



fimp Federazione Italiana Medici *Pediatr*i
Sezione di Caserta

SIPPS & FIMPAGGIORNA 2012

3 maggio 2012

Le nuove e le vecchie indicazioni della vitamina D

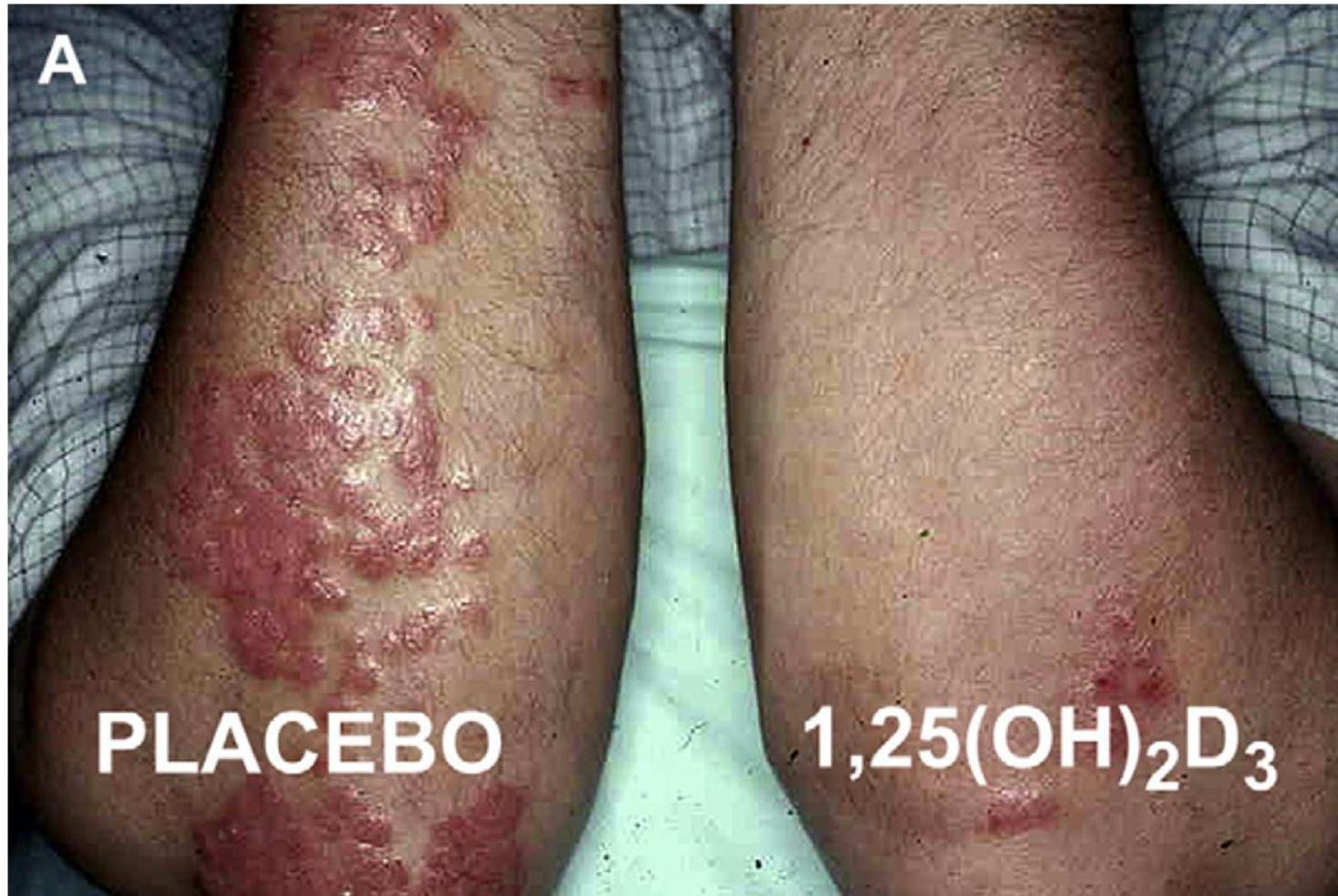
G. Saggese, F. Vierucci

Clinica Pediatrica, Università di Pisa

Vitamin D . Extraskeletal Actions

PSORIASIS

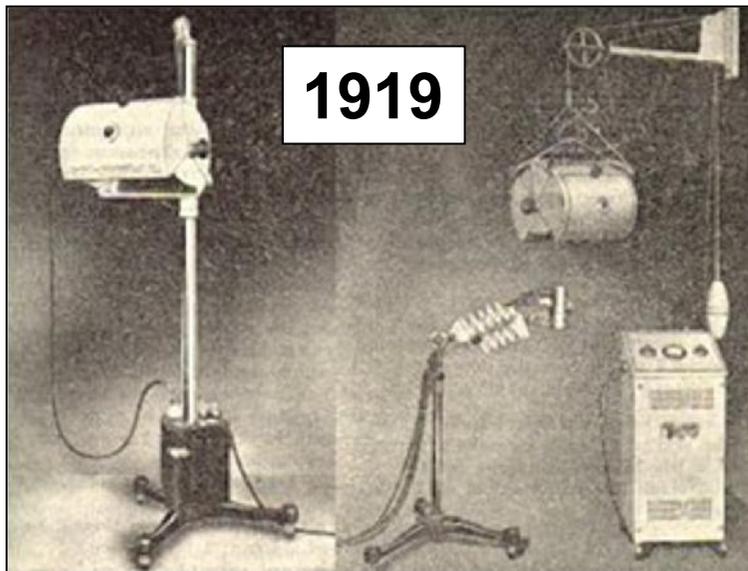
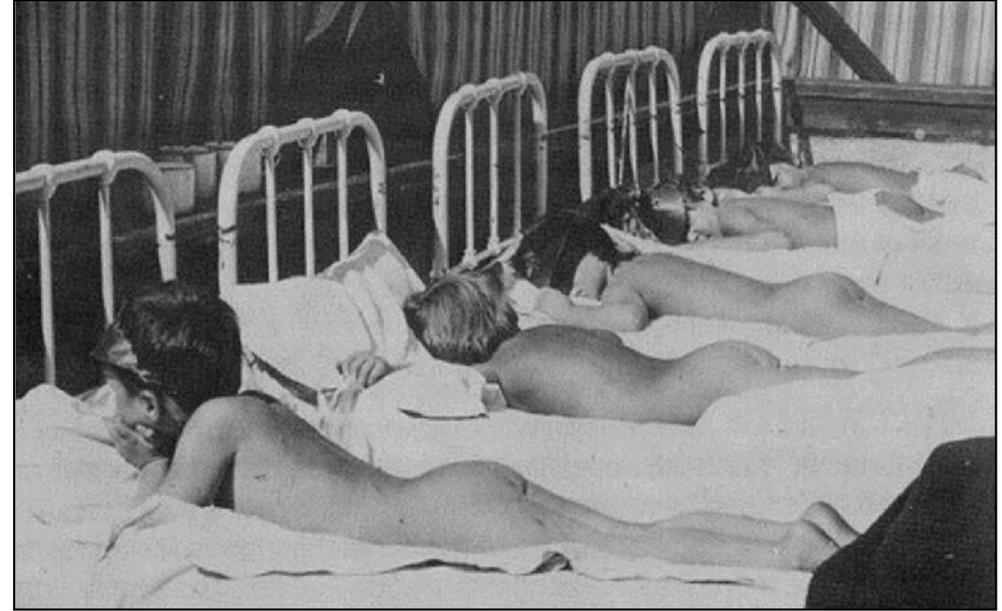
28-year-old man with a more than 20-year history of psoriasis.



(Courtesy dr. Holick MF. 1979)

Fine XIX - prima metà XX secolo

L'elioterapia per il trattamento del Rachitismo e della TBC



1919



Istituto marino
Messina

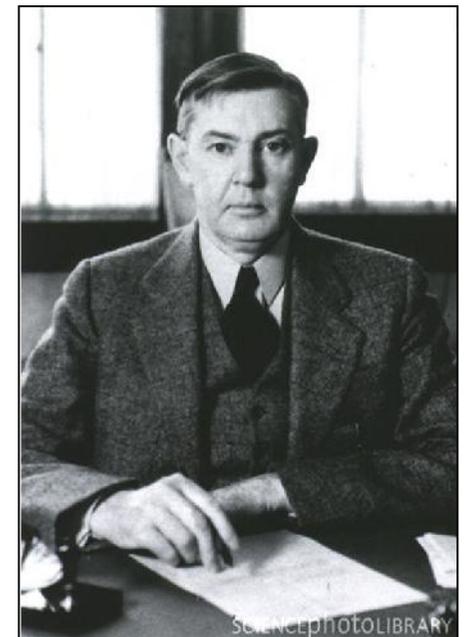
1919

Edward Mellanby intuì il ruolo dei fattori dietetici nell'eziopatogenesi del rachitismo. Alimenti “... *ricchi di vitamina A*”, come l'olio di fegato di merluzzo, contenevano un “**fattore antirachitico**”.



1921

Elmer McCollum identificò questo fattore antirachitico come una nuova vitamina liposolubile, la quarta sino ad allora scoperta e per questo chiamata **vitamina D**.

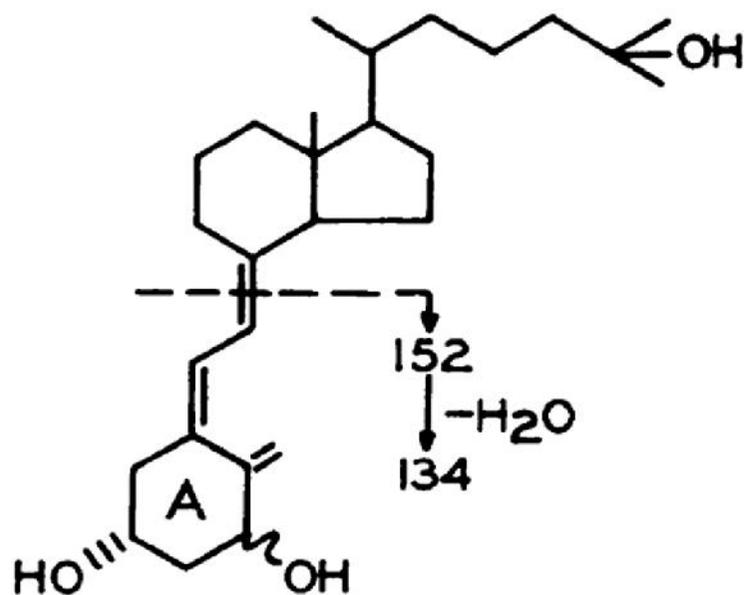


Proc. Nat. Acad. Sci. USA
Vol. 68, No. 4, pp. 803-804, April 1971

Identification of 1,25-Dihydroxycholecalciferol, a Form of Vitamin D₃ Metabolically Active in the Intestine

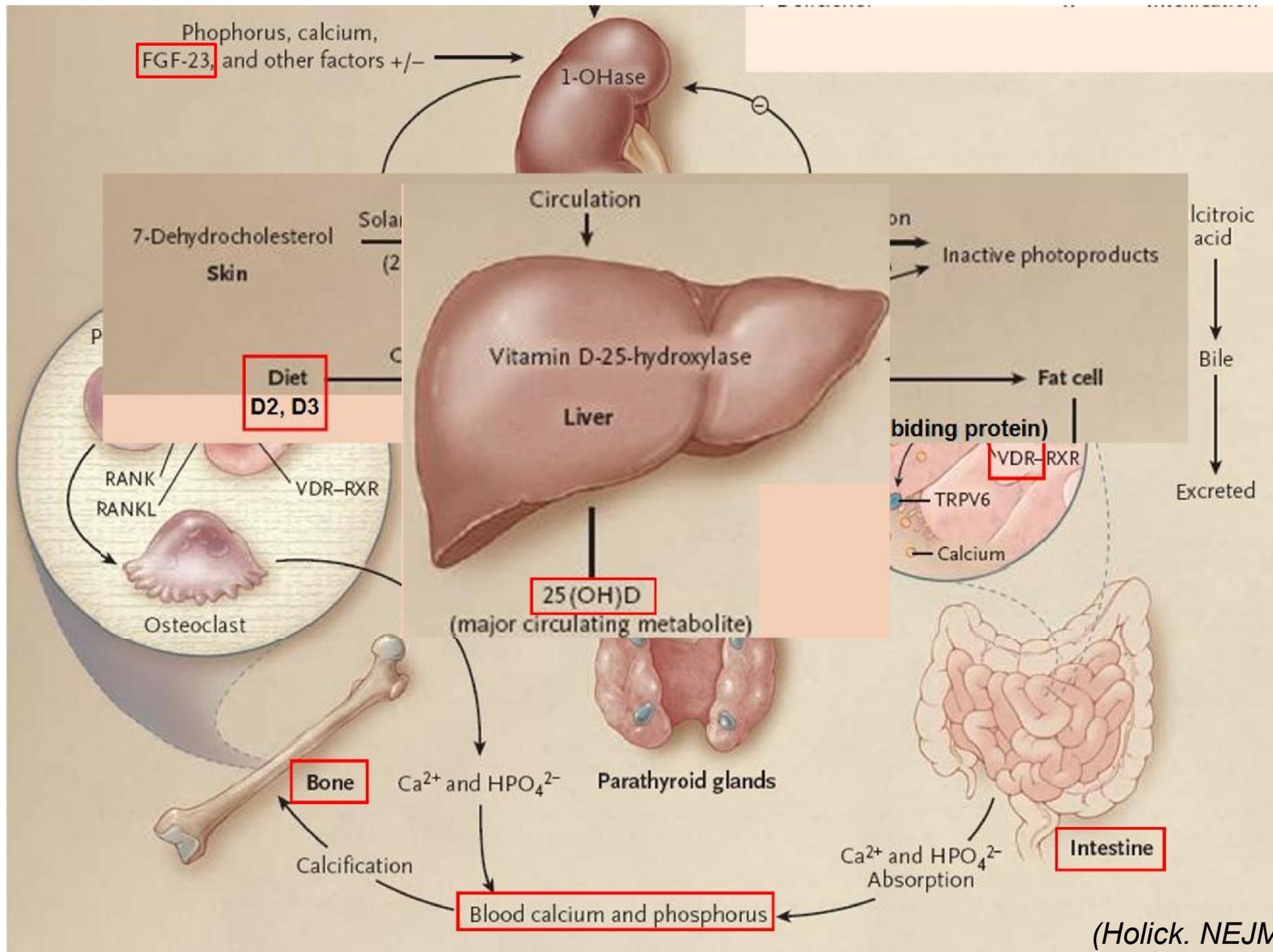
M. F. HOLICK, H. K. SCHNOES, AND H. F. DELUCA*

Department of Biochemistry, University of Wisconsin, Madison, Wis. 53706



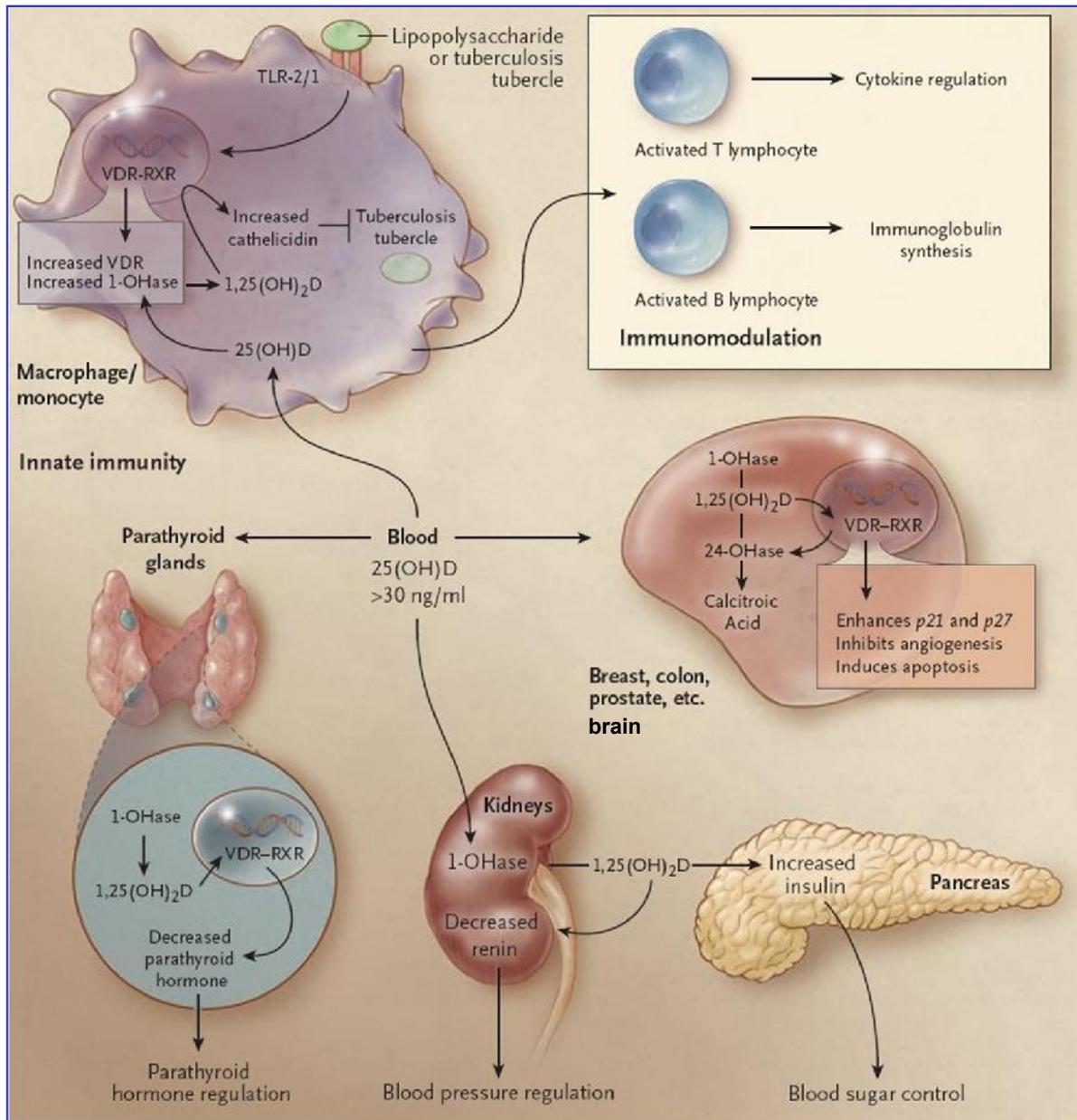
Sistema endocrino della vitamina D
Stato vitaminico D
(epidemiologia, fattori di rischio)

VITAMIN D ENDOCRINE SYSTEM



(Holick. NEJM 2007)

EXTRASKELETAL ACTIONS OF VITAMIN D



(Holick MF. NEJM 2007)

1,25(OH)₂D:

- controls directly or indirectly up to 2.000 genes;
- regulates cellular proliferation and differentiation; apoptosis and angiogenesis (reducing risk of cancer);
- exerts an immunomodulatory action, reducing risk of autoimmune diseases;
- promotes innate immunity, reducing risk of recurrent infections.

Assessment of Vitamin D Status

25-OH-D, ng/ml

	Deficiency	Insufficiency	Sufficiency
AAP	< 20	-	≥ 20
IOM	< 20	-	≥ 20
End. Soc.	< 20	20-29	≥ 30

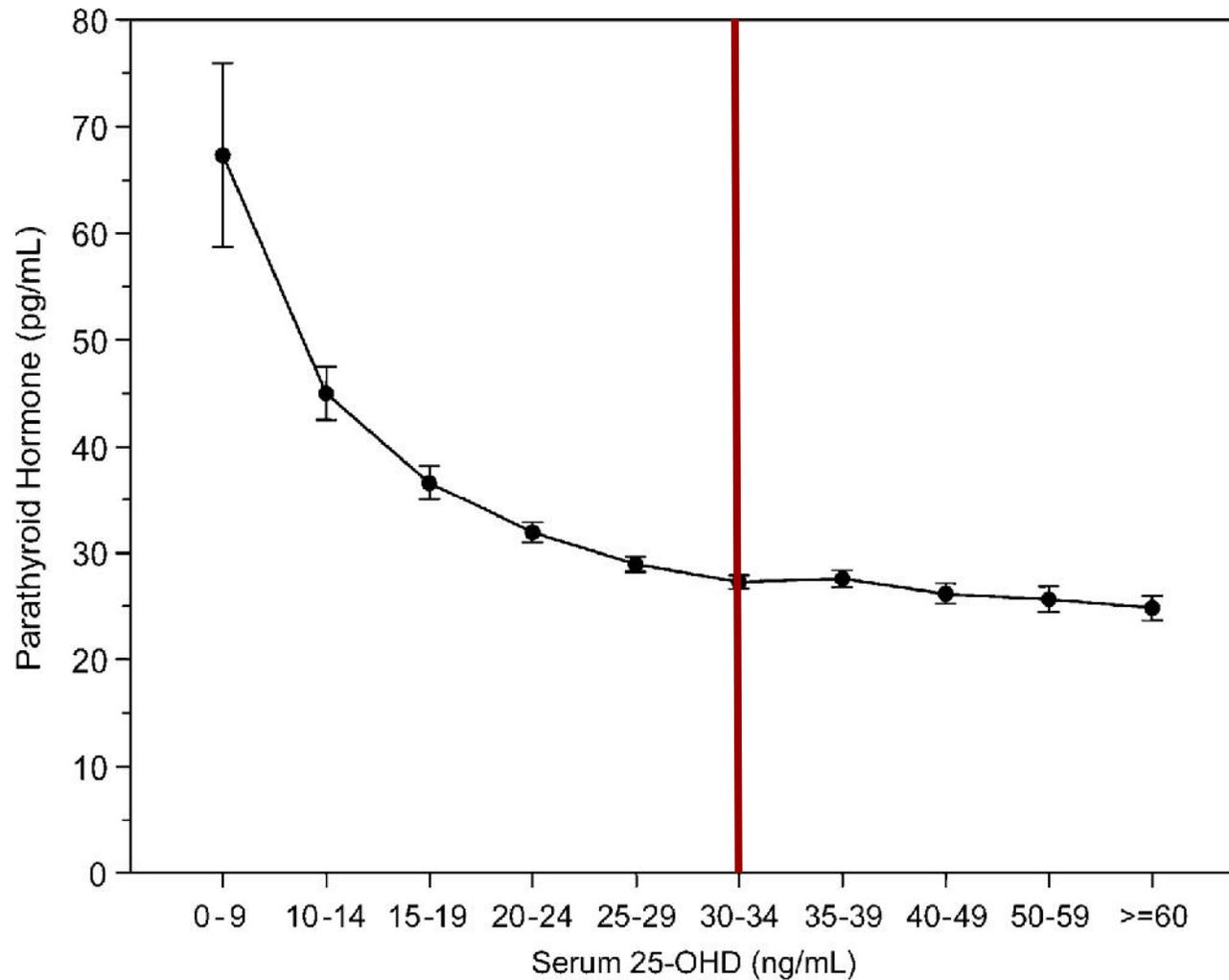
AAP (Wagner CL et al). Pediatrics 2008

IOM (Ross AC et al). Washington (DC) 2011

Endocrine Society (Holick MF et al). JCEM 2011

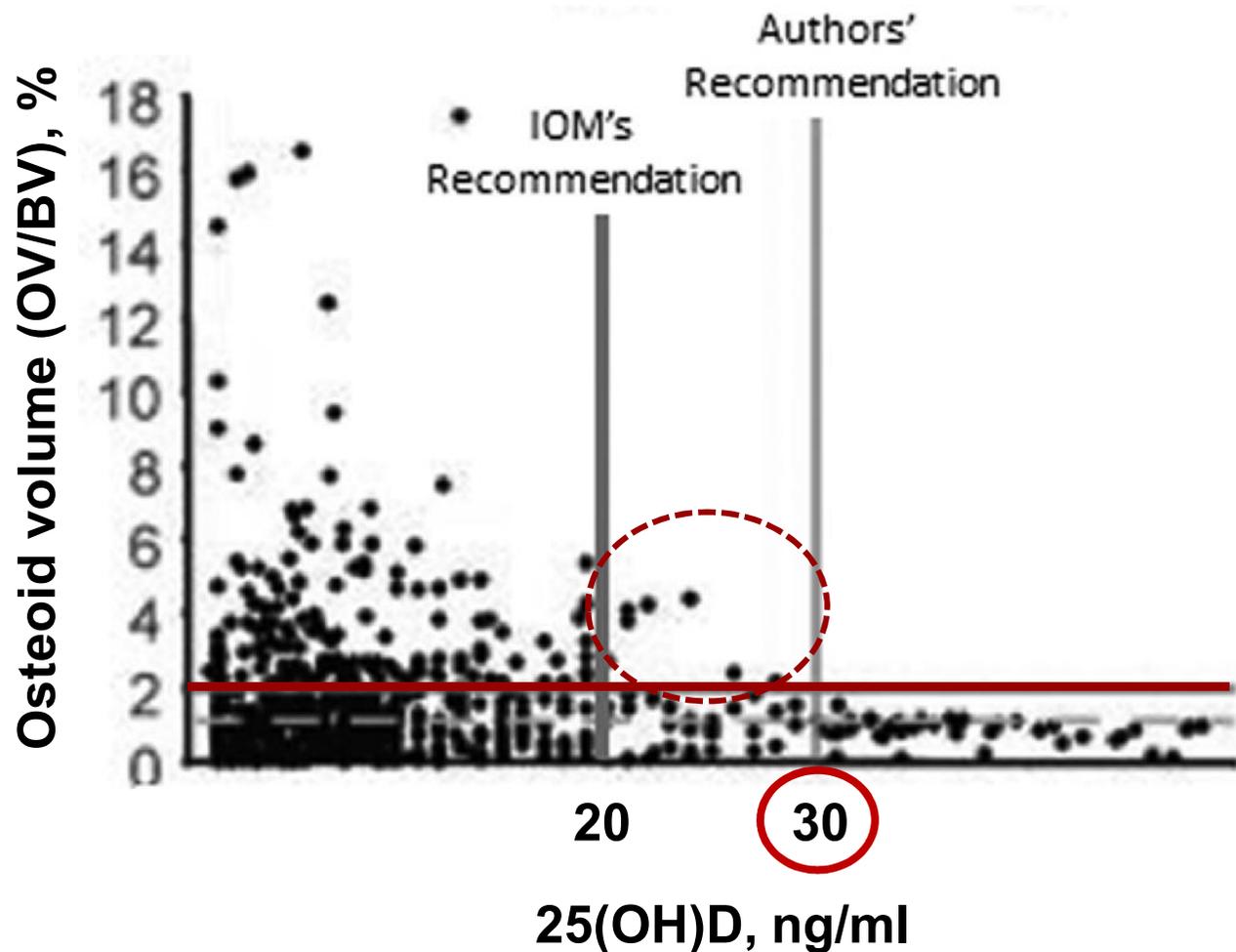
1 nmol/l = 0.4 ng/ml
50 nmol/l = 20 ng/ml
75 nmol/l = 30 ng/ml

