence in rats show that foetal alveolar type II epithelial cells express VDR, suggesting that pulmonary maturation is responsive to vitamin D exposure.

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

Elastance

thoracic gas volume

airway resistance

tissue elastance

C

\[ p < 0.001 \]

\[ \text{TGV (mL)} \]

\[ \text{R}_{\text{aw}} (\text{mPa} \cdot \text{L}^{-1}) \]

\[ \text{H (mPa} \cdot \text{L}^{-1}) \]

\begin{align*}
\text{Vit D +} & \quad \text{Vit D -} \\
0.0 & \quad 0.1 \\
0.2 & \quad 0.3 \\
0.4 & \quad 0.5 \\
\end{align*}

\begin{align*}
\text{Vit D +} & \quad \text{Vit D -} \\
0 & \quad 200 \\
400 & \quad 600 \\
800 & \quad 1000 \\
1200 & \quad 1400 \\
\end{align*}

\begin{align*}
\text{Vit D +} & \quad \text{Vit D -} \\
0 & \quad 20000 \\
40000 & \quad 60000 \\
80000 & \quad 100000 \\
120000 & \quad 140000 \\
\end{align*}
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.
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-tract infections (RTIs)
- lower respiratory-tract infections (LRTIs)
- bronchiolitis

(a) Predicted probability of RTI
(b) Predicted probability of LRTI
(c) Predicted probability of 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.


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.

OR for wheeze during childhood

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.58</td>
</tr>
<tr>
<td>E</td>
<td>0.60</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Higher maternal intake
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

\[ aOR \text{ of asthma/recurrent wheeze by age 3 years } = 0.45 \] (95% CI, 0.19-0.91)
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
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 10 yrs

2.5

OR for sensitization at age 10 yrs

0.0
1.0
2.0
3.0

with each additional 25 OH D deficient (< 50 nmol/L) (< 20ng/mL) follow up
25 (OH) D deficiency at 6 months is associated with younger age at first febrile LRI.
Vitamin D over the first decade and susceptibility to childhood allergy and asthma

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

- 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).

- $172\text{mL}$, $p<0.0001$ for FVC
- $126\text{mL}$, $p<0.0001$ for FEV$_1$
BACKGROUND:
Chronic obstructive pulmonary disease (COPD) is thought to result from an accelerated decline in 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.
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

- Folate Deficiency
- Vitamin D Insufficiency

- Folate Deficiency alone: 7.9
- Vitamin D Insufficiency alone: 1.8
- Folate Deficiency and vitamin D Insufficiency: 1.8
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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (All of the following)</th>
<th>Partly Controlled (Exacerbation present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (none/wk)</td>
<td>More than twice/wk</td>
<td></td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms/awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for reliever/rescue treatment</td>
<td>None (twice/wk)</td>
<td>More than twice/wk</td>
<td></td>
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<tr>
<td>Lung function (PEF or FEF37)</td>
<td>Normal</td>
<td>&lt; 80% predicted or personal best (if known)</td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>None</td>
<td>One or more/year</td>
<td>One in any week</td>
</tr>
</tbody>
</table>

* 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.
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

$\text{Vitamin D serum levels (ng/ml)}$

$\text{C-ACT total score}$

$r=0.29$ $p<0.01$
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, FEV₁
- ΔFEV₁ after a standardized exercise challenge

severity of EIB by vitamin D serum levels

R=0.48; p=0.001

Serum vitamin D ng·mL⁻¹
Vitamin D and pulmonary function in obese asthmatic children
Lautenbacher LA, Pediatr Pulmonol 2016;51:1276-1283


25-OHD levels ≥30 ng/ml categorized as sufficient, <30 and ≥20 ng/ml as insufficient, and <20 ng/ml as deficient.