Relationship between serum 25-OHD concentrations and serum concentrations of PTH in osteoporotic patients receiving vitamin D



(Holick MF. *Vitamin D: Physiology, Molecular Biology, and Clinical Applications*. 2nd edition, 2010)

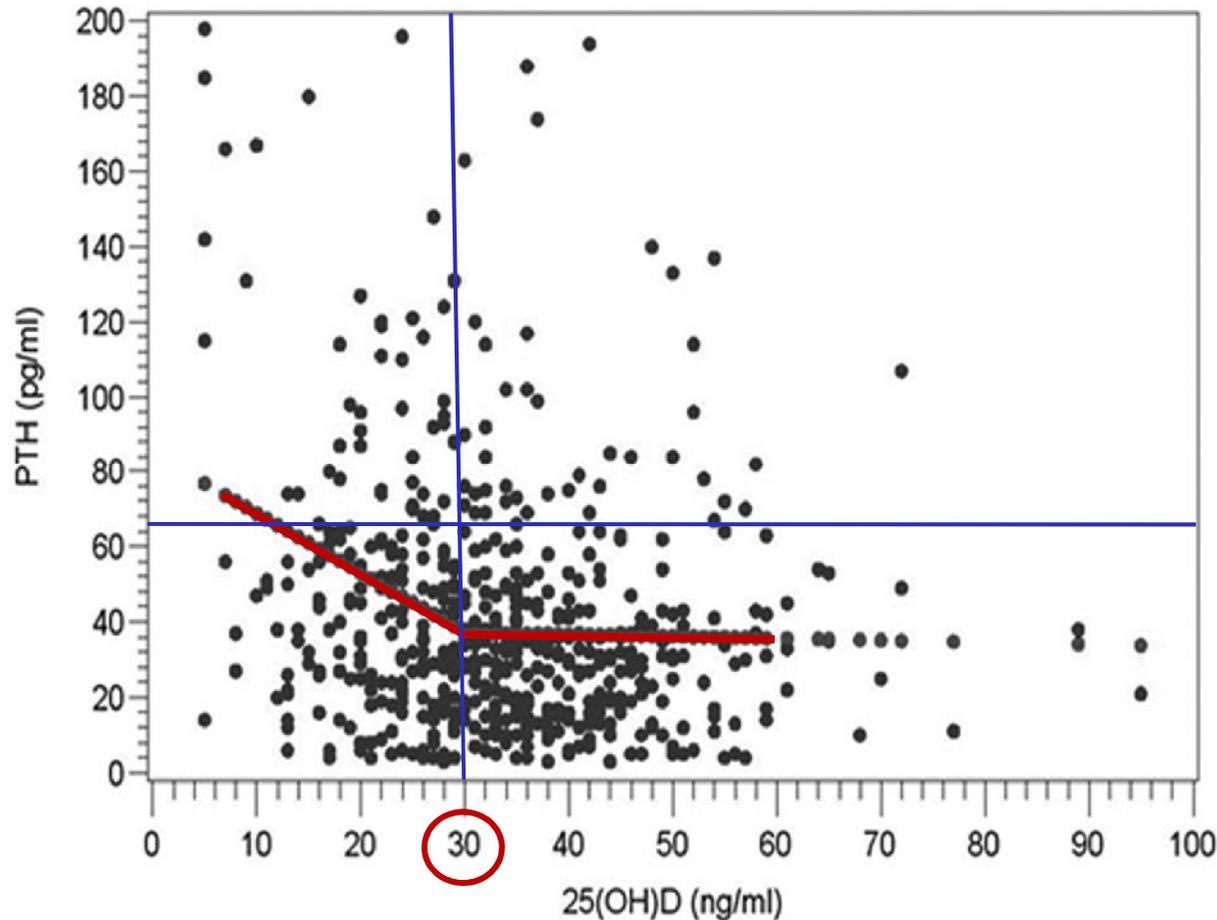
Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients



- Pathologic accumulations of osteoid are absent in subjects with 25(OH)D >30 ng/mL.
- The horizontal line indicates a threshold of 2% osteoid volume used as a histopathologic border to osteomalacia.
- 8.5% of the victims had osteomalacia when their blood level of 25(OH)D was 21–29 ng/mL.

(Priemel M et al. JBMR 2010)

Serum 25(OH)Vitamin D Level in Children: Is There a Need to Change the Reference Range Based on 2011 IOM Report?



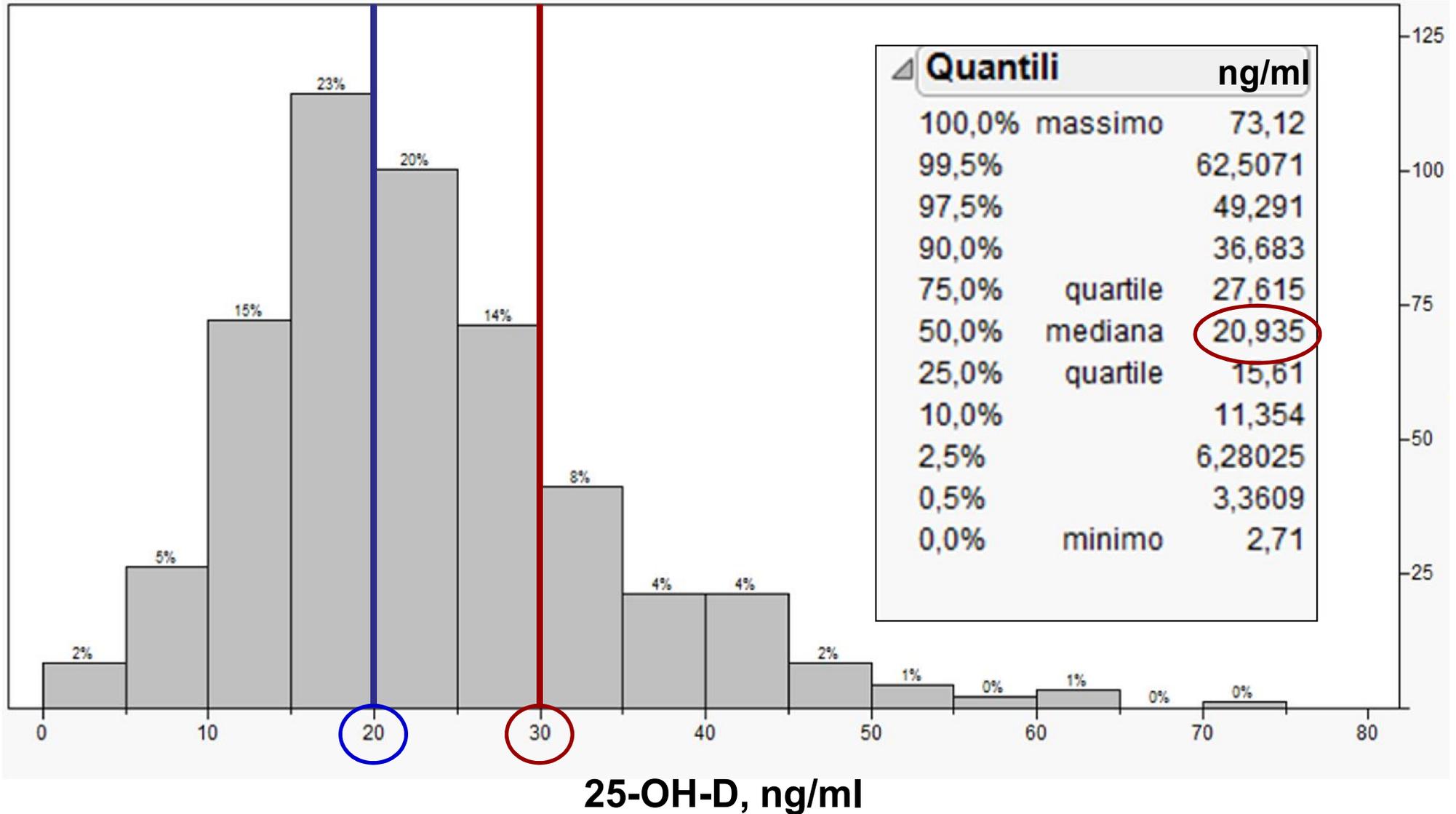
n = 553, age 10.1 ± 5.9 yr

- **25-OH-D > 30 ng/ml: 60.6%**
- **25-OH-D: 20-30 ng/ml: 28.0%**
- **25-OH-D < 20 ng/ml: 11.4%**

Based on their analysis Authors believe that pediatricians should maintain the normal cutoff for serum 25(OH)D at ≥ 30 ng/mL

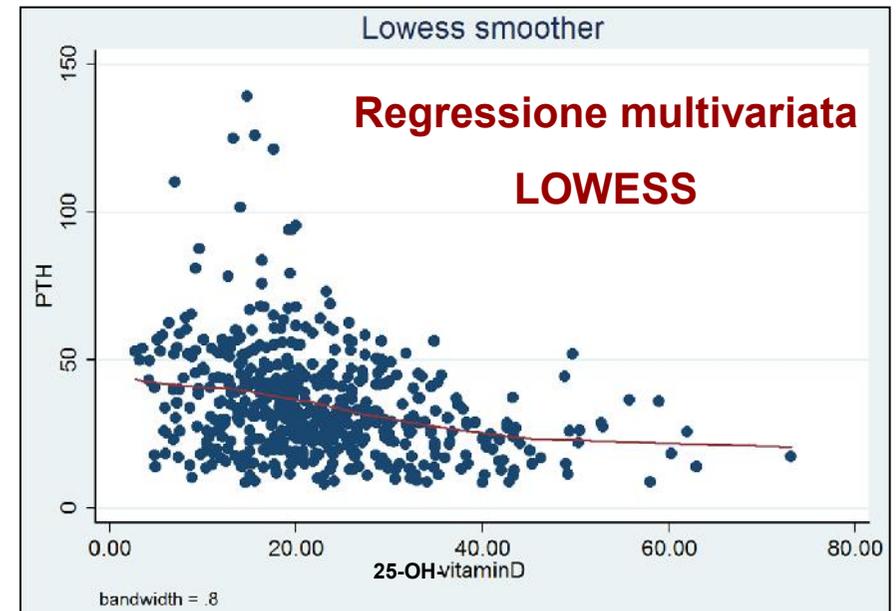
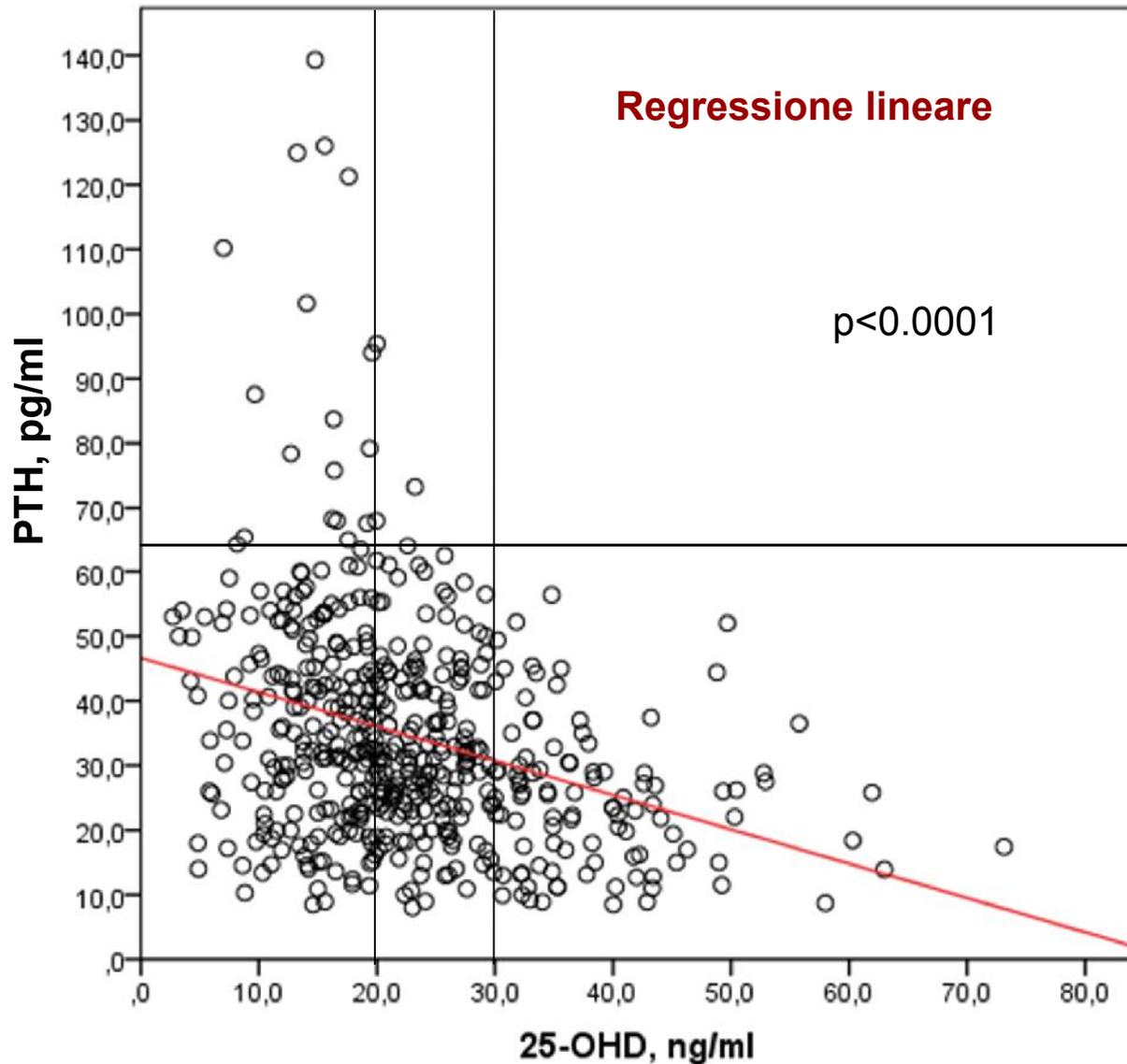
Valutazione dello stato vitaminico D

Clinica Pediatrica Università di Pisa (n = 520; 2.0-21.0 anni)



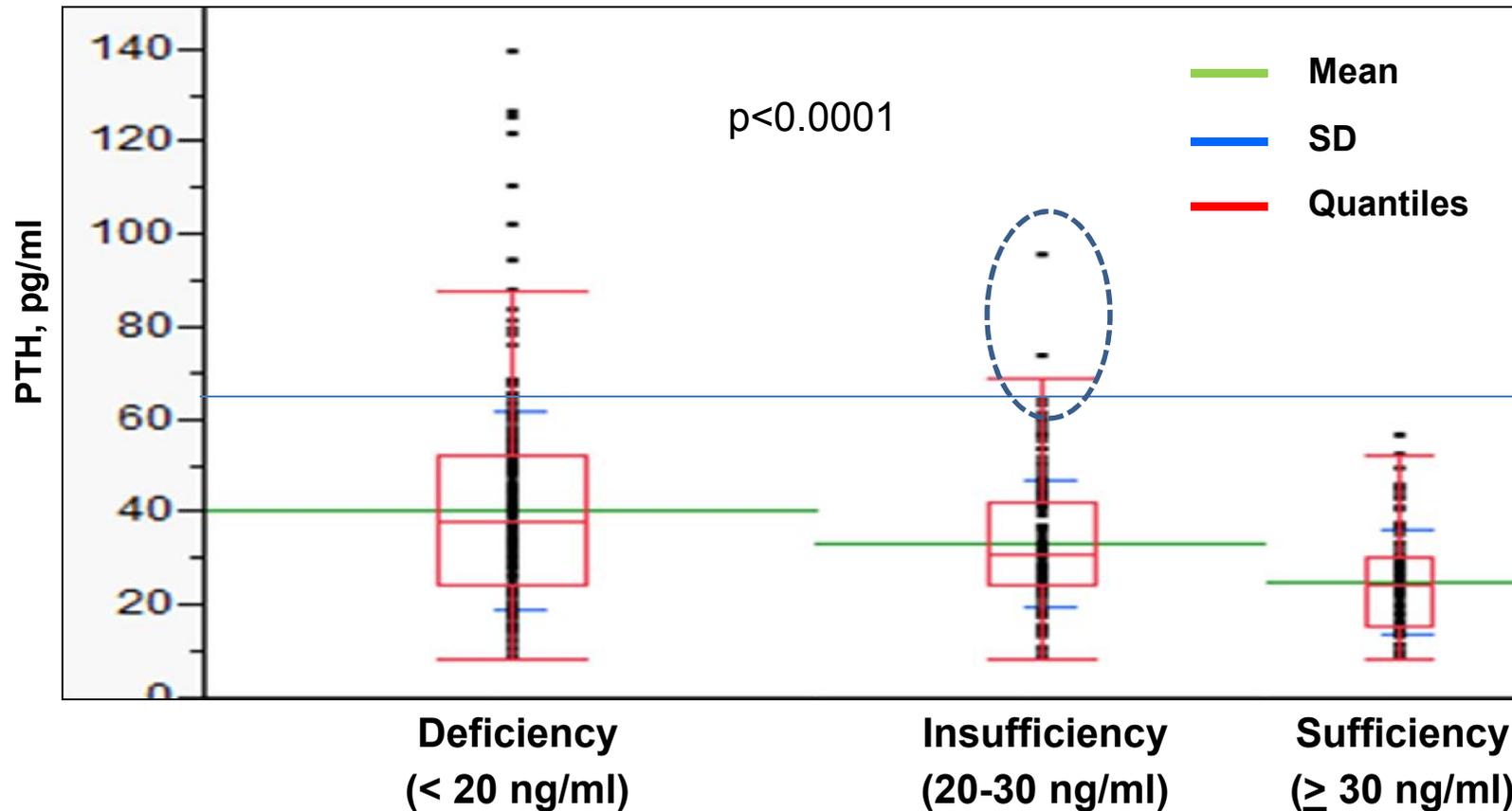
Relazione tra livelli di 25-OH-D e PTH (1)

Clinica Pediatrica Università di Pisa (n = 520; 2.0-21.0 anni)



Relazione tra livelli di 25-OH-D e PTH (2)

Clinica Pediatrica Università di Pisa (n = 520; 2.0-21.0 anni)

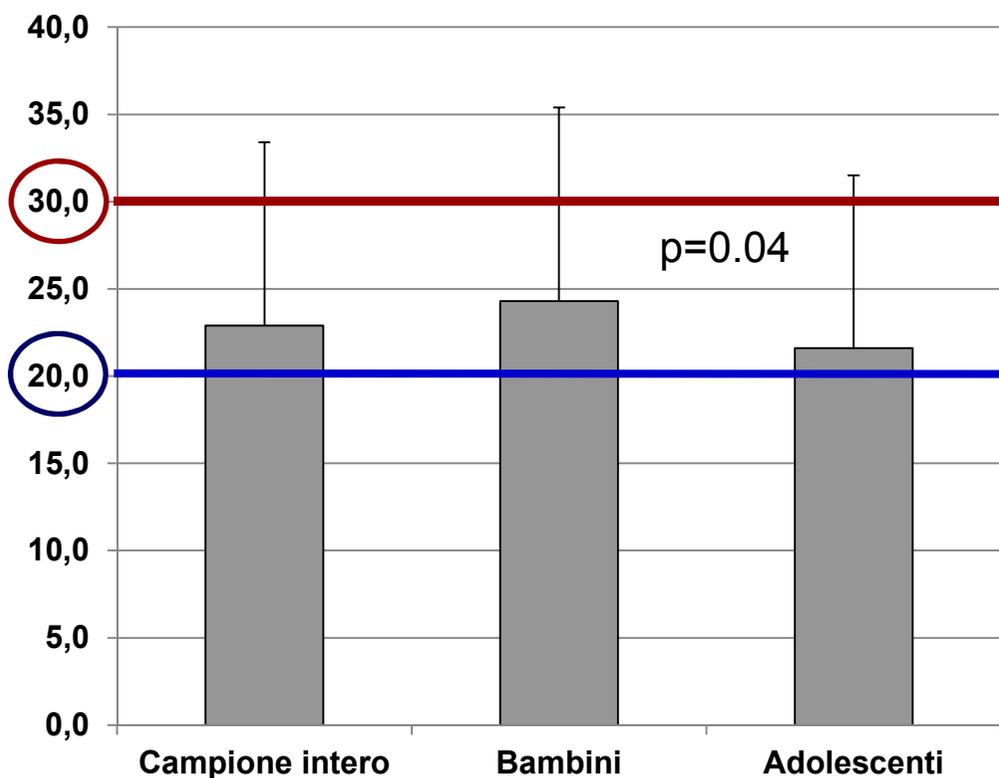


Per valori di 25-OH-D \geq 30 ng/ml non si osserva alcun caso di iperparatiroidismo secondario; pertanto tale livello potrebbe essere proposto come cut-off di uno stato vitaminico D sufficiente (o desiderabile) anche in età pediatrica.

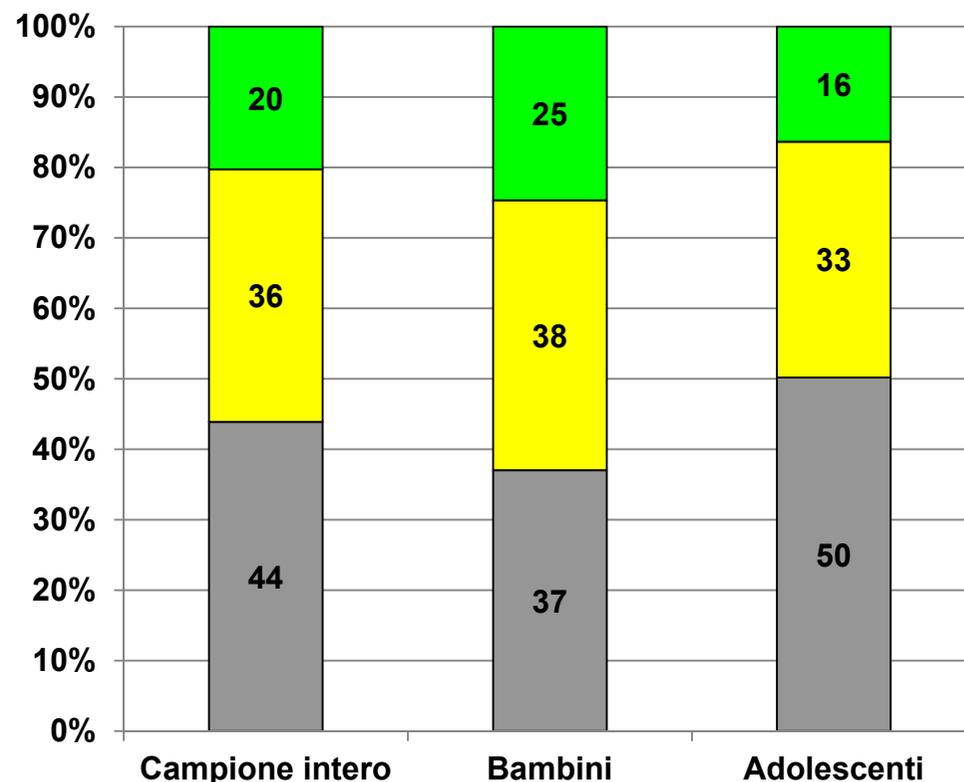
Livelli circolanti di 25-OH-D nelle varie classi di età

Clinica Pediatrica Università di Pisa (n = 520; 2.0-21.0 anni)

■ 25-OH-D, ng/ml



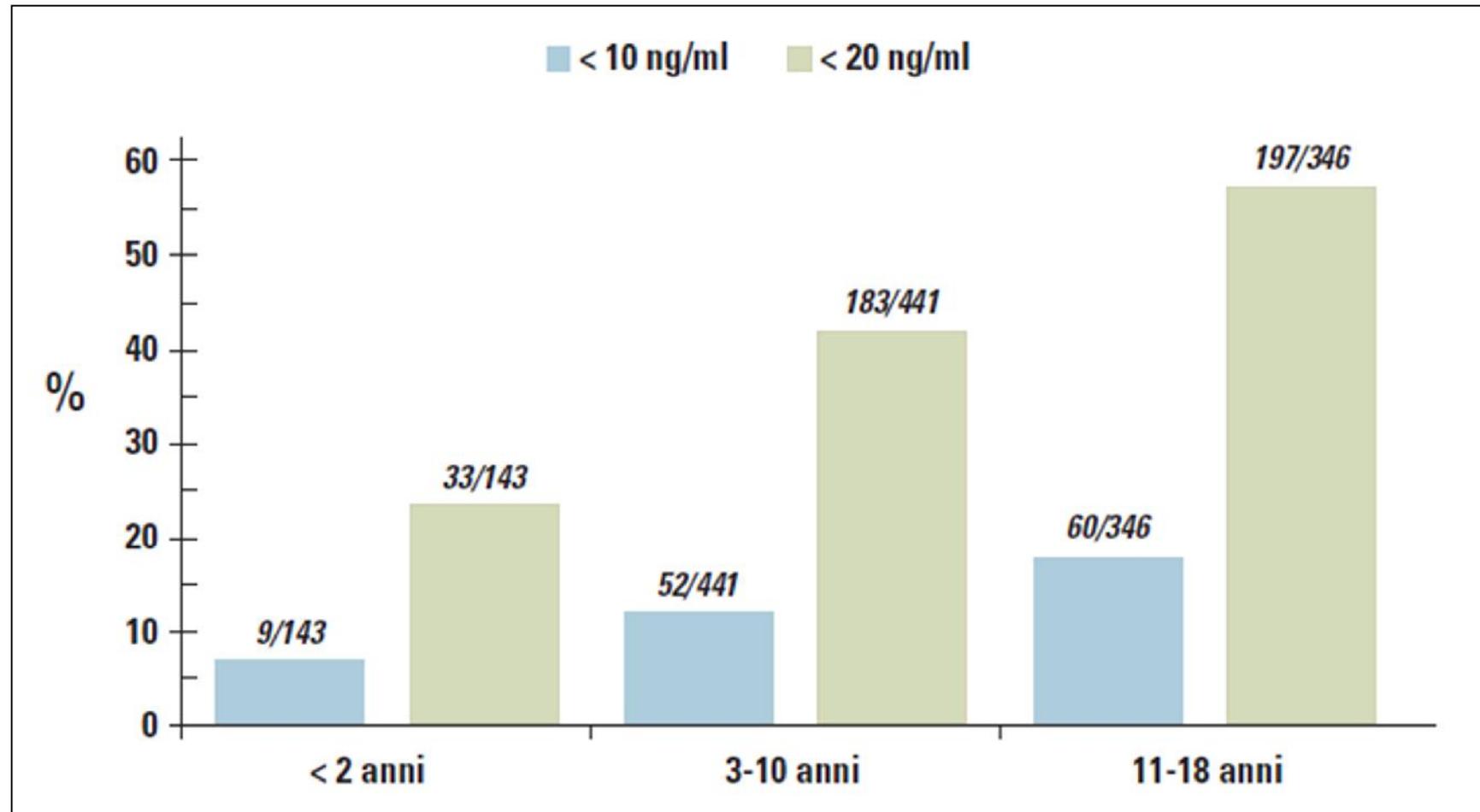
■ Sufficienza, %
■ Insufficienza, %
■ Deficienza, %



p=0.007

Vitamin D deficiency during childhood

- n = 930, range 0-18
- 25-OH-D < 20 ng/ml: 44%
- 25-OH-D \leq 10 ng/ml: 13%



(Lippi G et al. Aging Clin Exp Res 2012)

Prevalence of Vitamin D deficiency in Italy

VERONA (45°27' N)

n = 59 (9-12 yr).

25-OH-D (ng/ml):

- ≥ 30 : 11.9%
- 20-30: 45.8%
- < 20 : **42.4%**

(Chinellato I et al. Eur Respir J 2011)

PISA (43°43' N)

n = 520 (2-21 yr).

25-OH-D (ng/ml):

- ≥ 30 : 20.3%
- 20-30: 35.8%
- < 20 : **43.9%**

UDINE (46°4' N)

n = 93 (2-220 months).

25-OH-D (ng/ml):

- ≥ 20 : 45.2%
- < 20 : **54.8%**

(Marrone G et al. Eur J Nutr 2011)

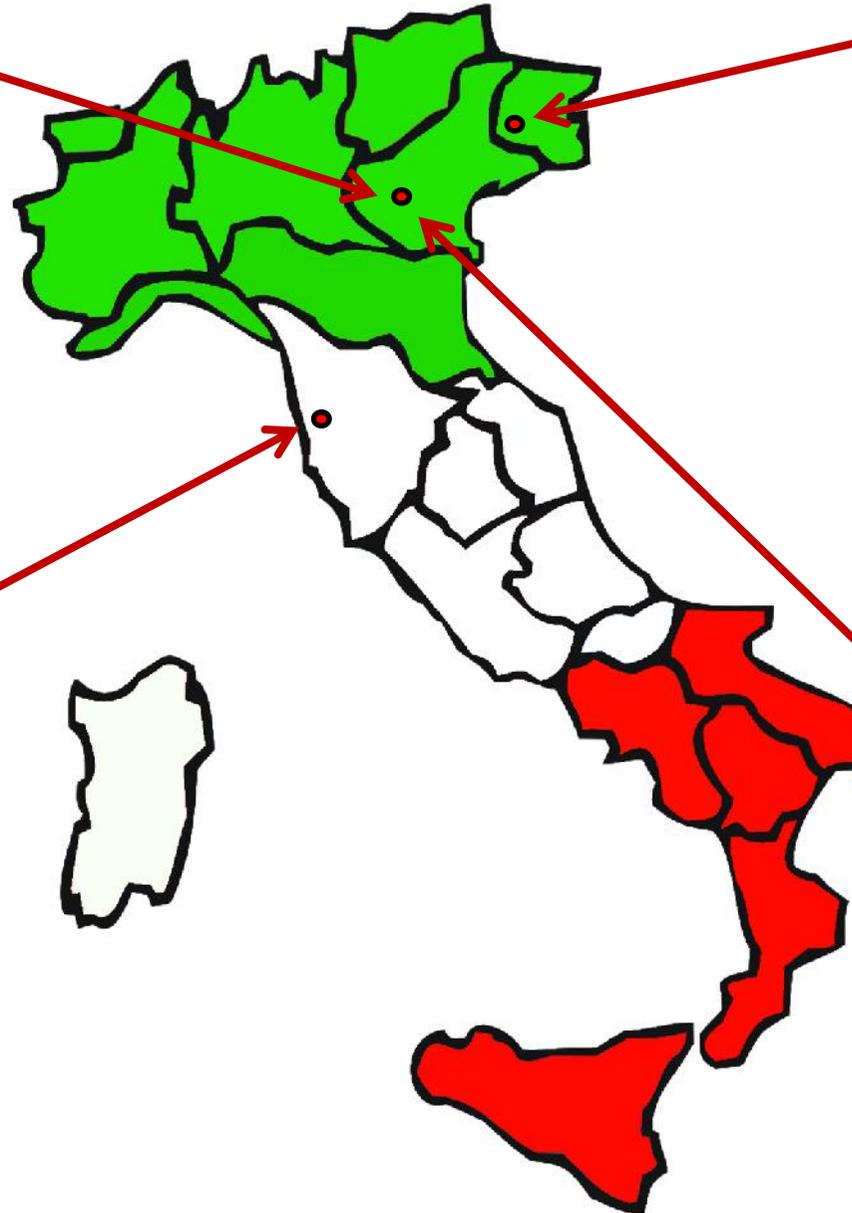
VERONA (45°27' N)

n = 930 (0-18 yr).

25-OH-D (ng/ml):

- < 20 : **44%**
- ≤ 10 : 13%

(Lippi G et al. Aging Clin Exp Res 2012)



Defining Vitamin D Deficiency in Newborns, Children and Adolescents

NHANES III (1988 – 1994) National Health and Nutrition Examination Survey

2.955 adolescents (12 – 19 yr)

25-OH-D < 20 ng/ml: 14%

25-OH-D < 30 ng/ml: 48%

(Saintonge et al. Pediatrics Mar 2009)

NHANES 2001 – 2004

6.275 subjects (0 – 21 yr)

25-OH-D < 15 ng/ml: 9%
(7.6 millions)

25-OH-D < 30 ng/ml: 61%
(50.8 millions)

(Kumar et al. Pediatrics Sept 2009)

NHANES 2001 – 2006

4.558 children (1 – 11 yr)

25-OH-D < 20 ng/ml: 18%
(6.3 millions)

25-OH-D < 30 ng/ml: 69%
(24 millions)

(Mansbach et al. Pediatrics Nov 2009)

BOSTON (42°N) (2005 - 2007)

376 newborns (<3 days)

25-OH-D < 20 ng/ml: 58%

433 mothers

25-OH-D < 20 ng/ml: 30%

(Merewood et al. Pediatrics Jun 2010)

ATLANTA (33°N) (2006 - 2007)

290 children (2.5 ± 1.2 yr)

25-OH-D < 20 ng/ml: 22.3%

25-OH-D < 30 ng/ml: 73.6%

(Cole et al. Pediatrics Apr 2010)

AUGUSTA (33°N) (2001 - 05)

559 adolescents (14 – 18 yr)

25-OH-D < 20 ng/ml: 28.8%

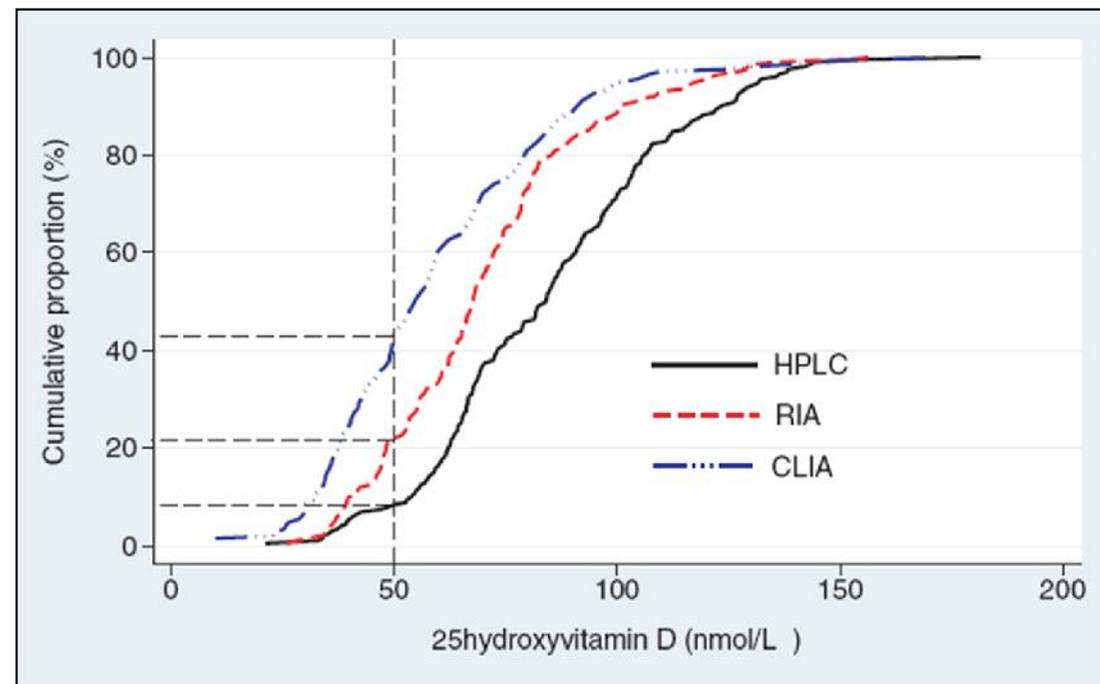
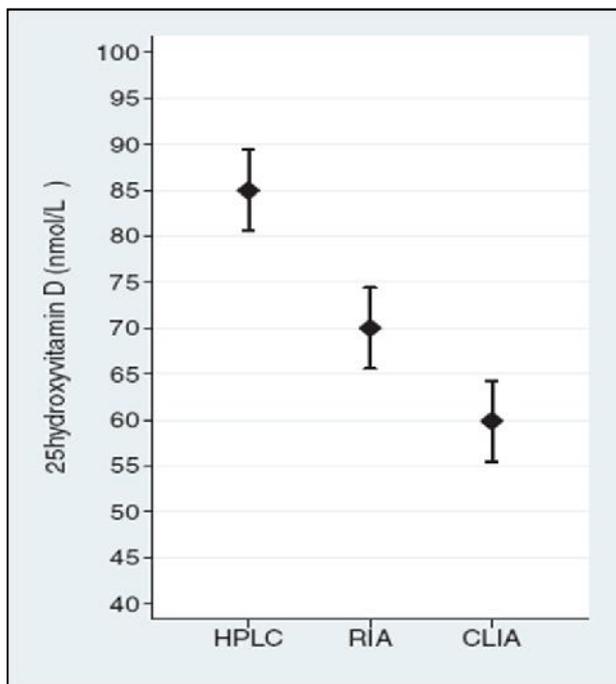
25-OH-D < 30 ng/ml: 56.4%

(Dong et al. Pediatrics Jun 2010)

Determining Vitamin D Status

A Comparison between Commercially Available Assays

- High-pressure liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry (**HPLCAPCI-MS**)
 - Radioimmunoassay (**RIA**)
 - Chemiluminescent immunoassay (**CLIA**)
- N = 204
 - Age: 57.5 ± 9.7 yr



There are substantial inter-assay differences between common commercially available assays for assessing vitamin D status.

Deficienza/insufficienza di vitamina D

FATTORI DI RISCHIO

- *Scarsa esposizione solare*
- *Elevata pigmentazione melaninica*
- *Mancata profilassi con vitamina D*
- *Allattamento al seno prolungato*
- *Deficienza materna di vitamina D*
- *Abitudini dietetiche e culturali*

NATURAL SOURCES OF VITAMIN D



→ **90 - 95%**



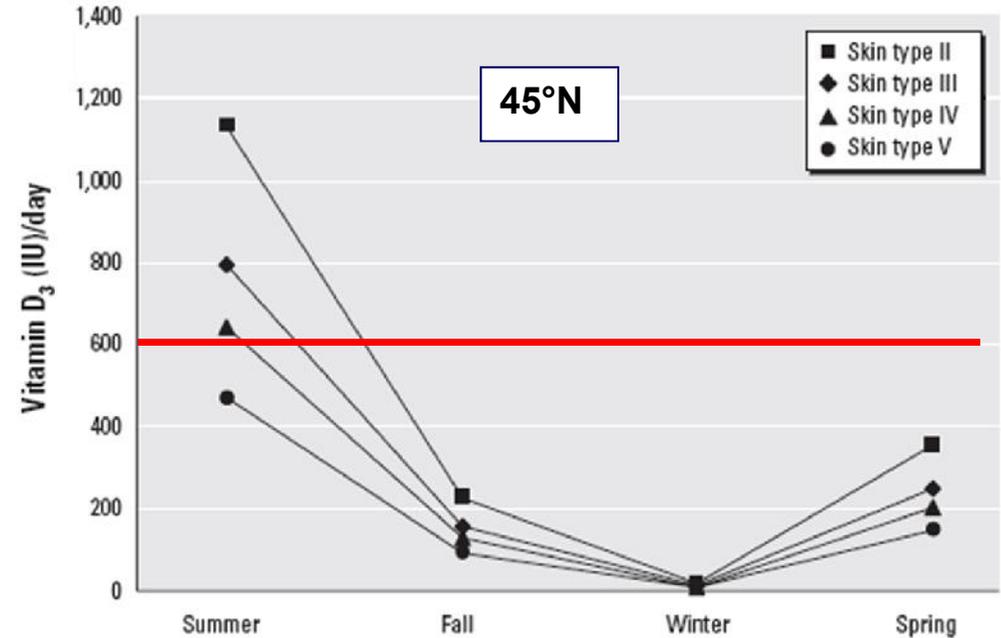
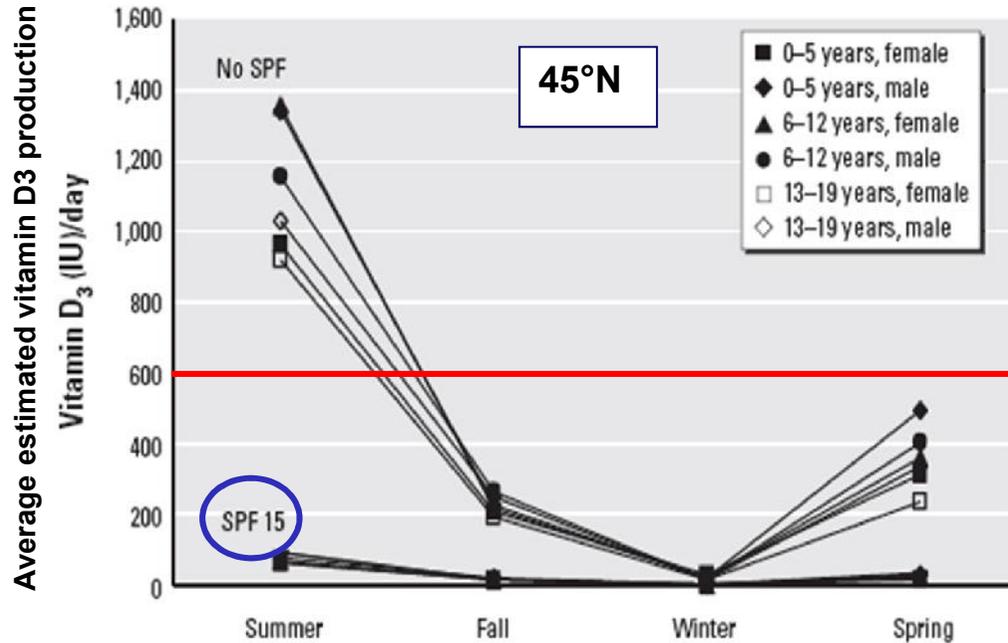
→ **5 - 10%**

CONTENUTO DI VITAMINA D (UI/100 g) NEI PIU' COMUNI ALIMENTI

- **Latte vaccino intero** **3 - 40 / L**
 - **Yogurt** **89**
 - **Emmenthal** **44**
 - **Parmigiano** **28**
 - **Burro** **35**
 - **Margarina fortificata** **60 / cucchiaino**
 - **Fegato di manzo** **40 - 70**
 - **Carne di maiale** **40 - 50**
 - **Dentice, Merluzzo, Orata, Palombo,
Sogliola, Trota, Salmone, Aringhe** **300 - 1500**
-
- **Latte umano** **50 / L**

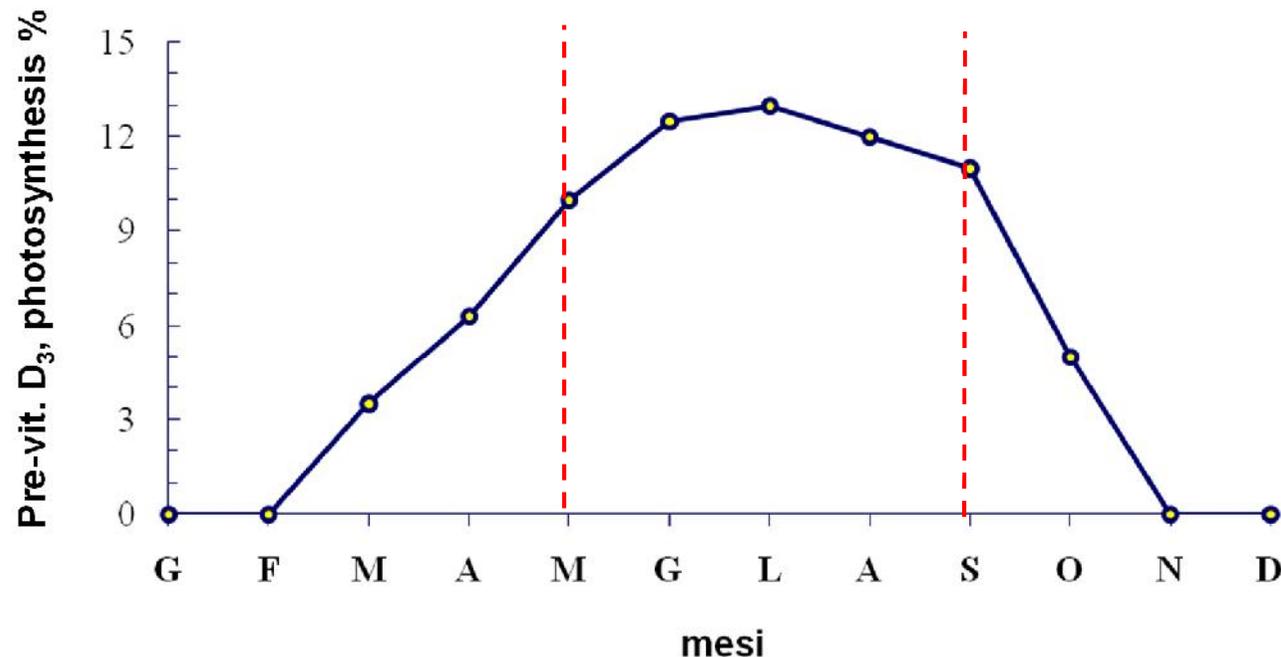
Solar UV Doses of Young Americans and Vitamin D3 Production (n = 2.000, 0-19 yr)

Skin type II



- *Sun exposure is the main determinant of vitamin D status, together with skin pigmentation.*
- *Application of sunscreens inhibits cutaneous vitamin D synthesis*

PRE-VITAMIN D₃ CONVERSION FROM 7-DEHYDROCHOLESTEROL DURING THE DIFFERENT MONTHS OF THE YEAR, IN VITRO, IN PISA (43°N)



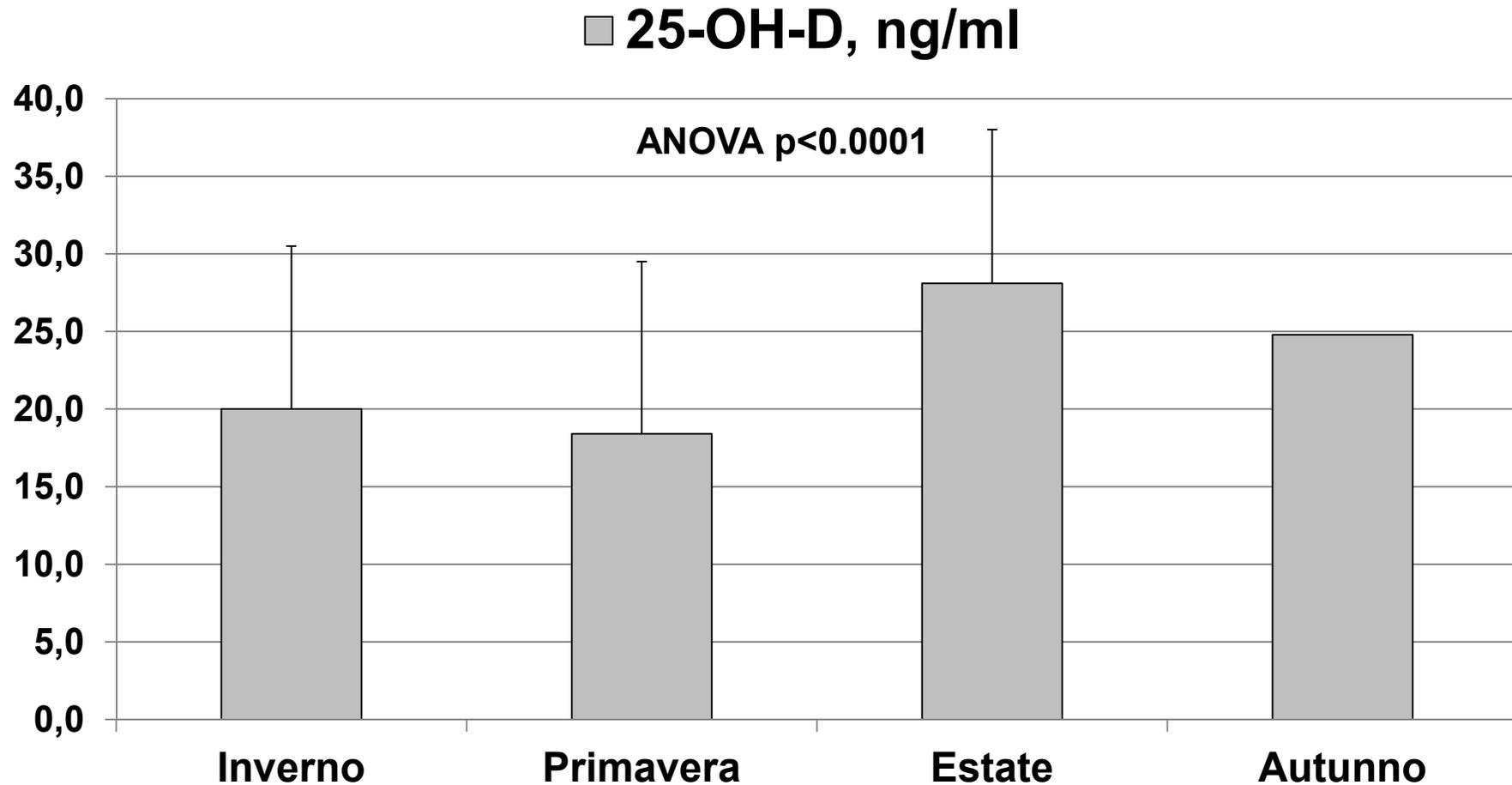
- *During wintertime no vitamin D is produced in the skin.*
- *An adequate vitamin D status depends on endogenous stores and/or supplementation.*

(Saggese G et al. *It J Ped* 1992)

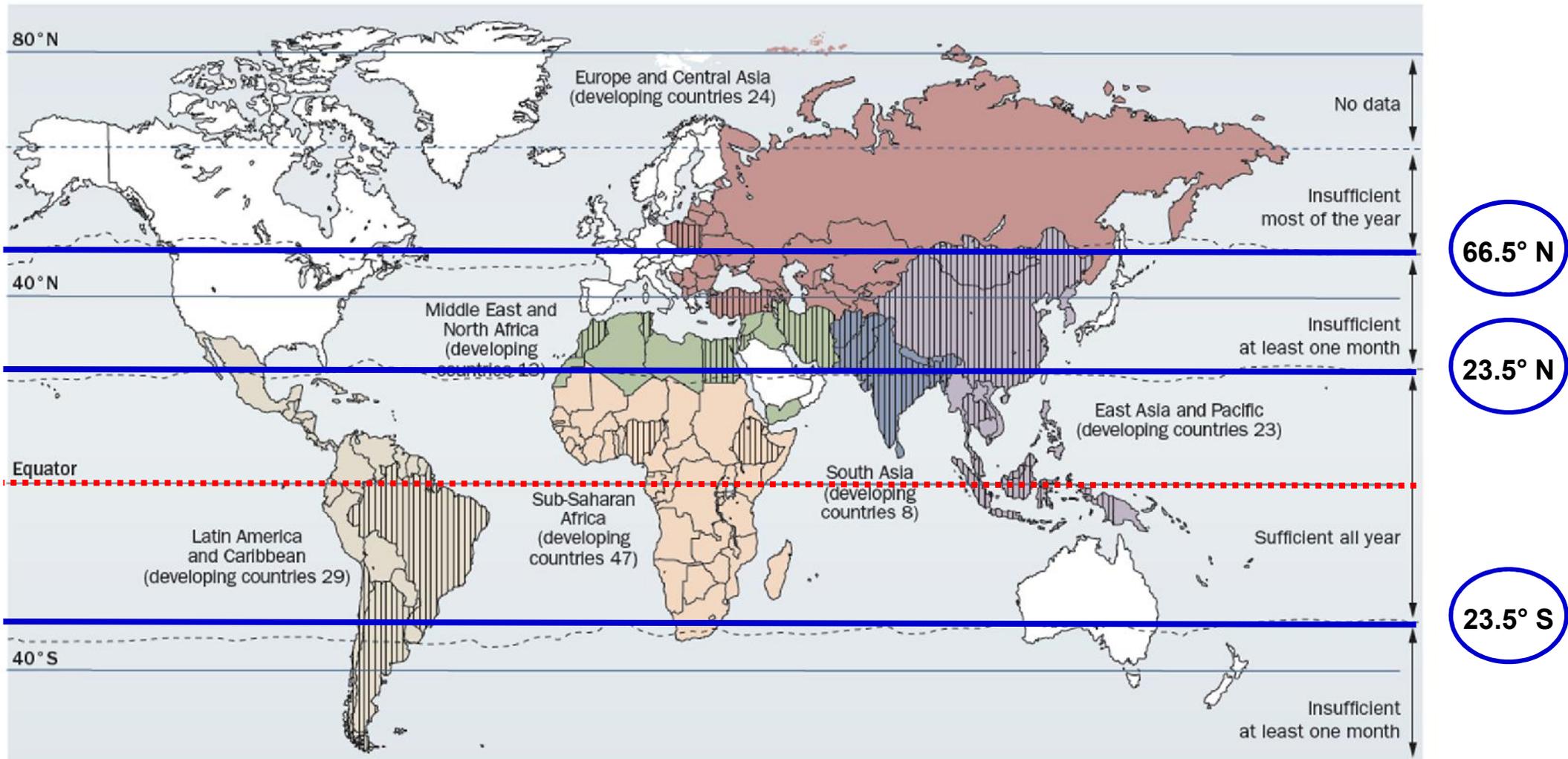
Fattori che influenzano lo stato vitaminico D

Periodo dell'anno del dosaggio del 25-OH-D

Clinica Pediatrica Università di Pisa (n = 520; 2.0-21.0 anni)



LATITUDE AND CUTANEOUS VITAMIN D SYNTHESIS



(Arabi A et al. Nat Rev Endocrinol 2010)

SUN EXPOSURE AND VITAMIN D STATUS

INFANTS

30 min/week of sun exposure for infants in diaper and 2 hours/week for fully clothed infants without a hat

CHILDREN AND ADOLESCENTS

exposure of arms and legs for 10-15 min/day, 2-3 times/week during summer

Serum 25-OH-D levels > 11 ng/ml

(Specker BL et al. J Pediatr 1985)

It is necessary to promote a “sensible sun exposure” to maintain adequate levels of vitamin D without increasing the risk of skin cancer.