<table>
<thead>
<tr>
<th>25-OHD</th>
<th>25-OHD</th>
<th>25-OHD</th>
<th>P-value^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>sufficient</td>
<td>insufficient</td>
<td>deficient</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>99.7 ± 4.7</td>
<td>98.4 ± 24</td>
<td>92.5 ± 10.4</td>
</tr>
<tr>
<td>FEV1</td>
<td>94.8 ± 8.4^e</td>
<td>94.7 ± 14.1^d</td>
<td>84.5 ± 9.4^e,d</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>84 ± 5.7</td>
<td>80.3 ± 6.1</td>
<td>80.9 ± 7.4</td>
</tr>
<tr>
<td>FEF25–75%</td>
<td>87.8 ± 25</td>
<td>80.5 ± 23.2</td>
<td>73.2 ± 19.5</td>
</tr>
<tr>
<td>TLC</td>
<td>86.3 ± 9</td>
<td>96.6 ± 10^e</td>
<td>86.9 ± 14.3^e</td>
</tr>
<tr>
<td>RV</td>
<td>68.5 ± 27.2</td>
<td>92 ± 36.3</td>
<td>76.8 ± 28.2</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>18.5 ± 6.3</td>
<td>21.5 ± 6.4</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>ERV</td>
<td>73.9 ± 19.3</td>
<td>67.8 ± 22.6</td>
<td>61.7 ± 24.5</td>
</tr>
<tr>
<td>FRC</td>
<td>79.3 ± 19^f</td>
<td>73.5 ± 19.3</td>
<td>67.5 ± 20.1^f</td>
</tr>
<tr>
<td>IC</td>
<td>92.1 ± 13.6</td>
<td>104.3 ± 12.2</td>
<td>93.9 ± 19.3</td>
</tr>
</tbody>
</table>

≥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

- 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 FEV₁ compared to that with V-D-sufficiency.

- 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
- 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

\[ OR = 1.5 \quad p=0.01 \]

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

OR for severe asthma exacerbation (hospitalization or ED visit)

ICS treatment

Vit D sufficient

1
1.7
1.7
2

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

- 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.

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

- Patients with severe asthma failing 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.

- 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.

![Graph showing RR for asthma exacerbation in asthmatics who had been vitamin D supplemented.](chart)

RR for asthma exacerbation

0.41

in asthmatics who had been vitamin D supplemented.

Estimated annual decline in FEV$_1$ in patients with infrequent or frequent asthma exacerbations

$P<0.05$
Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren.


- 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.

RR for asthma attacks

0.17

P=0.006

in asthmatic children who had been vitamin D supplemented
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

OR for respiratory tract infection

<table>
<thead>
<tr>
<th>vitamin D supplemented in</th>
<th>daily doses</th>
<th>vs</th>
<th>bolus doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>0.51</td>
<td>vs</td>
<td>0.86</td>
</tr>
</tbody>
</table>

P=0.01
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 D₃ 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

2.4
p=0.02

In cases vs controls
Vitamin D Promotes Pneumococcal Killing and Modulates Inflammatory Responses in Primary Human Neutrophils.


**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.**

- 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.

Exposed to TNFα or TGFβ for up to 72 h.

- Proliferation of fetal ASM cells
- Matrix metalloproteinase MMP-9 expression
- Collagen III expression and deposition
Vitamin D Attenuates Cytokine-Induced Remodeling in Human Fetal Airway Smooth Muscle Cells.

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

human fetal airway smooth muscle (ASM) cells
exposed to TNFα or TGFβ for up to 72 h.

pre-treatment with calcitriol

(-)
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

- 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  


- 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:

- First trimesters: OR 0.79
- Second trimesters: OR 0.80
Prenatal, perinatal, and childhood vitamin D exposure and their association with childhood allergic rhinitis and allergic sensitization  


- 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:

- First trimester (0 to 13 weeks): OR 0.79
- Second trimester (13 to 26 weeks): OR 0.80

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

• Canon P. Acta OtorhinolaryngolBelg 1951; 5:495-508.
Vitamin D status, aeroallergen sensitization, and allergic rhinitis: A systematic review and meta-analysis.


✓ 21 observational studies

![Graph showing prevalence of AR](image)

- Prevalence of AR: 0.71
- 95% CI: 0.56-0.89
- p = 0.04

Individuals with serum 25(OH)D ≥75 nmol/L vs those with serum 25(OH)D <50 nmol/L

- 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

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

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

100 children, ages 5-12 years, sensitive to grass pollen, with allergic rhinitis

- 5-gram grass SLIT 300 IR tablets with either vitamin D 1000 IU daily supplementation, probiotic, or placebo for 5 months

Control group

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

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

<table>
<thead>
<tr>
<th>Coactivators</th>
<th>VDR Function</th>
<th>Target genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRC</td>
<td>Barrier formation</td>
<td>ABCA12, UGCG, ELOVL4</td>
</tr>
<tr>
<td></td>
<td>Innate Immunity</td>
<td>Cathelicidin, CD14</td>
</tr>
<tr>
<td>DRIF</td>
<td>Epidermal Differentiation</td>
<td>K1, K10, FLG, LOR</td>
</tr>
<tr>
<td></td>
<td>Hair Differentiation</td>
<td>Hair keratins</td>
</tr>
<tr>
<td></td>
<td>Proliferation</td>
<td>Cyclin D1, Gli 1</td>
</tr>
<tr>
<td></td>
<td>Wnt signaling</td>
<td></td>
</tr>
</tbody>
</table>