Policy Statement—Ultraviolet Radiation: A Hazard to Children and Adolescents (1)

American Academy
of Pediatrics



DEDICATED TO THE HEALTH OF ALL CHILDREN™

- I Pediatri dovrebbero informare sui **rischi** correlati all'esposizione ai raggi UV, scoraggiando l'esposizione solare a scopi estetici e suggerendo adeguati **comportamenti protettivi** (indossare abiti, cappelli, occhiali ed utilizzare filtri solari).

Sarebbe opportuno promuovere le attività al coperto per limitare l'esposizione durante le ore di massimo irraggiamento solare (dalle **10.00** alle **16.00**).

- Quando un bambino o un adolescente si espone al sole dovrebbe utilizzare **filtri solari** con un Sun Protector Factor minimo di 15 (da applicare ogni 2 ore).

(Pediatrics Mar 2011)

Policy Statement—Ultraviolet Radiation: A Hazard to Children and Adolescents (2)

- **I bambini al di sotto dei 6 mesi di vita non dovrebbero essere esposti direttamente alla luce solare. I genitori dovrebbero applicare i filtri solari quando non è possibile evitare l'esposizione solare, solo a livello delle parti esposte.**
- **Si sconsiglia l'esposizione volontaria a fonti artificiali di raggi UV o di incrementare l'esposizione solare con lo scopo di aumentare i livelli circolanti di vitamina D. Uno stato vitaminico D sufficiente dovrebbe essere ottenuto mediante supplementazione esogena di alimenti o farmaci.**

(Pediatrics Mar 2011)



The vitamin D-lemma

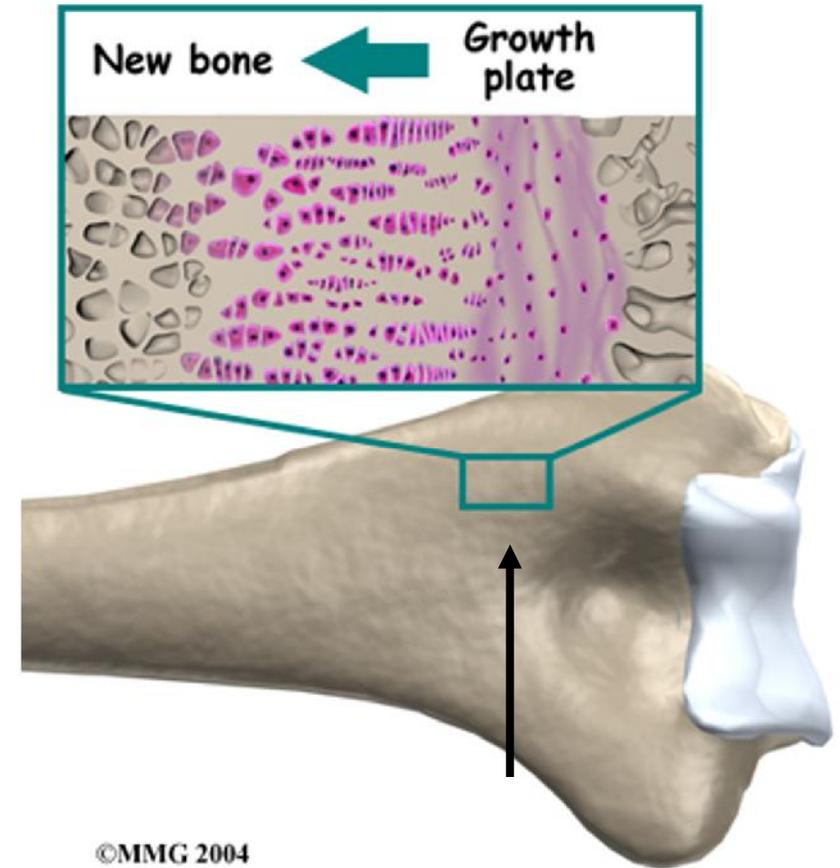
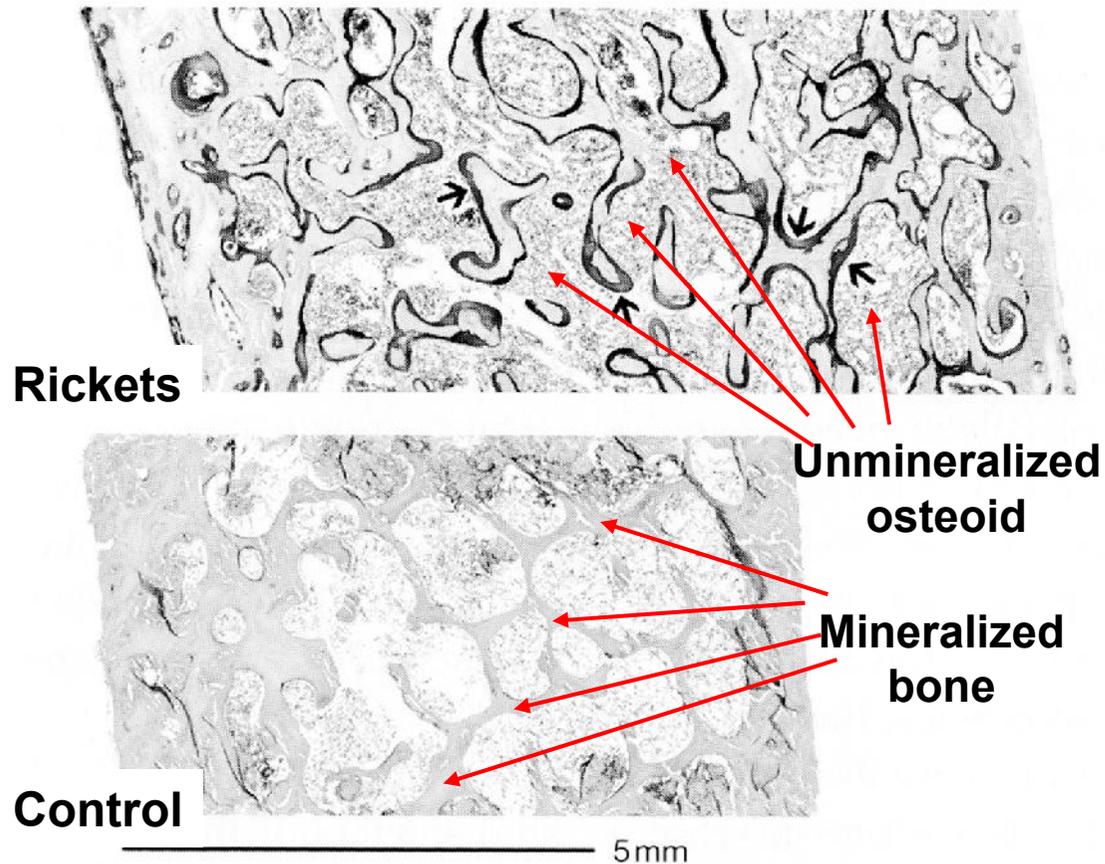
(Maxmen A. Nature 2011)

Azioni scheletriche della vitamina D

Aspetti clinici

(rachitismo, osteopenia/osteoporosi)

HISTOLOGIC ASPECTS OF MINERALIZATION DEFECT CAUSED BY RICKETS



(Rauch F, Endocr Dev, 2003)

... rickets is reappearing

Italy. *“Vitamin D deficiency rickets in five at-risk children”*.
Pediatrics International 2012

USA. *“The utility of alkaline phosphatase measurement as a screening test for rickets in breast-fed infants”*. Clin Pediatr 2010.

USA. *“Hypocalcemic rickets and dilated cardiomyopathy: case reports and review of literature”*. Pediatr Cardiol 2009.

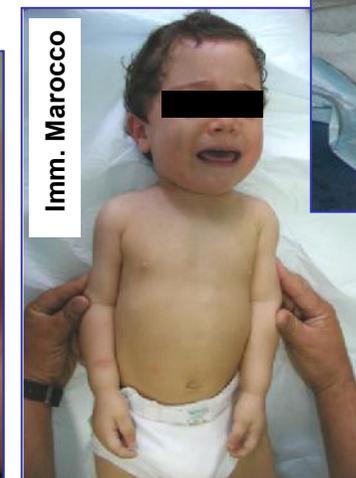
Denmark. *“Incidence and prevalence of nutritional rickets in southern Denmark”*. Eur J Endocrinol,2009 .

Spain. *“Symptomatic hypocalcaemia due to nutritional rickets”*.
An Pediatr (Barc) 2010.

South Africa. *“Maternal vitamin D status: implications for the development of infantile nutritional rickets”*. Endocrinol Metab Clin North Am 2010 .

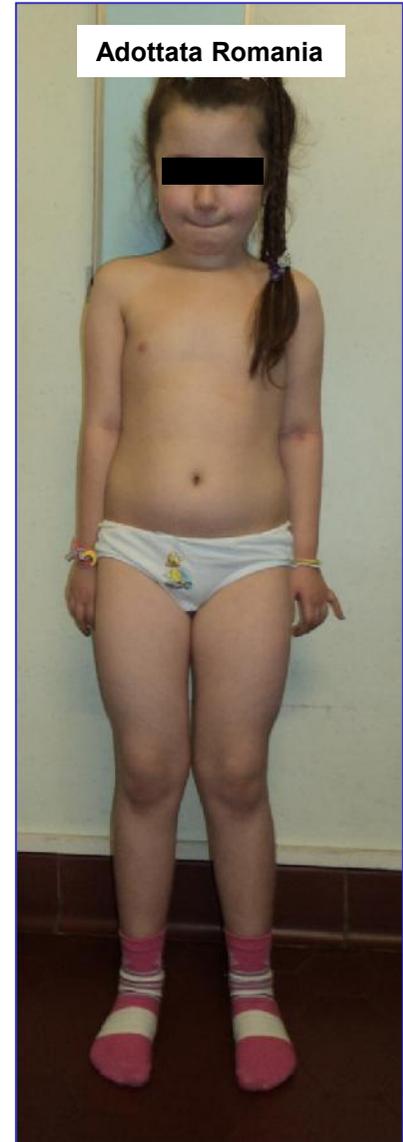
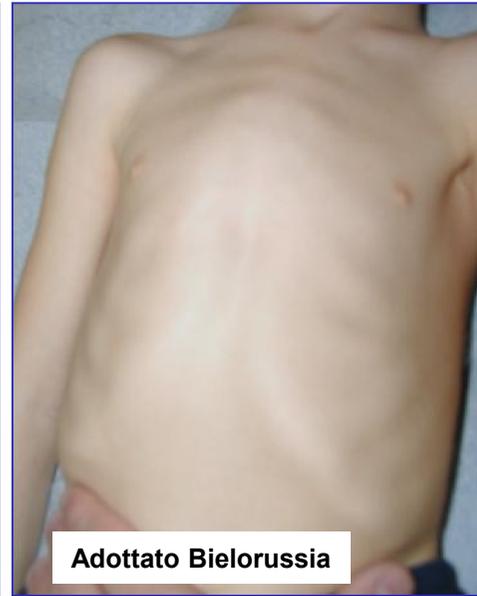
RACHITISMO CARENZIALE IN BAMBINI IMMIGRATI

Clinica Pediatrica, Università di Pisa

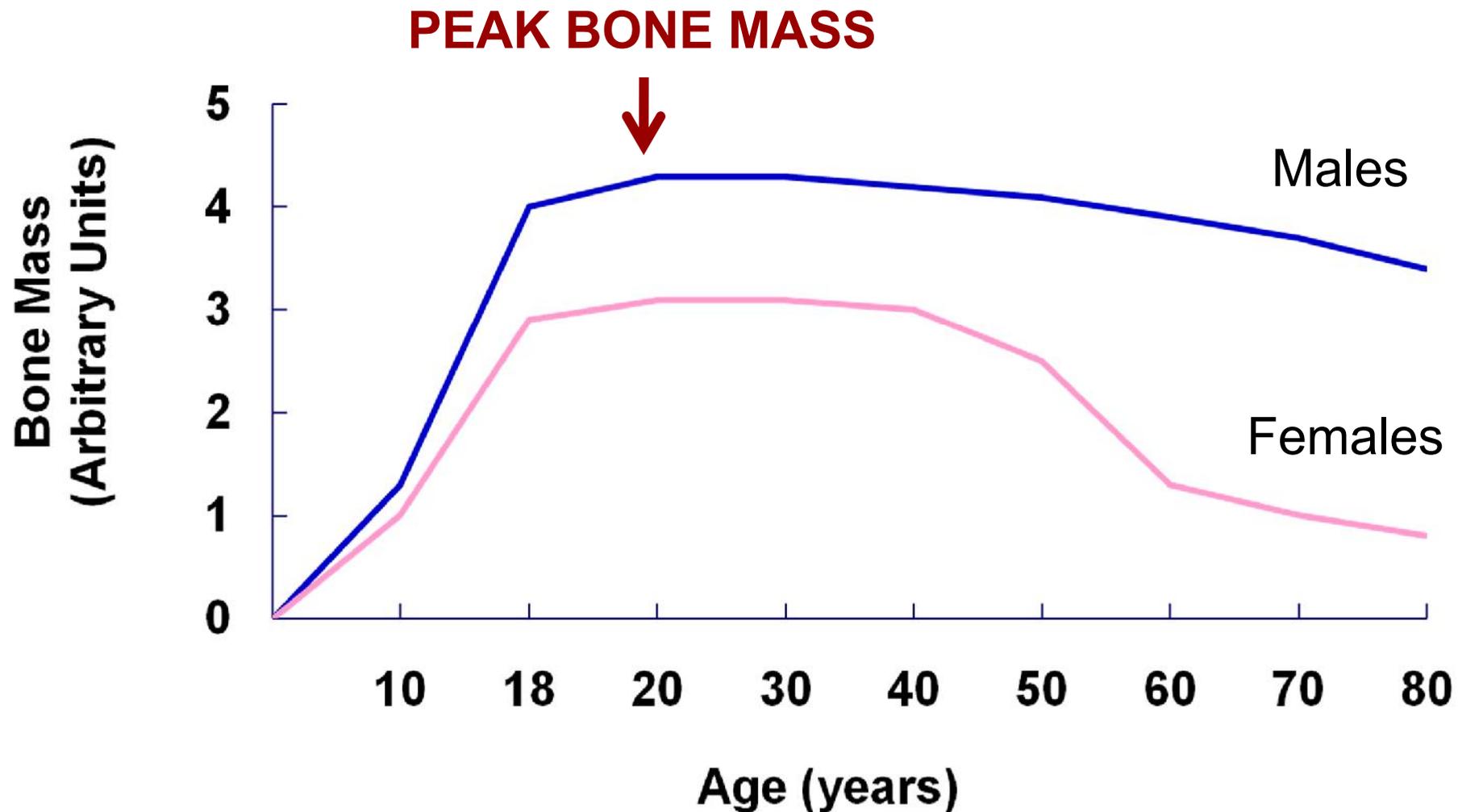


RACHITISMO CARENZIALE IN BAMBINI ADOTTATI

Clinica Pediatrica, Università di Pisa



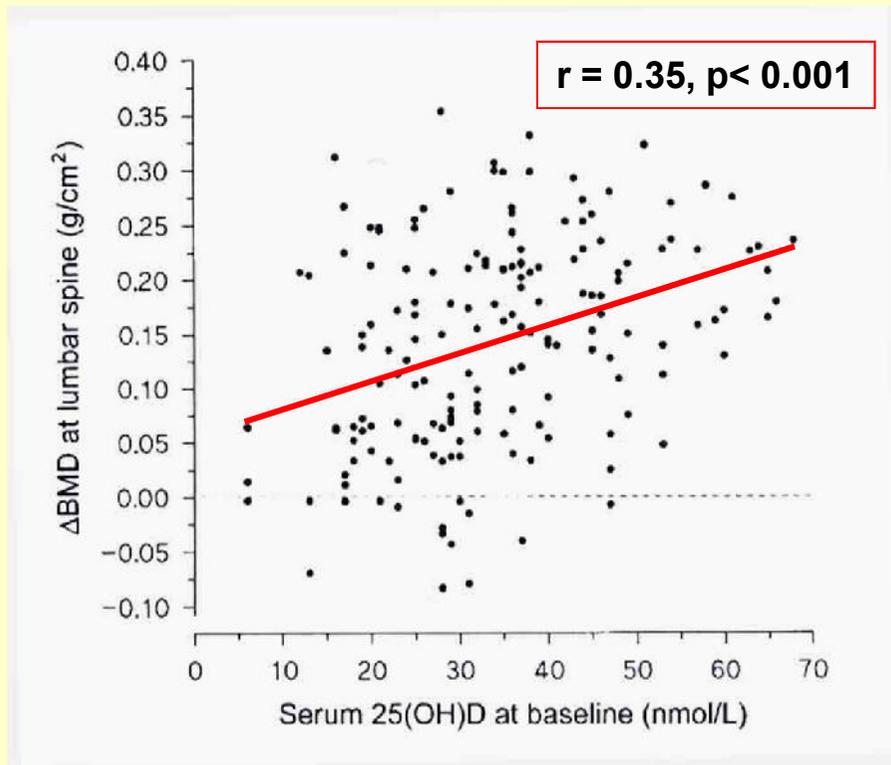
CHANGES IN BONE MASS WITH AGE



(Cooper C. 1990)

VITAMIN D STATUS AS A DETERMINANT OF PEAK BONE MASS

Relationship between Δ change (3-y) of lumbar BMD and serum 25-OH-D levels in peripubertal girls (n = 171, age 9 - 15 y).



Median serum 25-OH-D at baseline: 13.6 ng/ml

(Lehtonen-Veromaa et al. Am J Clin Nutr 2002)

Relationship between peak bone mass and 25-OH-D levels in young Finnish men (n = 220, age 18.3 - 20.6 y)

<i>Skeletal site</i>	<i>p</i>
Lumbar spine BMD	0.04
Femoral neck BMC	0.04
Trochanter BMC	0.01
Total hip BMC	0.03

Median serum 25-OH-D at baseline: 17.6 ng/ml

(Valimaki et al. JCEM 2004)

Vitamin D supplementation for improving BMD in children

- Combining data from **6** randomized controlled **trials** (343 participants receiving placebo and **541** receiving vitamin D), vitamin D supplementation had no statistically significant effects on total body BMC, hip or forearm BMD. There was a trend to a small effect on lumbar spine BMD ($p=0.07$).
- In **low serum vitamin D studies**, significant effects on total body BMC and lumbar spine BMD were approximately equivalent to a 2.6% and 1.7% percentage point greater change from baseline in the supplemented group.

These results do not support vitamin D supplementation to improve BMD in healthy children with normal vitamin D levels, but suggest that supplementation of deficient children may be clinically useful.

Azioni extrascheletriche

**(infezioni, asma, allergia, DMT1,
obesità, DMT2, neoplasie)**

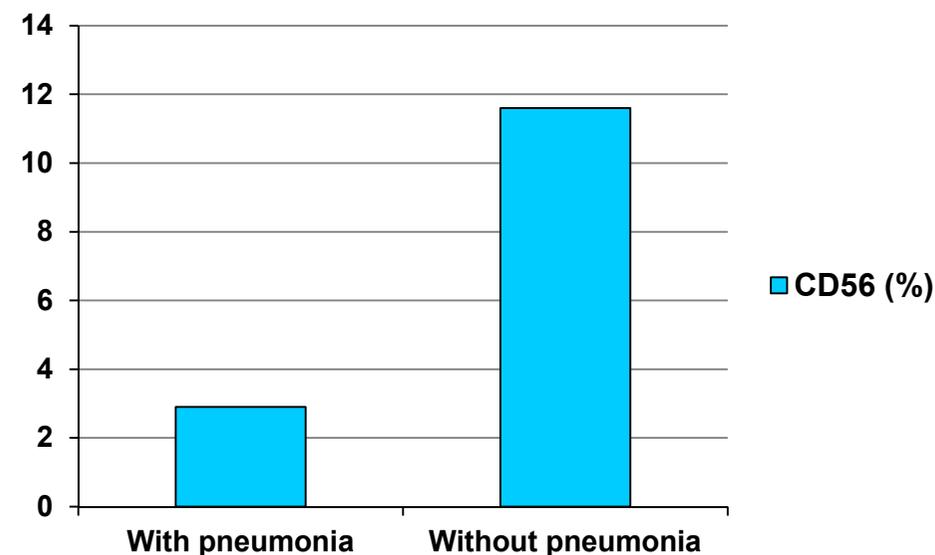
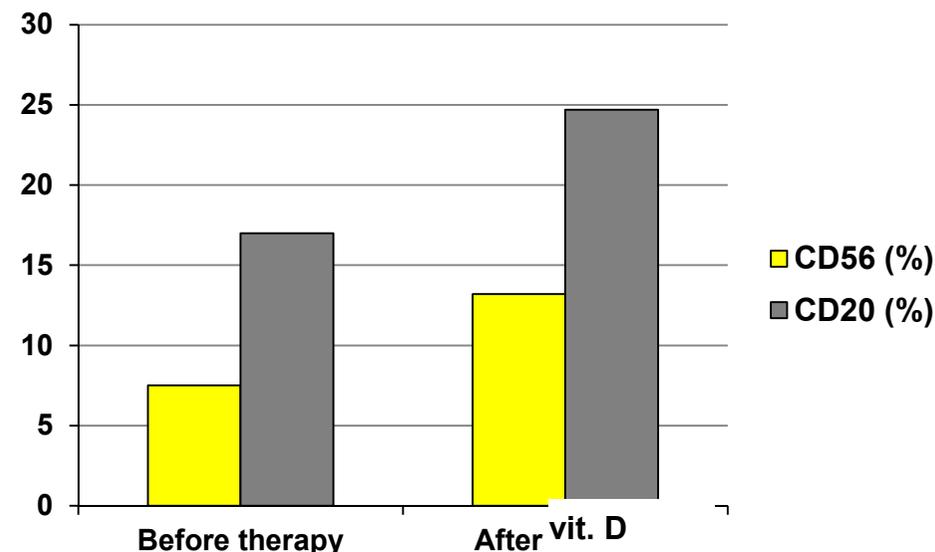
The Effect of 25-OH-D on the Immune System in Children with Rickets (n = 53, 0-4 yr)

Children with rickets: reason of admission

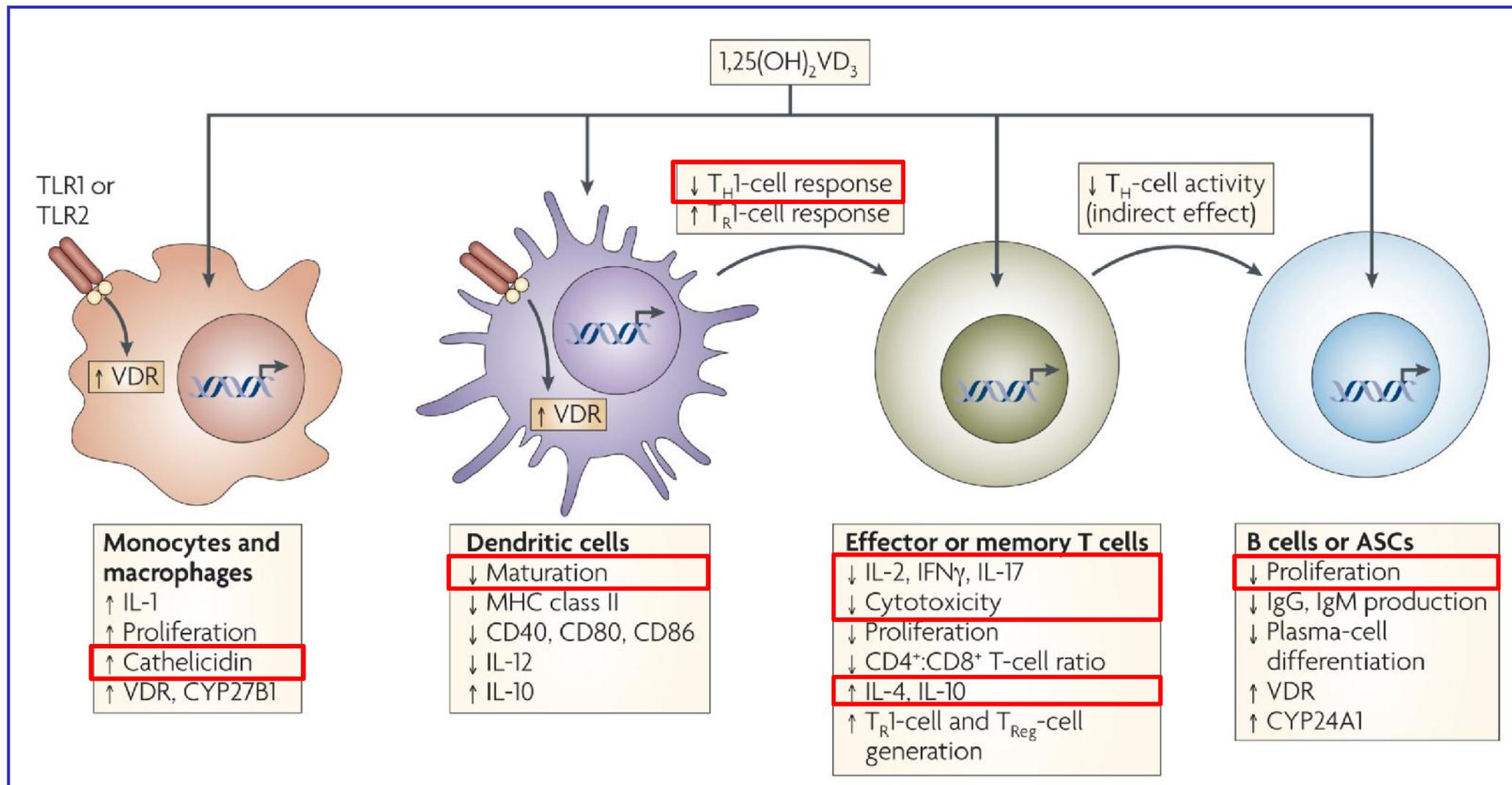
reason of admission	%
Pneumonia	47,1
Acute gastroenteritis	13,2
Upper respiratory tract infections	15,0
Meningitis	3,7
Acute otitis media	1,8
Conjunctivitis	1,8
Urinary tract infections	1,8
No infection	15,0

B (CD 20) and NK (CD 56) cells reduction may contribute to the development of infections in patients with rickets.

(Dogan M et al. 2009)



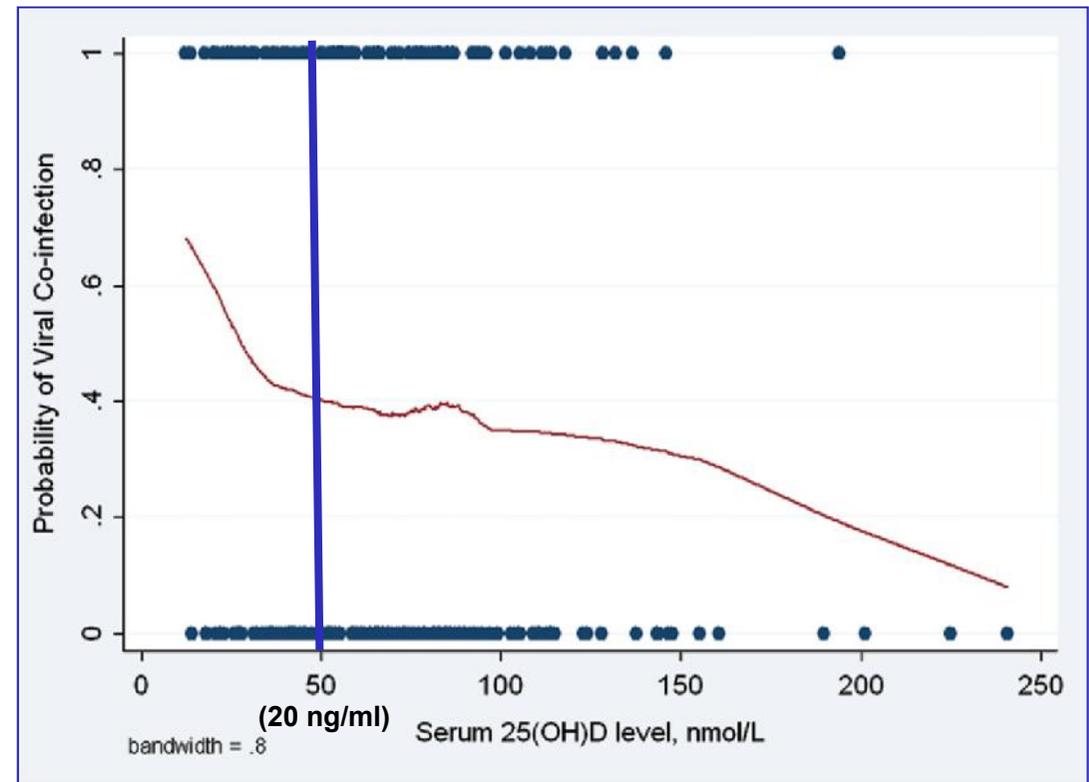
Vitamin D effects on the immune system



(Mora JR et al. Nat Rev Immunol 2008)

Low serum 25-hydroxyvitamin D levels are associated with increased risk of viral co-infections in wheezing children

- N = 284 hospitalized wheezing children (median age 1.6 yr; range 1.0-2.8; 67% M).
- 31% serum 25-OH-D < 20 ng/ml (50 nmol/l)
- 6% serum 25-OH-D < 10 ng/ml (25 nmol/l)

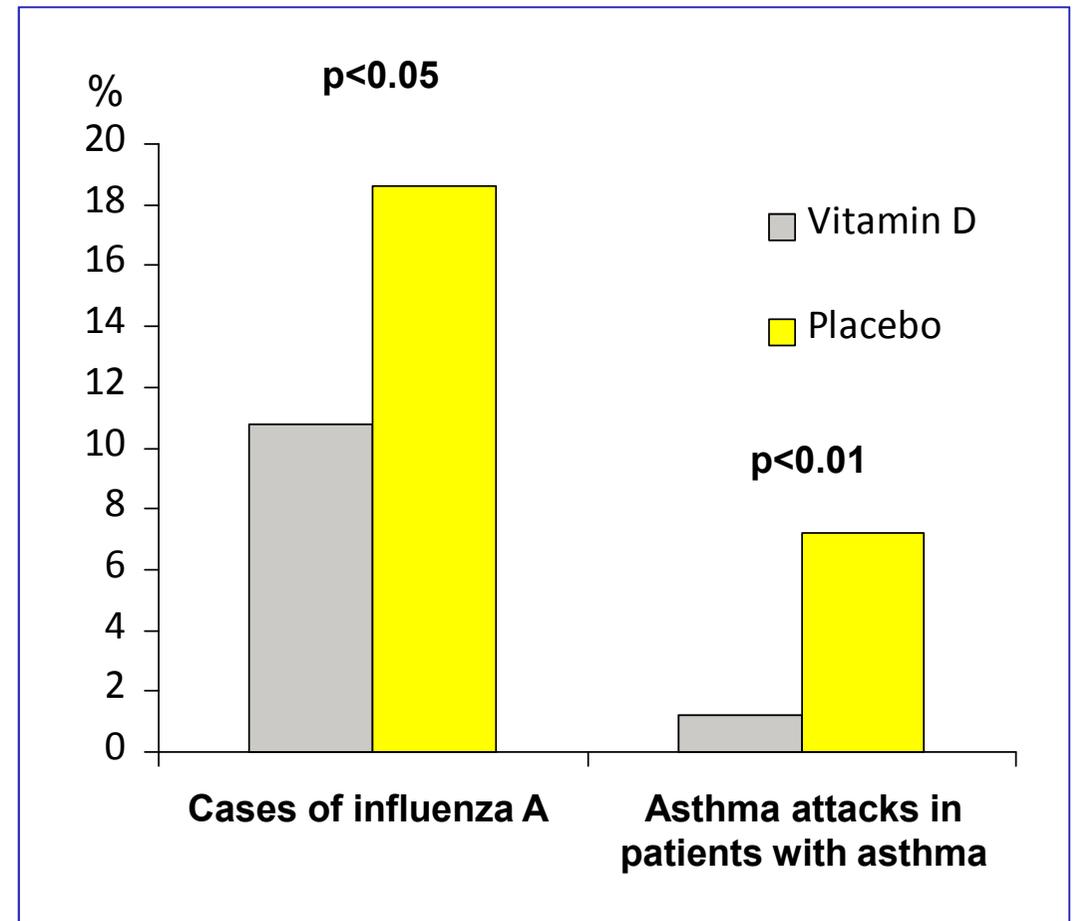


Serum 25-OHD levels were inversely associated with viral co-infections (RSV, rhinovirus and multiple viral causes) supporting a role of vitamin D in antiviral defense and suggesting that it might be particularly important in wheezing children.

(Jartti T et al. J Allergy Clin Immunol 2010)

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

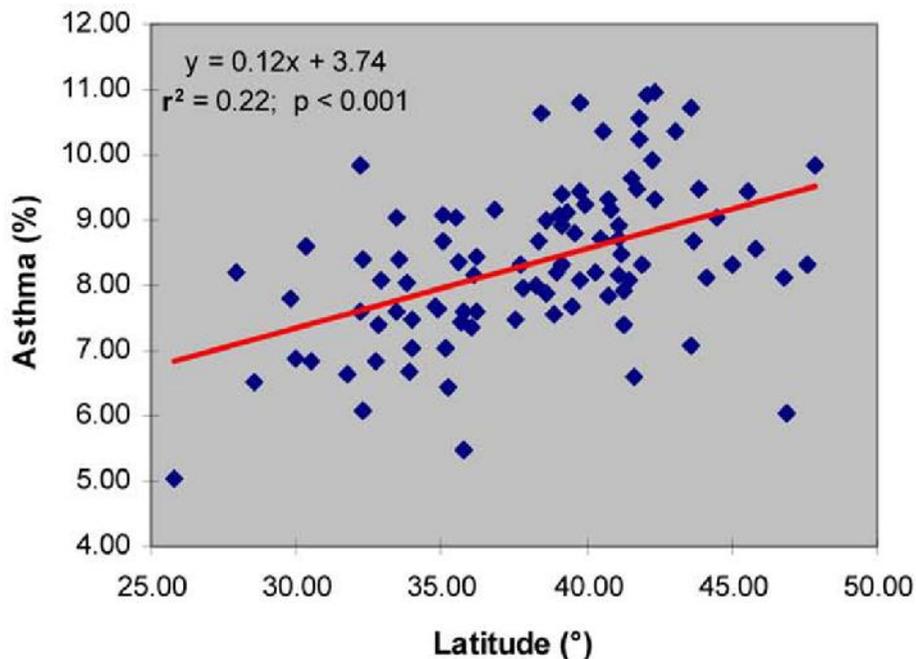
- Randomized, double-blind, placebo-controlled trial conducted from December 2008 through March 2009 comparing vitamin D supplementation (1.200 IU/die) with placebo.
- N = 430 children (10.2 yr; M = 56 %).
- 56% previous diagnosis of asthma



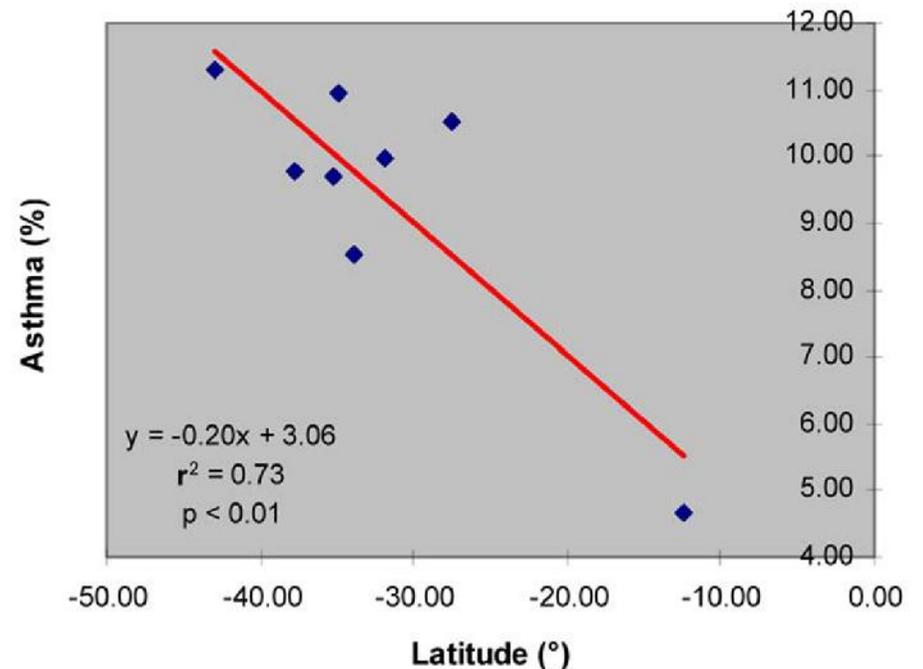
Vitamin D supplementation during the winter season may reduce the incidence of influenza A and prevent asthma attacks in children with asthma.

Asthma prevalence associated with geographical latitude and regional insolation in the United States of America and Australia

Asthma prevalence vs. latitude, in adult population of 97 major metropolitan-micropolitan areas of **continental U.S.**

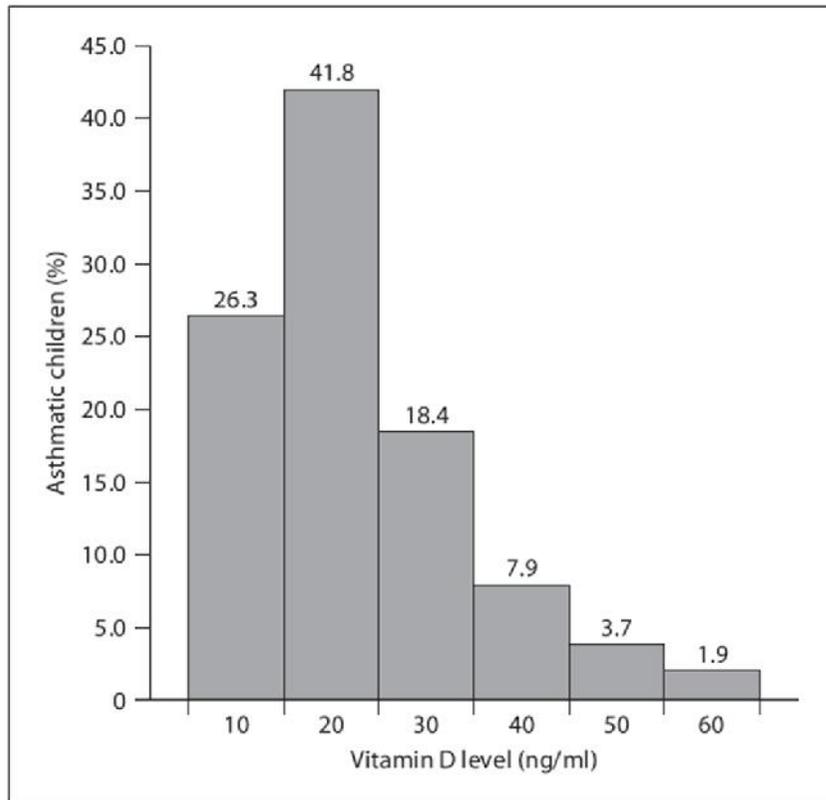


Asthma prevalence vs. latitude in the population of 8 major metropolitan areas of **Australia.**



As a known modulator of the immune response closely linked with the geographical latitude, vitamin D may play an important role in the prevalence of asthma.

Vitamin D Deficiency as a Strong Predictor of Asthma in Children (Qatari, n = 483, < 16 yrs)



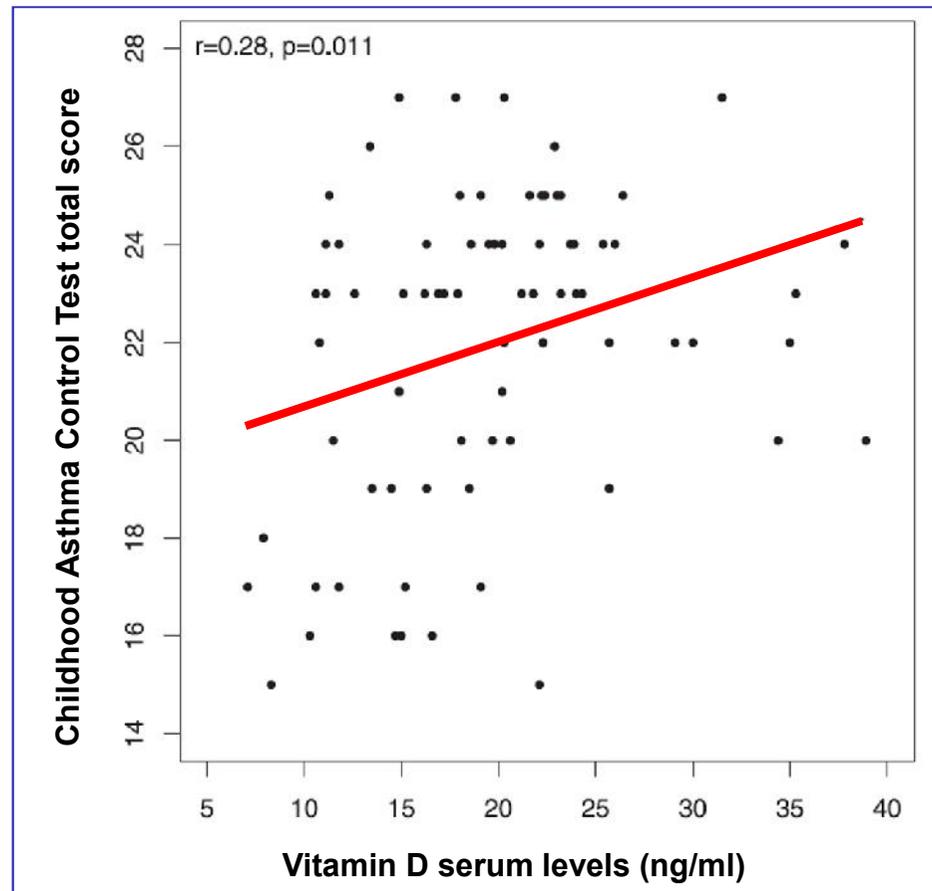
Independent variables	OR	95% CI	p
Vitamin D deficiency	4.82	2.41–8.63	<0.001
Low duration of outdoor time	3.13	1.50–5.75	<0.001
Familial history of asthma	2.45	1.30–4.19	<0.001
Less physical activity	2.37	1.77–3.18	<0.001
Breastfeeding >6 months	2.26	1.47–4.12	0.001
Serum IgE level	1.89	1.24–2.84	0.003
Parental consanguinity	1.78	1.15–2.62	0.005
Familial history of vitamin D deficiency	1.66	1.15–2.45	0.011
Child BMI	1.54	1.09–2.13	0.004

***The majority of asthmatic children had vitamin D deficiency.
Vitamin D deficiency was the major predictor of asthma in Qatari.***

(Bener A et al. Int Arch Allergy Immunol 2012)

Vitamin D Serum Levels and Markers of Asthma Control in Italian Children

75 children with asthma (5-11 yr; 43 M) Patient characteristics	Vitamin D levels		
	Deficient (< 20 ng/mL)	Insufficient (20-30 ng/mL)	Sufficient (≥ 30 ng/mL)
Absolute and relative (%) frequency distribution of patients	40 (53.3%)	28 (37.3%)	7 (9.4%)

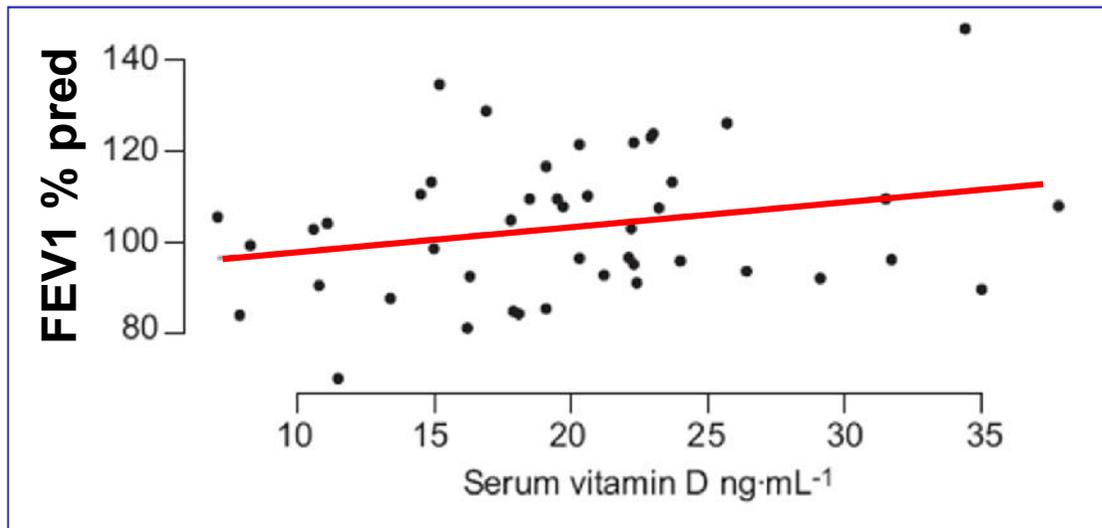


*(Chinellato I et al.
J Pediatr 2010)*

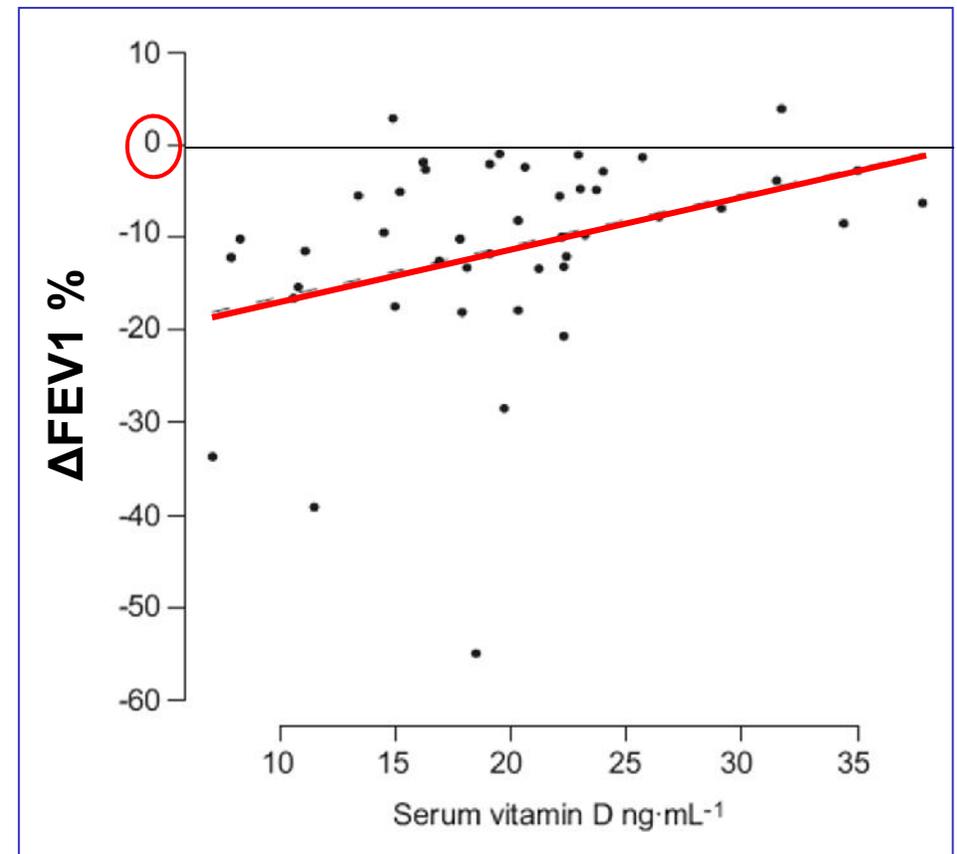
Serum vitamin D levels and exercise-induced bronchoconstriction in children with asthma (n = 45, 9-11 yr; Verona 45°27' N)