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


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

VDR null mice

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

Baiz N, JACI 2014;133:147

per 5 ng/mL increase in cord blood 25(OH)D levels OR for

early transient wheezing 1 y 2 y 3 y 5 y

atopic dermatitis by age

- - - - - - -

Cord Blood

- - - - - - -

25(OH)D levels

0.67

p=0.002

0.84

p=0.05

0.82

p=0.02

0.82

p=0.02

0.75

p=0.0005
Maternal vitamin D status and childhood asthma, wheeze and eczema: a systematic review and meta-analysis

Wei Z, PAI 2016;27:612-619

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

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nour Baiz</td>
<td>1.07 (0.78, 1.45)</td>
<td>1.51</td>
</tr>
<tr>
<td>Carlos A</td>
<td>0.99 (0.94, 1.04)</td>
<td>56.81</td>
</tr>
<tr>
<td>Katharine C Pike</td>
<td>0.98 (0.92, 1.04)</td>
<td>38.63</td>
</tr>
<tr>
<td>M. Erkkola</td>
<td>0.79 (0.64, 0.99)</td>
<td>3.05</td>
</tr>
<tr>
<td>Overall</td>
<td>0.98 (0.94, 1.02)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

favours vitamin D = OR 0.9
Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children.


- 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
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.
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.

- 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.

average % change from the baseline EASI score

- Placebo: -16%
- Vitamin D: -29%

p=0.02
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
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 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: 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.

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

• However, evidence from different research groups show that probiotics could have a 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 lymphopoi etin (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 regulatory T cells (Tregs) in the mesenteric lymphnodes of patients. These Tregs 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%, $P=0.009$).

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

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- 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 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.
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✓ Conclusions

OR for peanut allergy in children ≤72 mo.

<table>
<thead>
<tr>
<th>25(OH)D nmol/L in neonatal dried blood samples</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-74.9</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>75-99.9</td>
<td>0.37</td>
<td>0.02</td>
</tr>
<tr>
<td>≥100</td>
<td>0.66</td>
<td>(NS)</td>
</tr>
</tbody>
</table>

- 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)

- 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)
The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy. 


- 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)

OR for sensitization to food allergens

5.0
especially to milk (OR 10.4)
and
wheat (OR 4.2)
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.
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]

**Correlation of vitamin D levels and absolute counts of Treg cells (cells per µl of total blood).**

Pearson coefficient = 0.390; P = 0.027

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]

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.

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

(AUC = 0.850; 95% CI = 0.608-1; P = 0.040)

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

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

*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.


• 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.

- 2316 anaphylaxis admissions
- Median age of patients 41 yr;

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

Latitudes:
- 17.5 S
- 56.0 S
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

Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D.
1) Low vitamin D level in patients with chronic urticaria:

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

3) Vitamin D treatments leads to improvement/resolution of chronic urticaria:
Use of Vitamin D in Non-Bone Diseases: Prevention and Treatment

- Introduction
- Immunomodulation related to allergy
- Fetal development
- Prevention and modification of asthma & COPD
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- Conclusions
Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential.

• 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.

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).

**OR of pediatric-onset Multiple Sclerosis**

<table>
<thead>
<tr>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72</td>
<td>0.02</td>
</tr>
<tr>
<td>1.17</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Increasing levels of 25(OH)D vs. Increased BMI
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
-3.99 ng/mL
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

57.7%
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).

OR for type 1 diabetes

0.71

In infants supplemented with vitamin D
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).

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

OR for Type 1 Diabetes

0.71

In infants supplemented with vitamin D

- 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 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 levels in children at the onset of T1DM (n= 58) compared with children with other diseases (n= 166)
- Between May 2010 and July 2012

![Graph showing OR for developing T1DM with mean serum Vit D (nmol/L)]
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.
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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.
Vitamin D status in pediatric irritable bowel syndrome.

- Retrospective case-controlled study of 116 controls (age 14.6 ± 4.3 y), and 55 subjects with IBS (age 16.5 ± 3.1 y).
- 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.
An increasing amount of evidence points to the possibility that gestational and early childhood vitamin D deficiency \([25(OH)D < 40 \text{ ng/ml}]\) 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.
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%.
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.


- 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.

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.
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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• 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.

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 18 weeks.

- 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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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 diseases 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.


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. 

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),

- 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).

- 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.
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