- Deficient (25-OH-D < 20 ng/ml): 51.1%
- Insufficient (25-OH-D: 20-30 ng/ml): 37.8%
- Sufficient (25-OH-D ≥ 30 ng/ml): 11.1%

Relationship between 25-OH-D and forced expiratory volume in 1 s (FEV1)



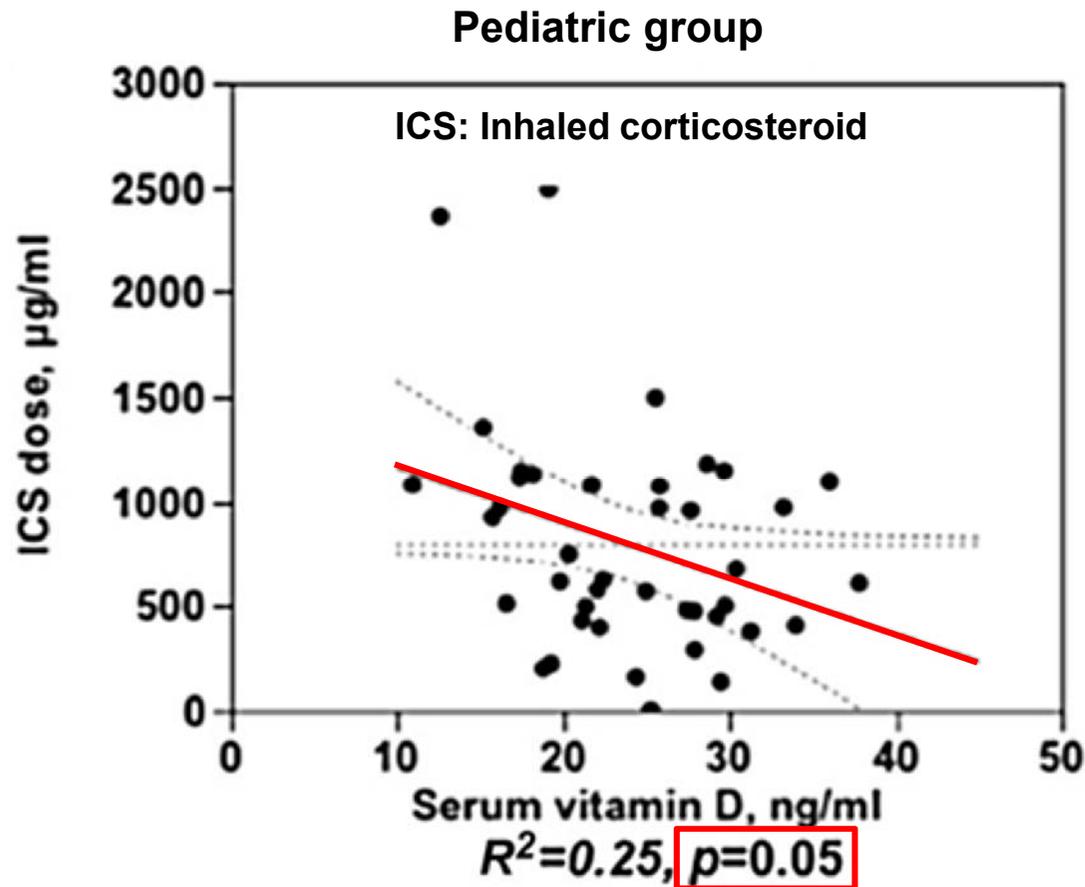
Relationship between 25-OH-D and change in forced expiratory volume in 1 s (Δ FEV1) after exercise challenge



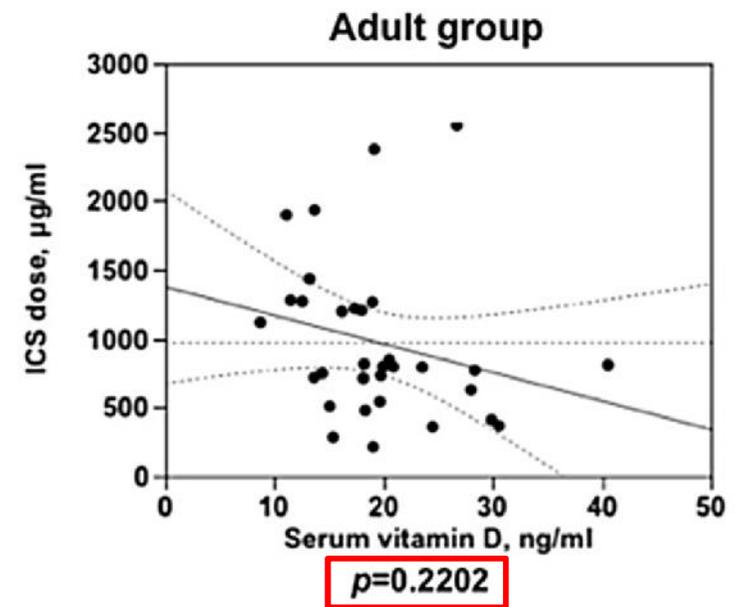
Hypovitaminosis D is frequent in asthmatic children. Lower levels of vitamin D are associated with reduced respiratory function and increased reactivity to exercise.

(Chinellato I et al. Eur Respir J 2011)

Steroid requirements and associations with vitamin D are stronger in children (n=53, 8.5-13 yr) than adults with asthma



- Deficient (25-OH-D < 20 ng/ml): 40%
- Insufficient (25-OH-D: 20-30 ng/ml): 38%
- Sufficient (25-OH-D ≥ 30 ng/ml): 22%



Serum vitamin D status was inversely related to steroid requirement in the pediatric asthma group but not in the adult group.

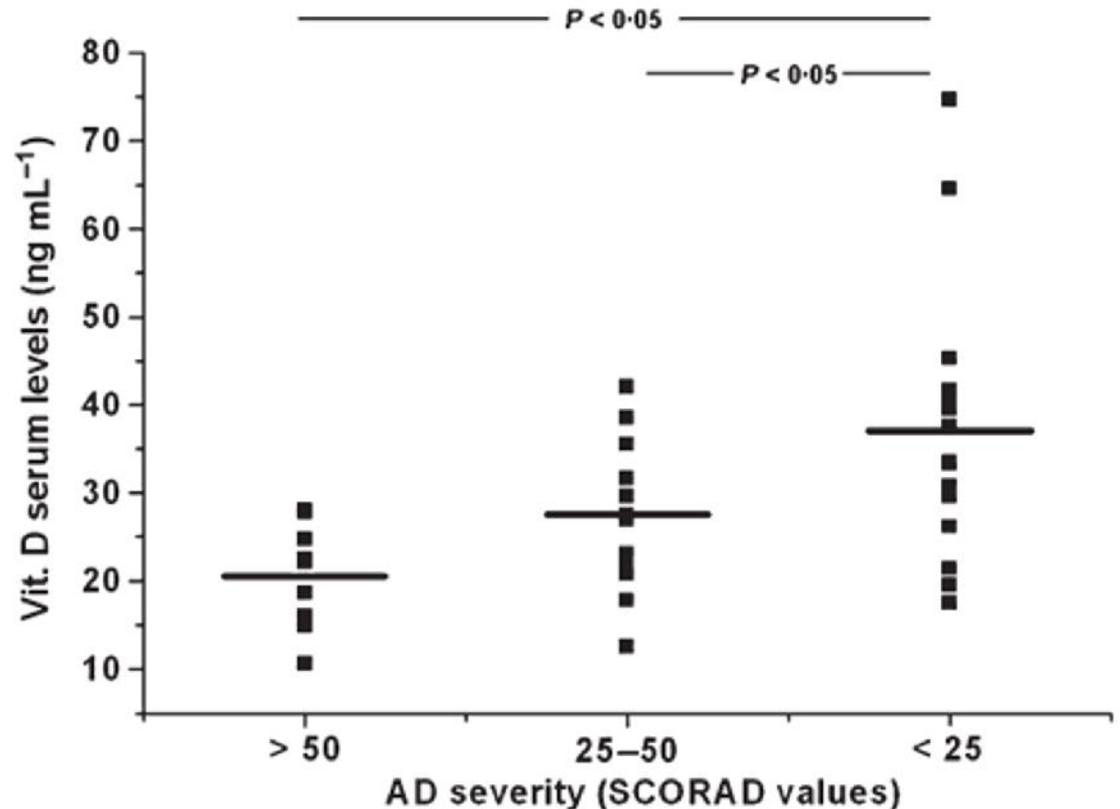
Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children

N = 37 (age 8 months – 12 years)

- Deficient (25-OH-D < 20 ng/ml): 21%
- Insufficient (25-OH-D: 20-30 ng/ml): 40%
- Sufficient (25-OH-D \geq 30 ng/ml): 37%

AD SCORAD index

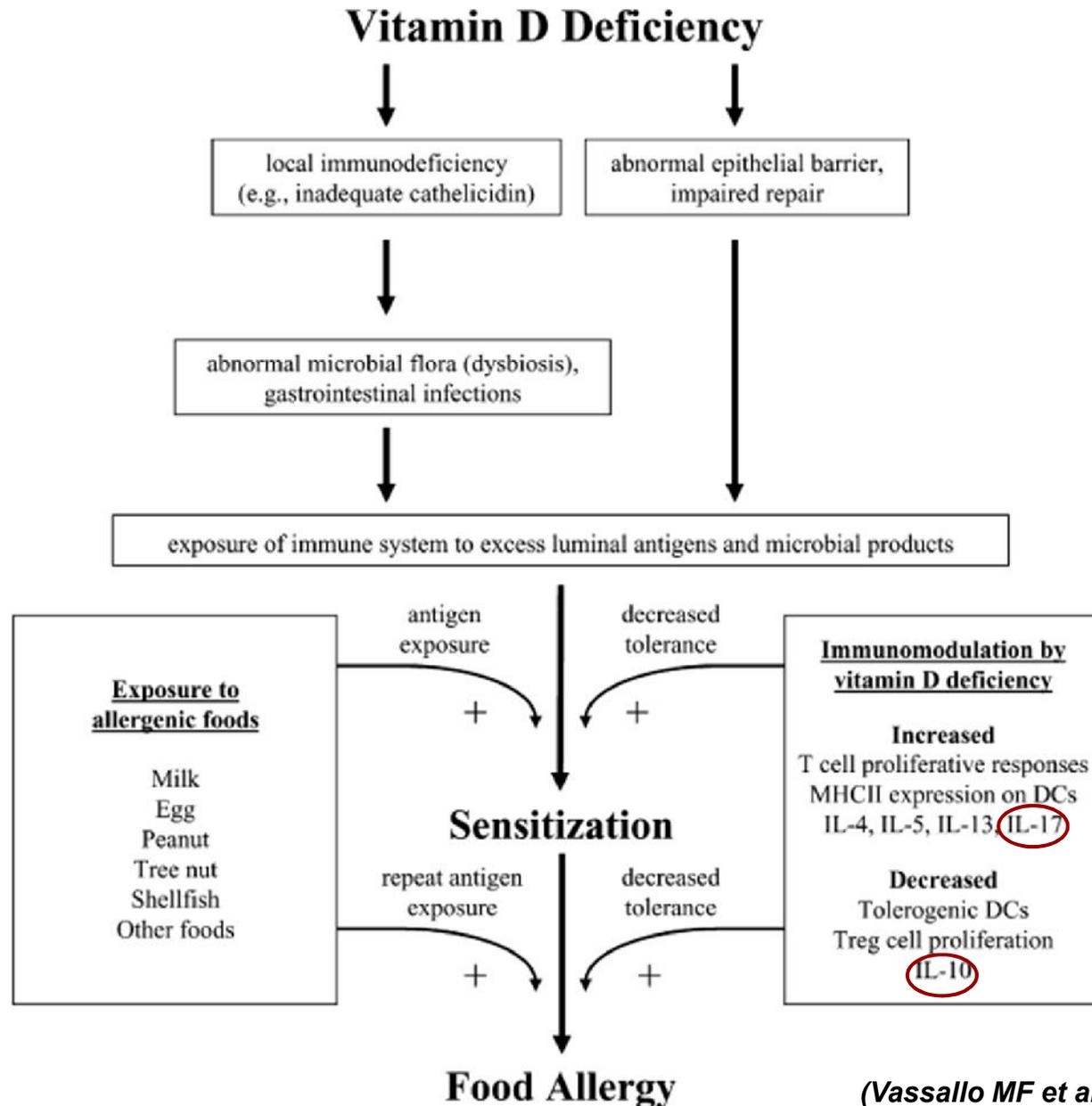
- mild (< 25),
- moderate (25–50)
- severe (> 50)



- *The severity of atopic dermatitis seems to be related to vitamin D status.*
- *More studies evaluating the use of vitamin D as a potential treatment in patients with this disease are needed.*

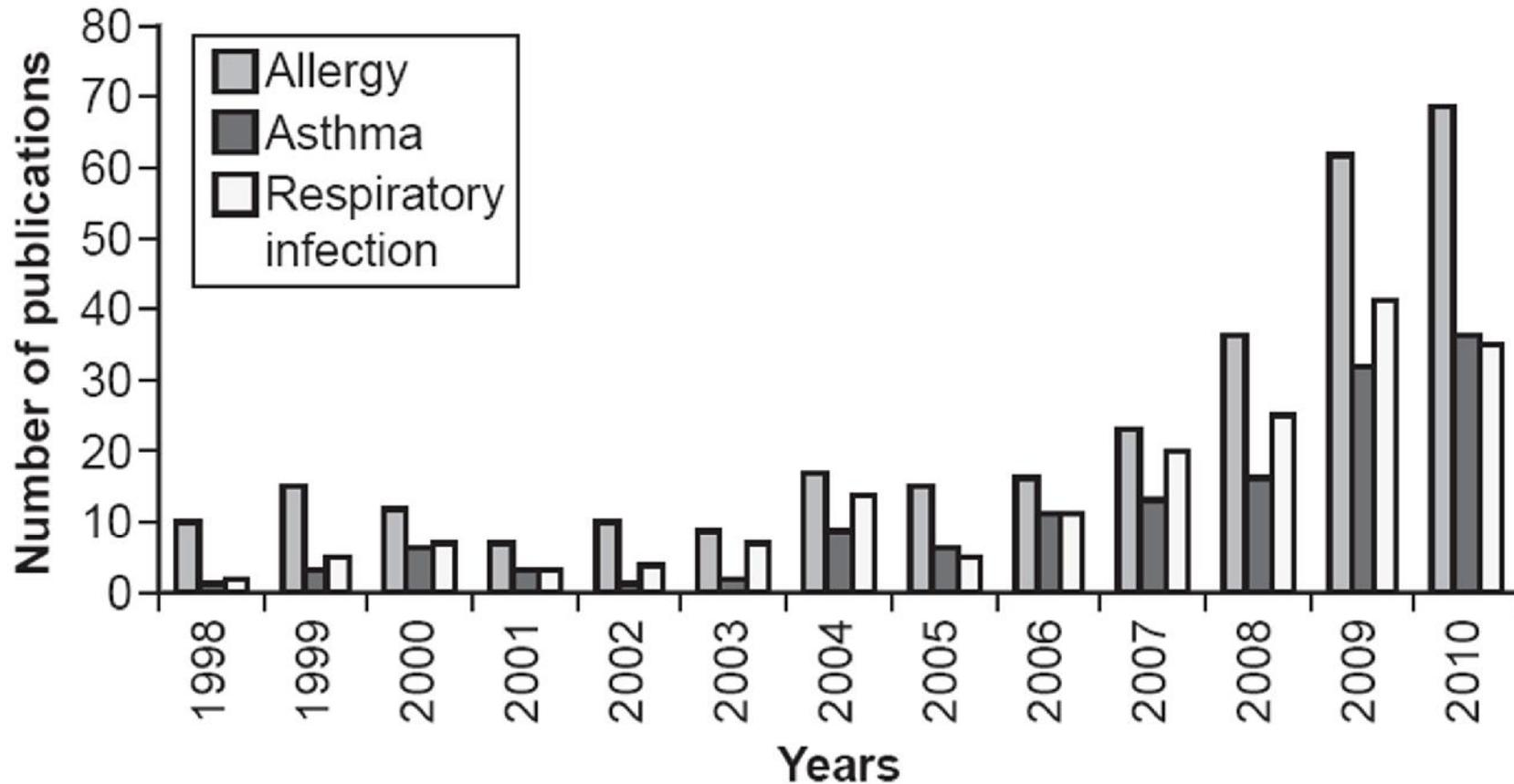
(Peroni DG et al. Ped Dermatology 2011)

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



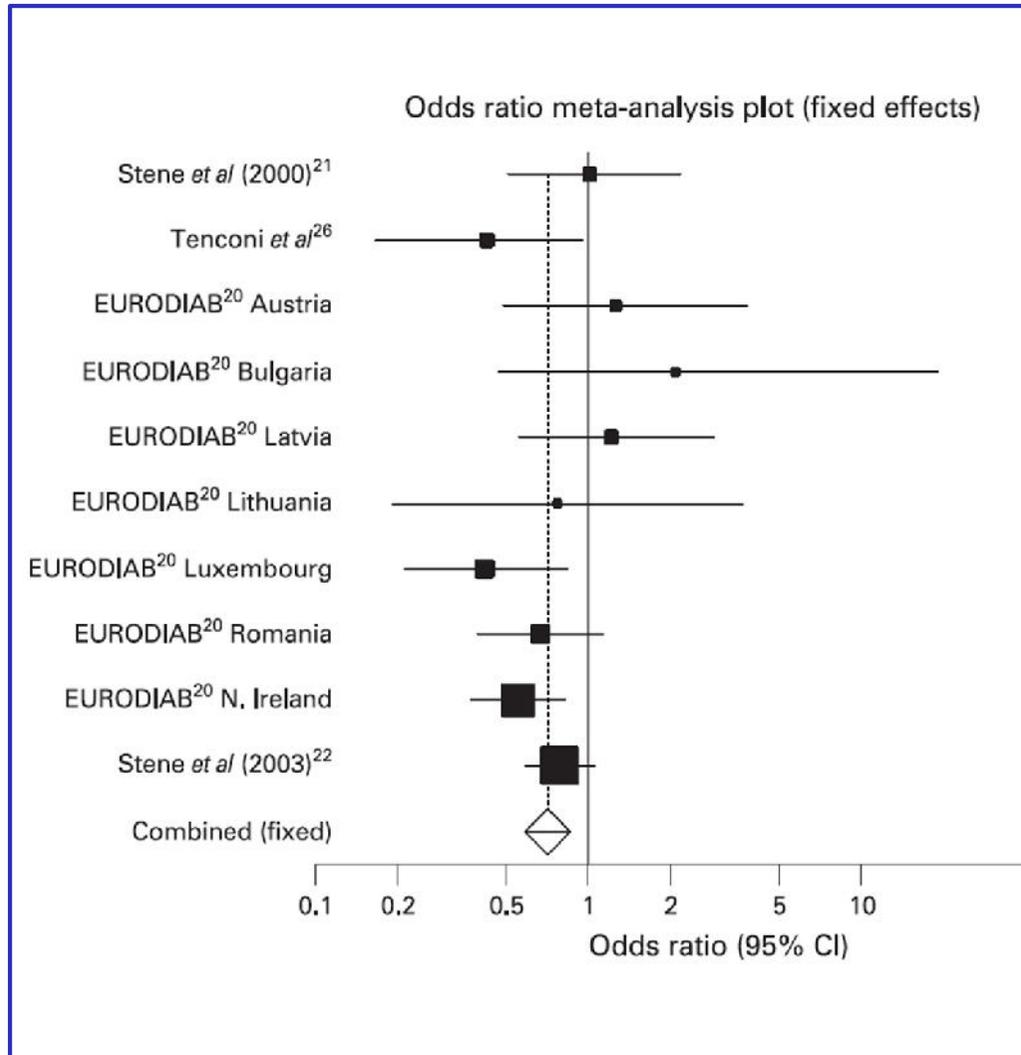
(Vassallo MF et al. J Allergy Clin Immunol 2010)

Publications on vitamin D and allergy, asthma and respiratory infections over the past 14 years (until 2010)



(Bozzetto S et al. Allergy 2011)

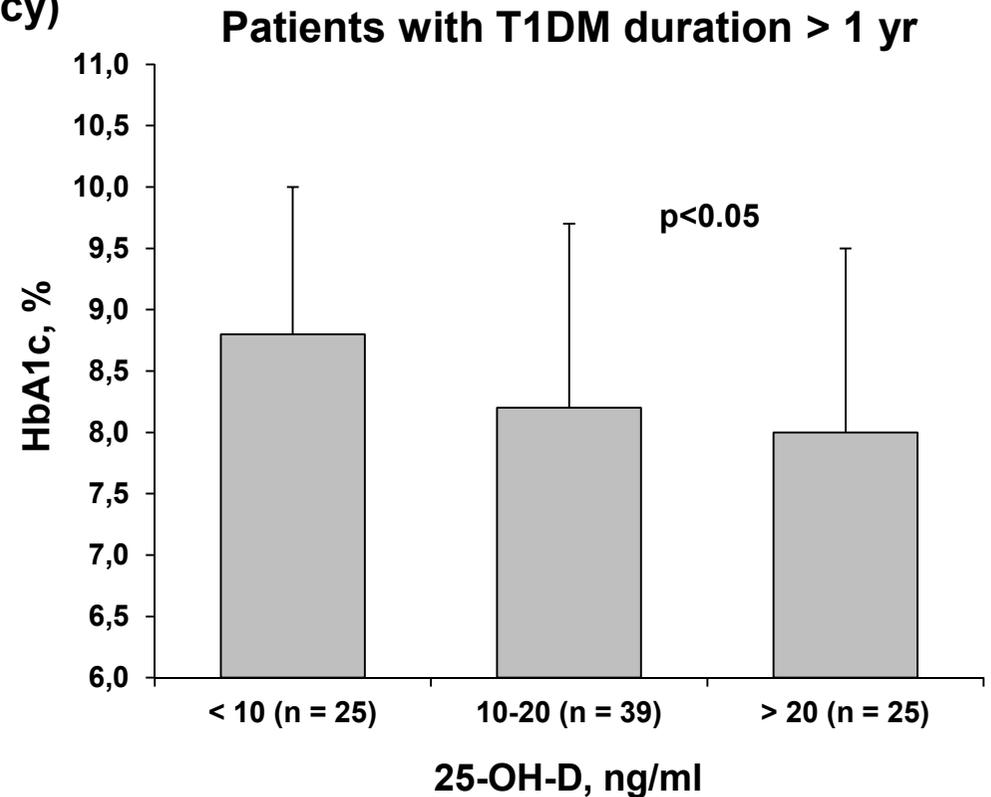
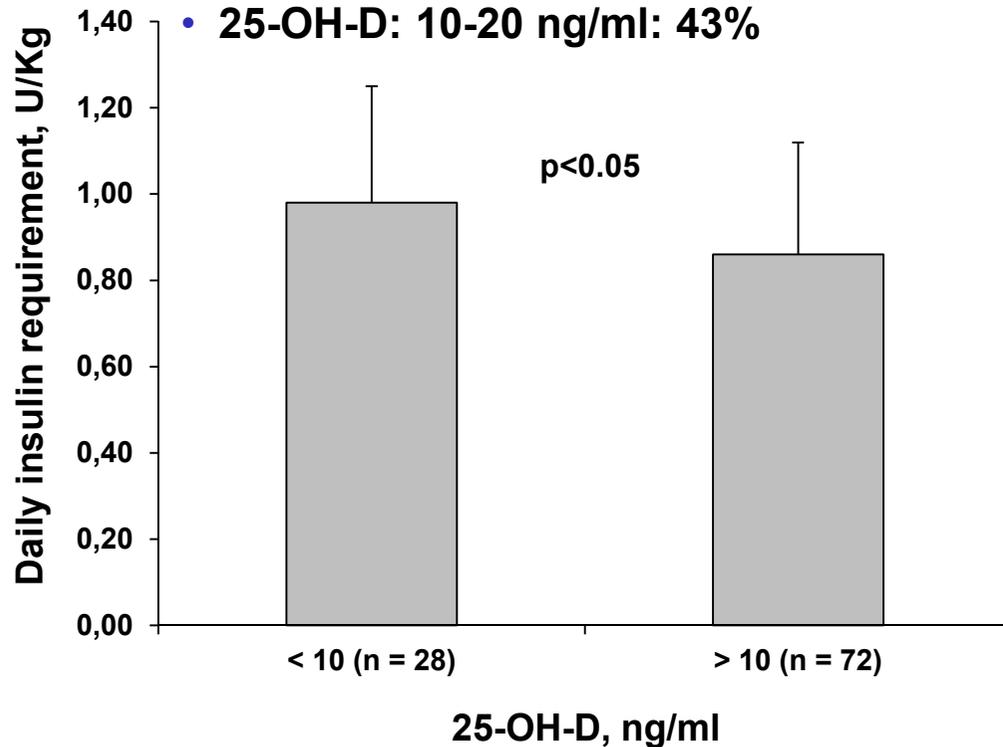
Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis



- Five observational studies (four case-control and one cohort studies). Cases 1.429; controls 5.026.
- Vitamin D supplementation in early childhood may offer protection (risk reduction 29%) against the development of type 1 diabetes.
- There was also some evidence of a dose-response effect, with those using higher amounts of vitamin D (2.000 IU/day) being at lower risk of developing type 1 diabetes.

Vitamin D status and insulin requirements in children and adolescent with type 1 diabetes (n = 100, 4.7-19.9 yr)

- 25-OH-D < 10 ng/ml): 28% (severe deficiency)
- 25-OH-D: 10-20 ng/ml: 43%



- *T1DM children with severe vitamin D deficiency have a higher insulin requirement and a worse control of disease.*
- *It is important to check vitamin D status in children with T1DM and to start treatment if it is deficient.*

(Tunc O et al. J Pediatr Endocr Met 2011)

Vitamin D Deficiency in Obese Children and Its Relationship to Glucose Homeostasis (Texas, USA)

- **N = 411 obese pz (6-16 yrs)**
- 25-OH-D < 20 ng/ml: **50%**
- 25-OH-D: 20-30 ng/ml: 42%
- 25-OH-D ≥ 30 ng/ml: 8%

- **N = 87 non-overweight controls (6-16 yrs)**
- 25-OH-D < 20 ng/ml: **22%**
- 25-OH-D: 20-30 ng/ml: 48%
- 25-OH-D ≥ 30 ng/ml: 32%

Relationship between **serum 25-OH-D** and markers of glucose homeostasis and blood pressure in obese

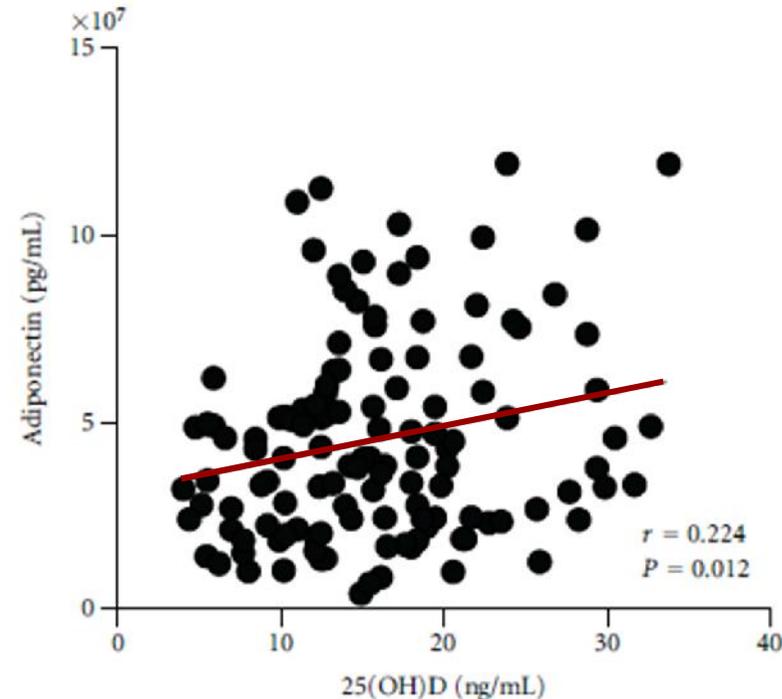
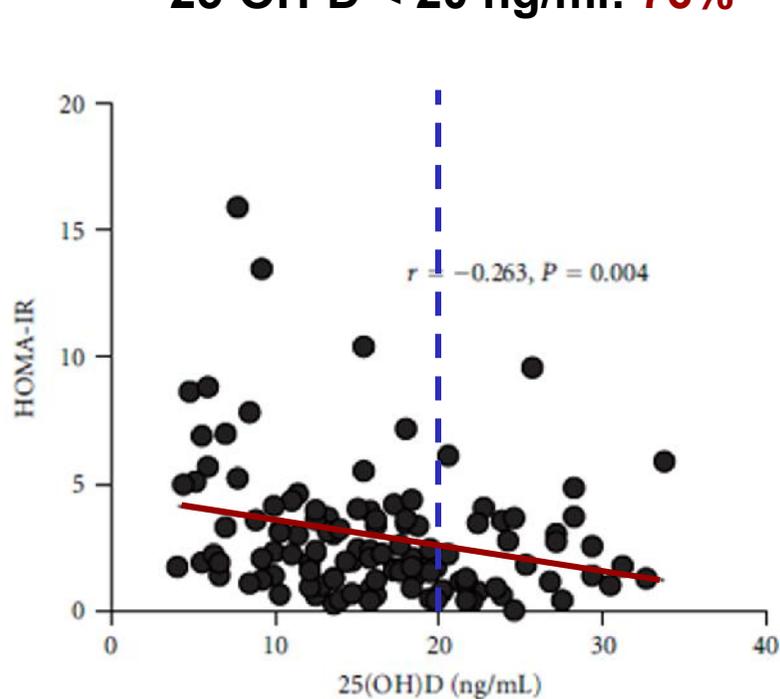
Variable	n	R	P
HOMA-IR	327	-0.19	0.001
2-h Glucose	298	-0.12	0.04
HgbA1c	384	-0.07	0.18
SBP	406	-0.07	0.14
DBP	406	-0.01	0.86

Adjusted for age and BMI Z score

- ***Vitamin D deficiency is common in obese children.***
- ***Lower 25-OH-D levels are associated with risk factors for type 2 diabetes in obese children.***

Vitamin D Deficiency in Obese Children and Its Relationship to Insulin Resistance and Adiponectin (Bonn, Germany)

- N = 125 obese (6-16 yrs)
- 25-OH-D < 20 ng/ml: **76%**



- *Prevalence of hypovitaminosis D is high among obese children living in Germany.*
- *Low serum concentrations of 25(OH)D are associated with impaired insulin sensitivity and low adiponectin serum levels.*

(Roth CI et al. J of Obesity 2011)

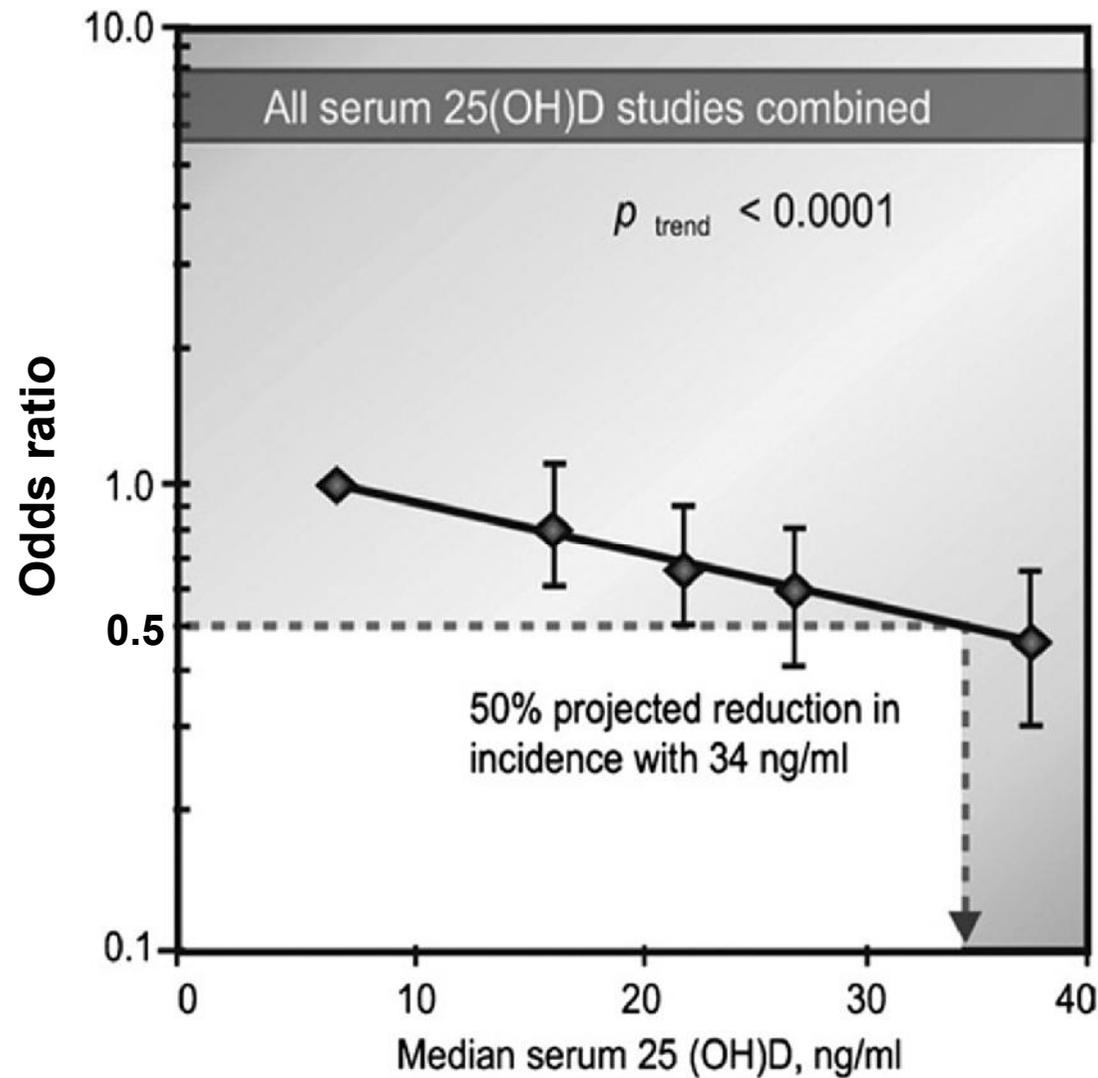
Vitamin D Status and Cardiometabolic Risk Factors in the United States Adolescent Population

- N = 3.577 (12-19 yr).
- Mean 25-OH-D: 24.8 ng/mL.
- Low 25-OH-D levels were strongly associated with **overweight** and **obesity**.

ODDS RATIO (After adjustment for BMI)	25-OH-D < 15 vs > 26 ng/ml
Hypertension	2.36
Fasting hyperglycemia	2.54
Low HDL cholesterol	1.54
Hypertriglyceridemia	1.00
Metabolic syndrome	3.88

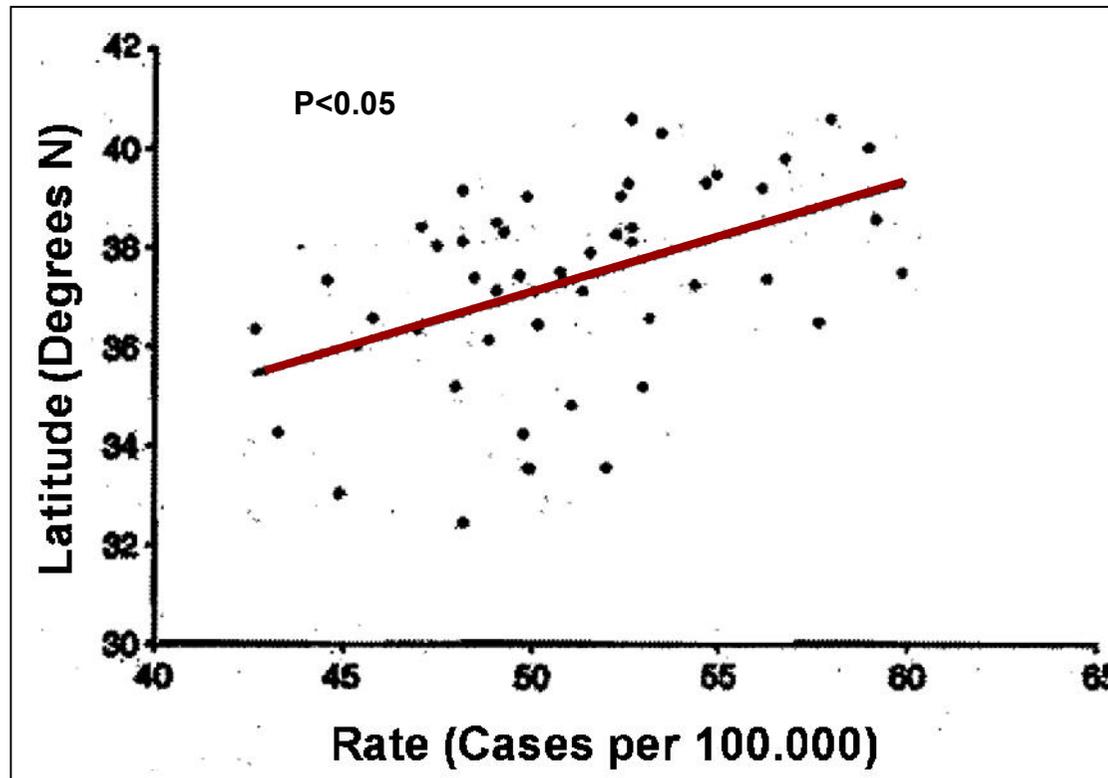
Low serum vitamin D in adolescents is strongly associated with an increased risk of hypertension, hyperglycemia, and metabolic syndrome, independently of adiposity.

Optimal Vitamin D Status for Colorectal Cancer Prevention: A Quantitative Meta Analysis



(Gorham ED et al. Am J Prev Med 2007)

Latitude and number of adults diagnosed with colon cancer in California



An overall increase in occurrence of colon cancer, was observed by 7.5% to 10.5% per degree latitude independently of race.

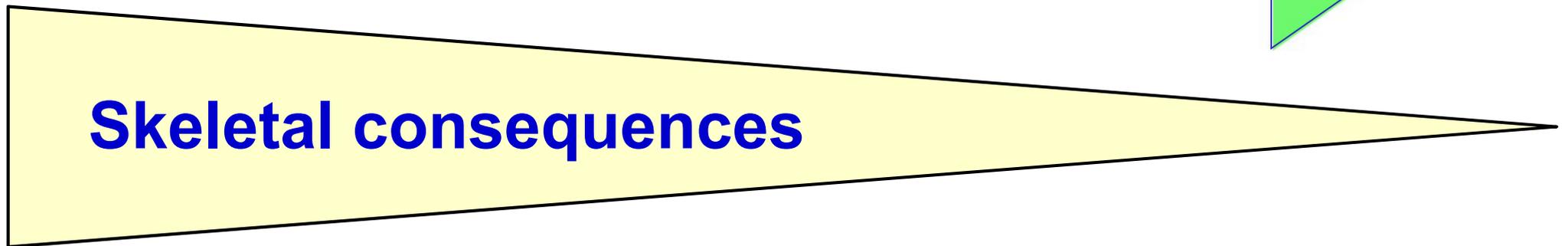
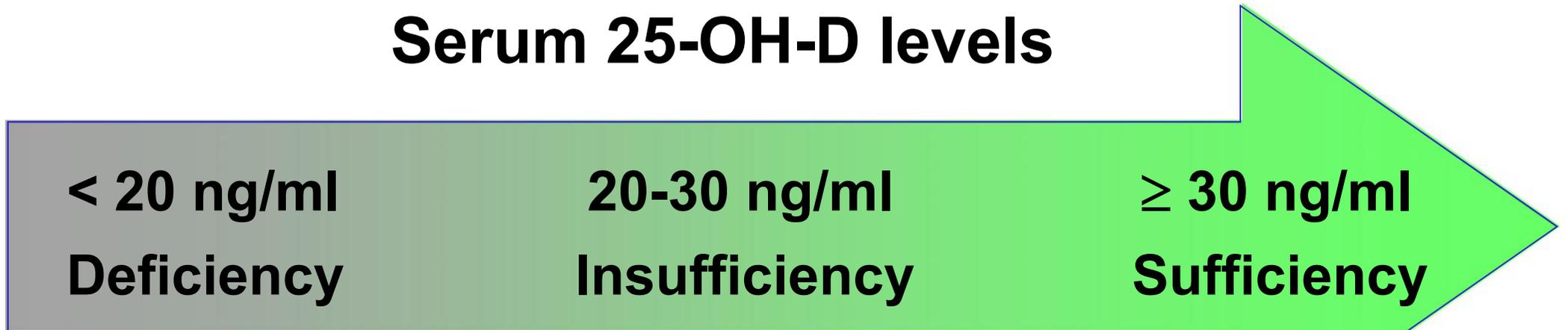
Health Benefits and Disease Incidence Prevention Related to Serum 25-OH-D Level

Serum 25(OH)D ng/ml	0	10	20	30	40	50	60	70
Rickets			100%					
Osteomalacia			90%	100%				
Cancers, all combined						75%		
Breast cancer				30%		50%		67%
Ovarian cancer					20%	25%		
Colon cancer				50%		67%		
Non-Hodgkins lymphoma				25%	30%			
Kidney cancer				50%		67%		
Endometrial cancer						35%		
Type I diabetes				50%		80%		
Type 2 diabetes				50%				
Fractures, all combined				50%				
Falls, women				72%				
Multiple sclerosis					50%		66%	
Heart attack (men)				50%				
Peripheral vascular disease				80%				
Preeclampsia				50%				
Cesarean section				75%				

(Holick MF. Vitamin D: Physiology, Molecular Biology, and Clinical Applications. 2nd edition, 2010)

Hypovitaminosis D and clinical consequences

Serum 25-OH-D levels



Dietary Reference Intakes for Vitamin D

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

REPORT BRIEF  NOVEMBER 2010

- IOM committee found that **25-OH-D > 20 ng/ml** is the level that is needed for good bone health for practically all individuals.
- Sun exposure currently contributes meaningful amounts of vitamin D to North Americans and indicates that a **majority of the population is meeting its needs for vitamin D**. However, some subgroups may be at increased risk for getting too little vit D.
- Calcium and vitamin D play key roles in **bone health**. The current evidence, however, does **not** support **other benefits for vitamin D** or calcium intake.

Vitamin D Supplementation: Potential Indications, Dosages, and Level of Evidence

Indication	Recommended Dosage (Duration)	Level of Evidence
General health		
Age 18–65 yrs, no chronic illnesses	Sensible sun exposure (indefinitely)	D
Age ≥ 65 yrs, for bone health	800–2000 IU/day (indefinitely)	A
Age ≥ 65 yrs, for fall prevention	800–5000 IU/day (indefinitely)	A
Age < 18 yrs, no chronic illnesses	400 IU/day (until age 18)	B
Vitamin D deficiency (< 20 ng/ml)	50,000 IU/wk (12 wks) or 50,000 IU 3 times/wk (6 wks)	B
Cardiovascular disease		
Hypertension	800–2000 IU/day (indefinitely)	C
Heart failure	800–2000 IU/day (indefinitely)	D
Atherosclerotic vascular disease	800–2000 IU/day (indefinitely)	D
Statin-induced myopathy	5000 IU/day (12 wks) or 50,000 IU/wk (12 wks)	C
Endocrine disorders		
Diabetes mellitus	800–2000 IU/day (indefinitely)	C
Neurologic disease		
Multiple sclerosis	10,000 IU/day (1 yr)	B
Depression	5000 IU/day (indefinitely)	C
Dementia	800–2000 IU/day (indefinitely)	D
Migraine headache	1200–2000 IU/day (indefinitely)	D
Respiratory disease		
Asthma	800–2000 IU/day (indefinitely)	C
COPD	800–2000 IU/day (indefinitely)	C
Infectious diseases		
Tuberculosis	10,000 IU/day (6 wks) or 100,000 IU every 2 wks (42 days)	B
Upper respiratory tract infections	800–2000 IU/day (indefinitely)	B
Cancer		
Cancer prevention	800–2000 IU/day (indefinitely)	B
Colorectal cancer	800–2000 IU/day (indefinitely)	D
Breast cancer	800–2000 IU/day (indefinitely)	D

Levels of evidence are as follows: A = supported by multiple randomized controlled trials; B = supported by a single randomized controlled trial, multiple uncontrolled studies, or multiple cohort studies; C = supported by a single cohort study or uncontrolled trial; D = epidemiologic association but no data to support supplementation.

(Haines ST et al. *Pharmacotherapy* 2012)

Profilassi con vitamina D

APPORTI RACCOMANDATI DI VITAMINA D DURANTE L'ETÀ EVOLUTIVA

Età	LARN-'96 UI/die	AAP-'03 UI/die	AAP-'08 UI/die	IOM-'10 UI/die
<i>Lattanti</i>				
0 - 6 mesi	400 - 1000	200	400°	400
6 - 12 mesi	400 - 1000	200	400°	400
<i>Bambini</i>				
1 - 3 anni	400	200	400^	600
4 - 10 anni	0 - 400	200	400^	600
<i>Adolescenti</i>				
11 - 18 anni	0 - 600	200	400^	600

° ogni lattante / bambino che non assume almeno 1 litro/die di latte formulato supplementato con 400 UI/l , a partire dai primi giorni di vita.

^ dose da somministrare nei soggetti che non assumono con la dieta 400 UI/die di vitamina D.



Prevention of Rickets and Vitamin D Deficiency in Infants, Children and Adolescents

- Serum 25-OH-D concentrations in infants and children should be > 50 nmol/L (**20 ng/mL**).
- Children with **increased risk** of vitamin D deficiency, such as those with chronic fat malabsorption and those chronically taking antiseizure medications, may continue to be vitamin D deficient despite an intake of 400 IU/day. **Higher doses** of vitamin D supplementation may be necessary to achieve normal **vitamin D status** in these children, and this status **should be determined with laboratory tests**.

APPORTI RACCOMANDATI DI VITAMINA D DURANTE L'ETÀ EVOLUTIVA

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^ dose da somministrare nei soggetti che non assumono con la dieta 400 UI/die di vitamina D.

Prodotti per la profilassi con vitamina D

<i>Prodotto</i>	<i>Contenuto di vitamina D, UI/gtt^a</i>	<i>Forma di vitamina</i>	<i>Fascia S.S.N.</i>	<i>Altre vitamine o composti</i>
Abidec	54	D2	C	Polivitaminico
Adisterolo	250	D3	C	Vitamina A
AD Pabyrn	100	D3	C	Vitamina A
Bimbovit D3	100	D3	C	-
Decodi	400 (1 ml) ^b	D3	Integratore	Vitamina A, vitamina E, DHA ^c
Decodi K	400 (1 ml) ^b	D3	Integratore	Vitamina K, vitamina A, vitamina E, DHA ^c
DIBASE	250	D3	A	-
Dicovit D	400 (1 perla spremibile)	D3	Integratore	-
Dicovit DK	400 (1 perla spremibile)	D3	Integratore	Vitamina K
Ditreol	400 (1 capsula spremibile)	D3	Integratore	DHA ^c
Ditreol Kappa	400 (1 capsula spremibile)	D3	Integratore	Vitamina K, DHA ^c
Ditrevit	400 (1 ml)	D3	Integratore	Vitamina A, vitamina E, DHA ^c
Ditrevit K50	400 (1 ml)	D3	Integratore	Vitamina K, vitamina A, vitamina E, DHA ^c
Enavitamin	14,3	D3	Integratore	Polivitaminico, DHA ^c
FluorD ₃	80	D3	Integratore	Fluoro
Haliborange	40	D3	Integratore	Vitamina A, vitamina C
Idroplurivit	41,5	D3	C	Polivitaminico
Idroplurivit Baby	13,3	D3	Integratore	Polivitaminico
Lutein D ₃	14,3	D3	Integratore	Luteina, Zeaxantina, DHA
NeoDi	200 (0,5 ml)	D3	Integratore	-
NeoKD	200 (0,5 ml)	D3	Integratore	Vitamina K
Panavit-Zero	80	D3	Integratore	Polivitaminico
PediaCal	300 (1 ml)	D3	Integratore	Vitamina A, omega 3, omega 6
PediaKD	100	D3	Integratore	Vitamina K
PediaTre	100	D3	Integratore	-
PediaVit	20	D3	Integratore	Polivitaminico
Proton	50	D3	Integratore	-
Proton Infant DK	67	D3	Integratore	Vitamina K
Protovit	42	D3	C	Polivitaminico
Sanivit AD	40	D3	Integratore	Vitamina A
Sanivit DK	40	D3	Integratore	Vitamina K
VitaUno	40	D3	Integratore	Polivitaminico, zinco
VitaDue	40	D3	Integratore	Polivitaminico
VitaTre	100 UI (5 ml)	D3	Integratore	Polivitaminico

^ao come altrimenti specificato

^b28 gtt; ^cacido docosaesaenoico

Adherence to Vitamin D Recommendations Among US Infants

(Infants 1-10.5 months-old; n = 1952-1633; Infant Feeding Practices Study II, 2005 – 2007)

% of infants who received an oral vitamin D supplement
(at least 3 days/week during the previous 2 weeks)

Infant Age, mo (wk)	Total, %	Breast Milk, %	Mixed, %	Formula, %
1 (3 to <7)	3.9	5.3	4.3	1.1
2 (7 to <11)	5.5	9.4	5.1	0.9
3 (11 to <15)	6.8	10.3	8.9	1.7
4 (15 to <19)	6.8	10.8	9.8	1.7
5 (19 to <24)	7.3	12.6	9.8	2.0
6 (24 to <29)	7.0	12.1	9.4	2.6
7.5 (29 to <36)	6.9	11.3	11.0	3.1
9 (36 to <43)	6.0	11.2	7.9	2.9
10.5 (43 to <51)	6.7	11.1	10.7	3.9

% of infants who met the 2003 (200 IU/day) and 2008 (400 IU/day) AAP vitamin D recommendation

Infant Age, mo (wk)	Total, %		Breast Milk, %		Mixed, %		Formula, %	
	2003	2008	2003	2008	2003	2008	2003	2008
1 (3 to <7)	NA ^a	11.4	NA ^a	5.3	NA ^a	8.7	NA ^a	24.8
2 (7 to <11)	43.6	16.4	9.4	9.4	29.8	8.5	98.1	31.2
3 (11 to <15)	48.5	20.1	10.3	10.3	33.5	12.4	98.0	34.9
4 (15 to <19)	52.2	22.1	10.8	10.8	33.0	12.6	98.2	36.6
5 (19 to <24)	55.4	23.7	12.6	12.6	35.3	13.0	97.4	36.7
6 (24 to <29)	56.3	25.0	12.1	12.1	31.6	14.4	95.0	37.4
7.5 (29 to <36)	57.8	19.6	11.3	11.3	29.3	13.9	93.3	26.0
9 (36 to <43)	57.9	16.9	11.2	11.2	28.0	12.2	88.2	20.9
10.5 (43 to <51)	57.0	16.8	11.1	11.1	33.3	13.3	81.3	19.9

NA: The 2003 recommendation does not apply to infants in this age category.

(Perrine CG et al. *Pediatrics* Apr 2010)

[chi siamo](#)[presidenza](#)[organigramma](#)[statuto nazionale](#)[nuovo acn per la
pediatria di famiglia](#)[piano sanitario
nazionale](#)[siti f.i.m.p.](#)[Ufficio Stampa](#)[Patrocinio FIMP](#)[Legislazione](#)[Pareri sindacali](#)[Speciali FIMP](#)[Medico Pediatra](#)[Calcolo Compenso
sostituto](#)[Consenso Dati Personali](#)[Moduli da scaricare](#)

QUESTIONARIO

LA PROFILASSI CON VITAMINA D

Gentile dottoressa, Egregio dottore chiediamo la Sua collaborazione per conoscere l'utilizzo dei medicinali equivalenti nella pratica clinica dei pediatri. A tale scopo Le sottoponiamo questo questionario anonimo.

Qual è la tua Regione?

Qual è la tua Provincia?

Sesso:

Maschio

Femmina

Evaluation, Treatment, and Prevention of Vitamin D Deficiency

An Endocrine Society Clinical Practice Guideline

Diagnostic Procedure

- We recommend screening for vitamin D deficiency in individuals **at risk** for deficiency.
- We do not recommend **population screening** for vitamin D deficiency in individuals who are not at risk.
- **Deficiency:** 25-OH-D < **20** ng/ml
- **Insufficiency:** 25-OH-D: **21-29** ng/ml

Coniditons at risk for vitamin D deficiency

Rickets
Osteomalacia
Osteoporosis
Chronic kidney disease
Hepatic failure
Malabsorption syndromes
Cystic fibrosis
Inflammatory bowel disease
Crohn's disease
Bariatric surgery
Radiation enteritis
Hyperparathyroidism
Medications
Antiseizure medications
Glucocorticoids
AIDS medications
Antifungals, e.g. ketoconazole
Cholestyramine
African-American and Hispanic children and adults
Pregnant and lactating women
Older adults with history of falls
Older adults with history of nontraumatic fractures
Obese children and adults (BMI > 30 kg/m²)
Granuloma-forming disorders
Sarcoidosis
Tuberculosis
Histoplasmosis
Coccidiomycosis
Berylliosis
Some lymphomas

(Holick MF et al. JCEM 2011, July)

Recommended Dietary Intakes of Vitamin D for Patients at Risk for Vitamin D Deficiency

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants						
0 to 6 months	400 IU (10 µg)			1,000 IU (25 µg)	400–1,000 IU	2,000 IU
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AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

^a Mother's requirement, 4,000–6,000 IU/d (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

Children 0–1 yr and 1–18 yr at risk of vitamin D deficiency may require at least 1,000 IU/d of vitamin D to raise the blood level of 25(OH)D consistently above 30 ng/ml.

(Holick MF et al. JCEM 2011, July)

Vitamin D: Still a topical matter in children and adolescents. A position paper by the Committee on Nutrition of the French Society of Paediatrics[☆]

- In children and adolescents, as in adults, the 25-OH-D serum level of **20 ng/ml** could be retained as a threshold for moderate vitamin D deficiency, below which defective mineralization can appear.

- **Breastfed infants: 1.000-2.000 IU/day** throughout breastfeeding
- **< 18 months** consuming milk **fortified** in vitamin D: **600-800 IU/day**
- **< 18 months** consuming milk **not fortified** in vitamin D: **1.000-1.200 IU/day**

- **18 months-5 years: 80.000-100.000 IU** in November and in February
- **5-10 years: ?**
- **10-18 years: 80.000-100.000 IU** in November and in February or a single **200.000 IU** dose in winter.

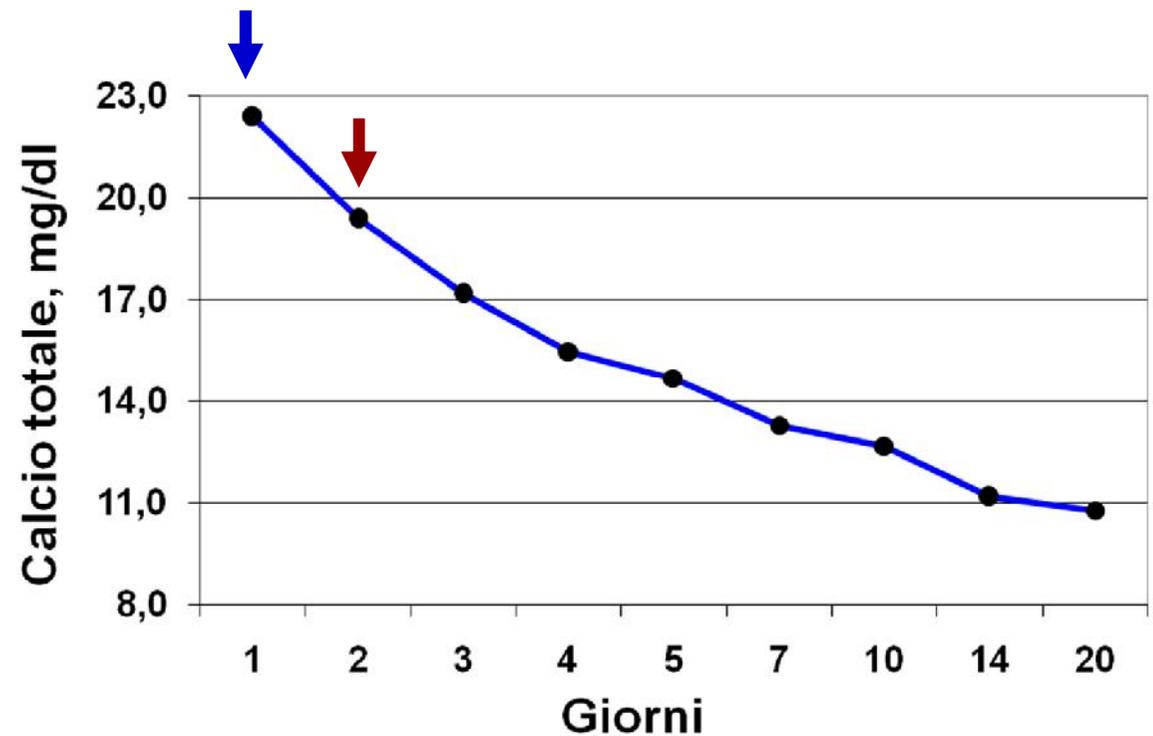
Intossicazione da vitamina D

Clinica Pediatrica, Università di Pisa

- Età: 4.5 mesi
- Somministrate 400.000 UI vitamina D una volta alla settimana per 5 settimane consecutive (totale **2.000.000 UI**)
- All'ingresso: irritabilità, ipotonia, disidratazione severa, stipsi.
- Nefrocalcinosi I grado.

- Calcio tot: **22.4 mg/dl**
- 25-OH-D: **1.135 ng/ml**

- **Idratazione con fisiologica** (200 ml/Kg/die)
- **Metilprednisolone ev** (2 mg/Kg/die)
- **Furosemide** (1 mg/Kg/die)



Sales of vitamin D in the United States



(Maxmen A. Nature 2011)

Vitamina D

Gravidanza, pretermine/SGA

Vitamin D status during pregnancy

**Prevalence of severe vitamin D deficiency
(25-OH-D < 10 ng/ml) in pregnant women**

Country	Percentage
United Kingdom	18
United Arab Emirates	25
Iran	80
North India	42
New Zealand	61
Netherlands	60–84 of non-Western women

High latitude, winter season, dark pigmentation and full-body skin covering all increase the risk of maternal vitamin D deficiency.

(Dawodu A, Wagner CL. Arch Dis Child 2007)

Vitamin D during Pregnancy

Stage	Serum 25(OH)D, ng/mL	Maternal adverse effects	Newborn infant adverse effects
Severe deficiency	<10	Increased risk of <u>preeclampsia</u> , calcium malabsorption, bone loss, poor weight gain, myopathy, higher parathyroid hormone levels	Small for gestational age, <u>neonatal hypocalcemia</u> , <u>hypocalcemic seizures</u> , infantile heart failure, enamel defects, large fontanelle, <u>congenital rickets</u> , rickets of infancy if breastfed
Insufficiency	11-32	Bone loss, subclinical myopathy	<u>Neonatal hypocalcemia</u> , <u>reduced bone mineral density</u> , <u>rickets of infancy if breastfed</u>
Adequacy	32-100	Adequate calcium balance, parathyroid hormone levels	None, unless exclusively breastfed

Serum 25-OH-D levels in pregnant women should be assessed to be sure they are > 30 ng/ml.

(Mulligan ML et al. Am J Obstet Gynecol May 2010)

Rachitismo congenito in neonato a termine

- Medhi: nato a termine da TC, origine algerina (madre portatrice di velo).
- Fontanella anteriore e posteriore ampie, senza soluzione di continuità.
- Suture diastasate, platibasia, rosario rachitico.

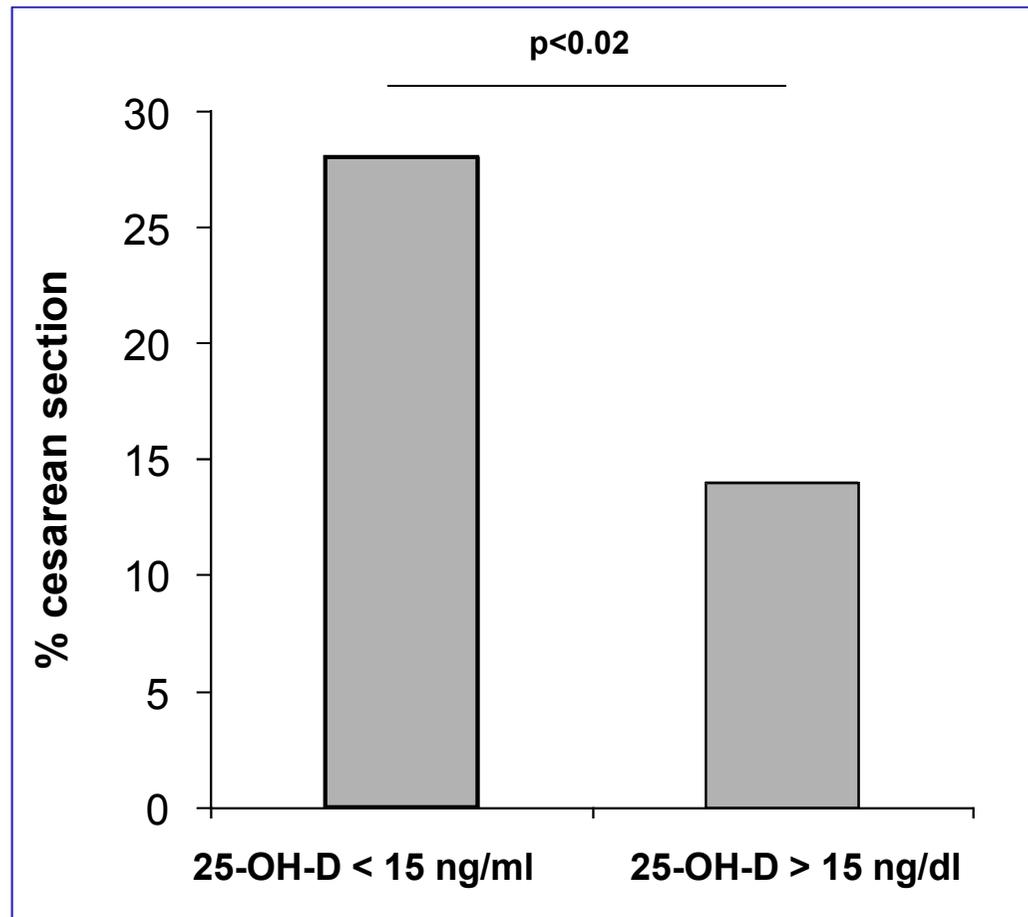


- Madre portatrice di velo
- No profilassi in gravidanza
- Concepito in inverno

- **Mehdi:** 25-OH-D: 9 ng/ml
- **Madre:** 25-OH-D 8 ng/ml

(F. Vierucci et al. Medico e Bambino 2011)

Association between Vitamin D Deficiency and Primary Cesarean Section (Boston 2005-07; 253 women; 17%: primary cesarean)



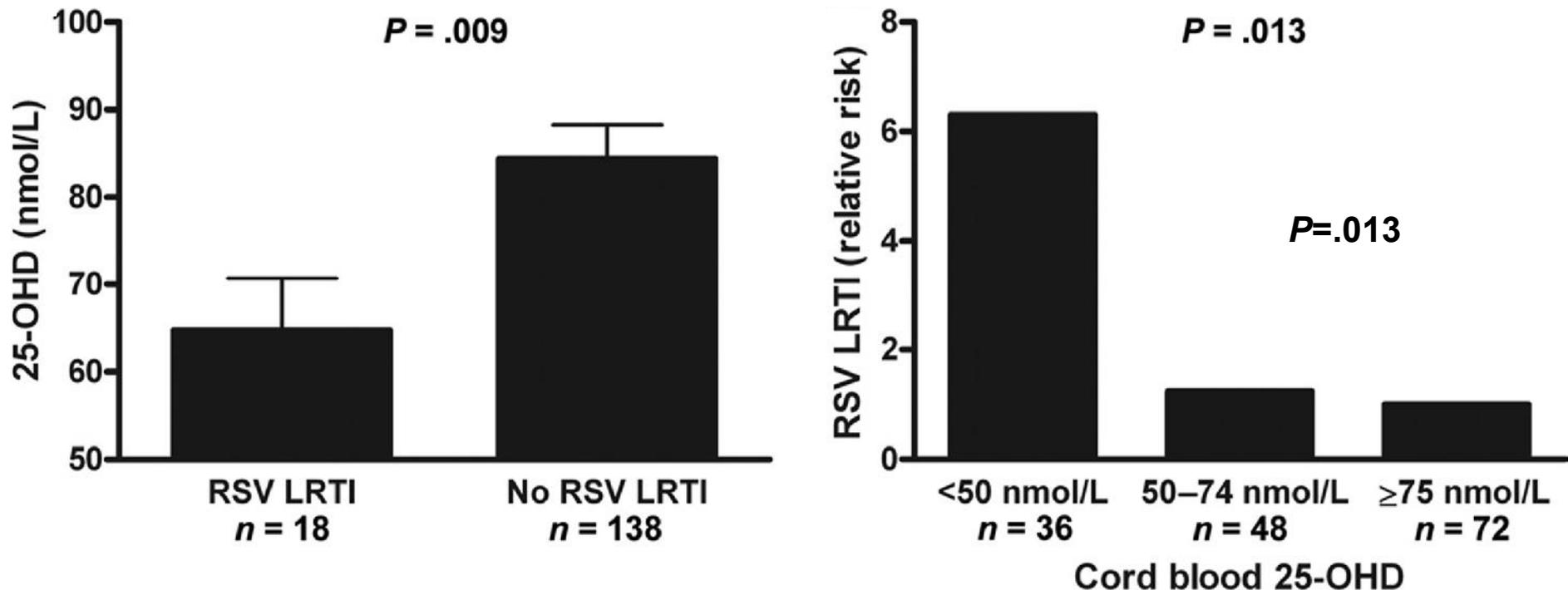
Women with 25-OH-D less than 15 ng/ml were 4 times as likely to have a cesarean section.

(Merewodd et al. JCEM 2009)

Cord blood vitamin D deficiency is associated with increased risk of RSV lower respiratory tract infections (LRTI) in th 1st year of life

N = 156 term neonates
Follow-up: 1 yr

- 25-OHD \geq 75 nmol/l (30 ng/ml): 46%
- 25-OHD: 50-75 nmol/l (20-30 ng/ml): 27%
- 25-OHD < 50 nmol/l (20 ng/ml): 27%

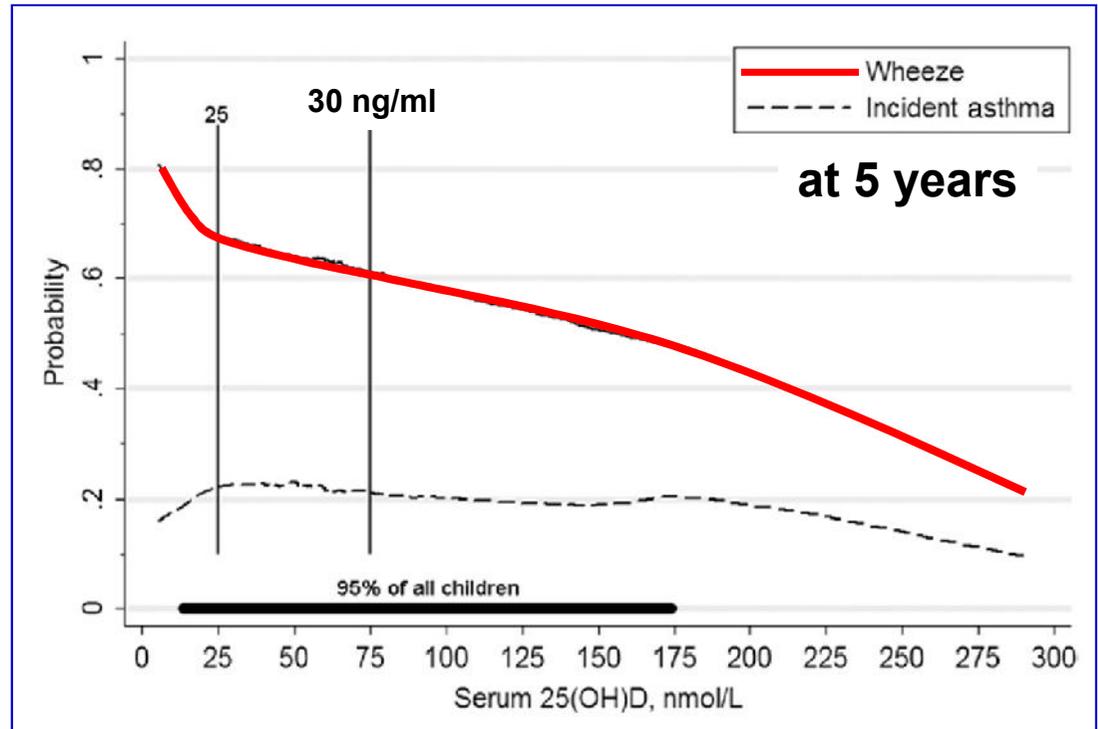


Vitamin D deficiency in healthy neonates is associated with increased risk of RSV lower respiratory tract infections (LRTI) in the first yr of life.

(Belderbos ME et al. Pediatrics Jun 2011)

Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma by the age of 3 months until 5 years

- N = 922 newborns
- Follow-up at 3 months, until 5 yr
- Mean cord-blood 25-OH-D = 17.6 ng/ml
- 25-OHD > 30 ng/ml (75 nmol/l) = 27.2 %
- 25-OHD: 10-30 ng/ml (25-75 nmol/l) = 53.2 %
- 25-OHD < 10 ng/ml (25 nmol/l) = 19.6 %



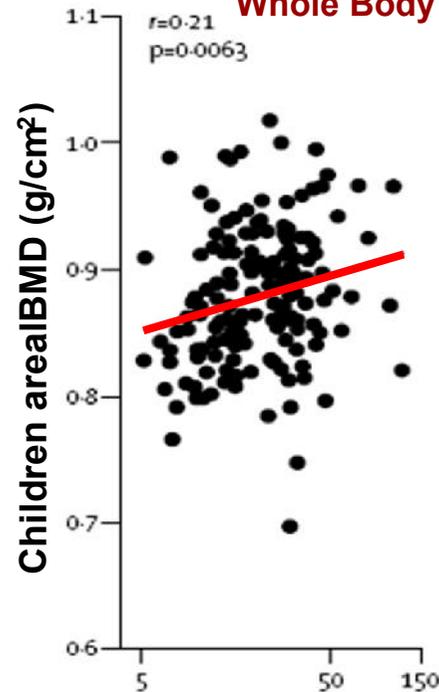
- *Low cord-blood levels of 25-OHD were common in newborns and were associated with higher risk of respiratory infections by the age of 3 months.*
- *Cord blood 25-OHD levels were inversely associated with wheezing throughout early childhood but had no association with incident asthma.*

(Camargo CA et al. Pediatrics Jan 2011)

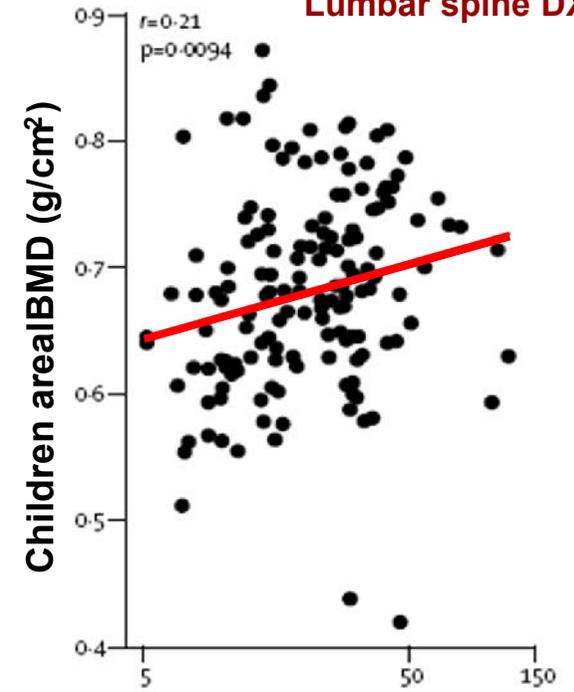
Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years

- N = 198 children (M = 104)
- Serum 25(OH)D levels measured at 34 weeks
- Singleton pregnancy, at term
- BMD assessment at 9 yr

Whole Body DXA



Lumbar spine DXA



Maternal vitamin D status seems to influence the programming of the acquisition of bone mass in the child.

Recommended Dietary Intakes of Vitamin D for Patients at Risk for Vitamin D Deficiency

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants						
0 to 6 months	400 IU (10 µg)			1,000 IU (25 µg)	400–1,000 IU	2,000 IU
6 to 12 months	400 IU (10 µg)			1,500 IU (38 µg)	400–1,000 IU	2,000 IU
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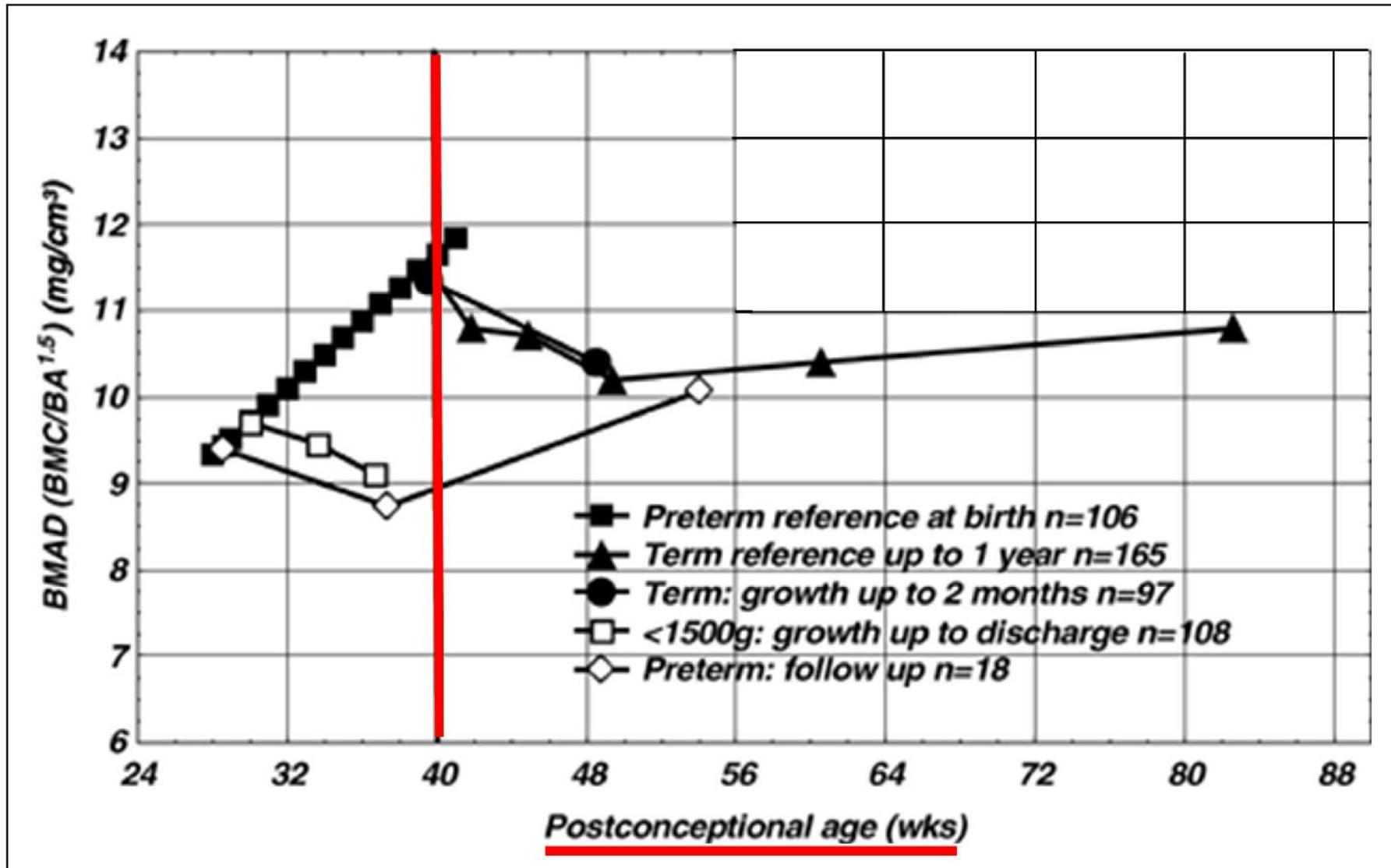
AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

^a Mother's requirement, 4,000–6,000 IU/d (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

Pregnant women require at least 600 IU/d of vitamin D; 1500–2000 IU/d of vitamin D may be needed to maintain a blood level of 25-OH-D above 30 ng/ml .

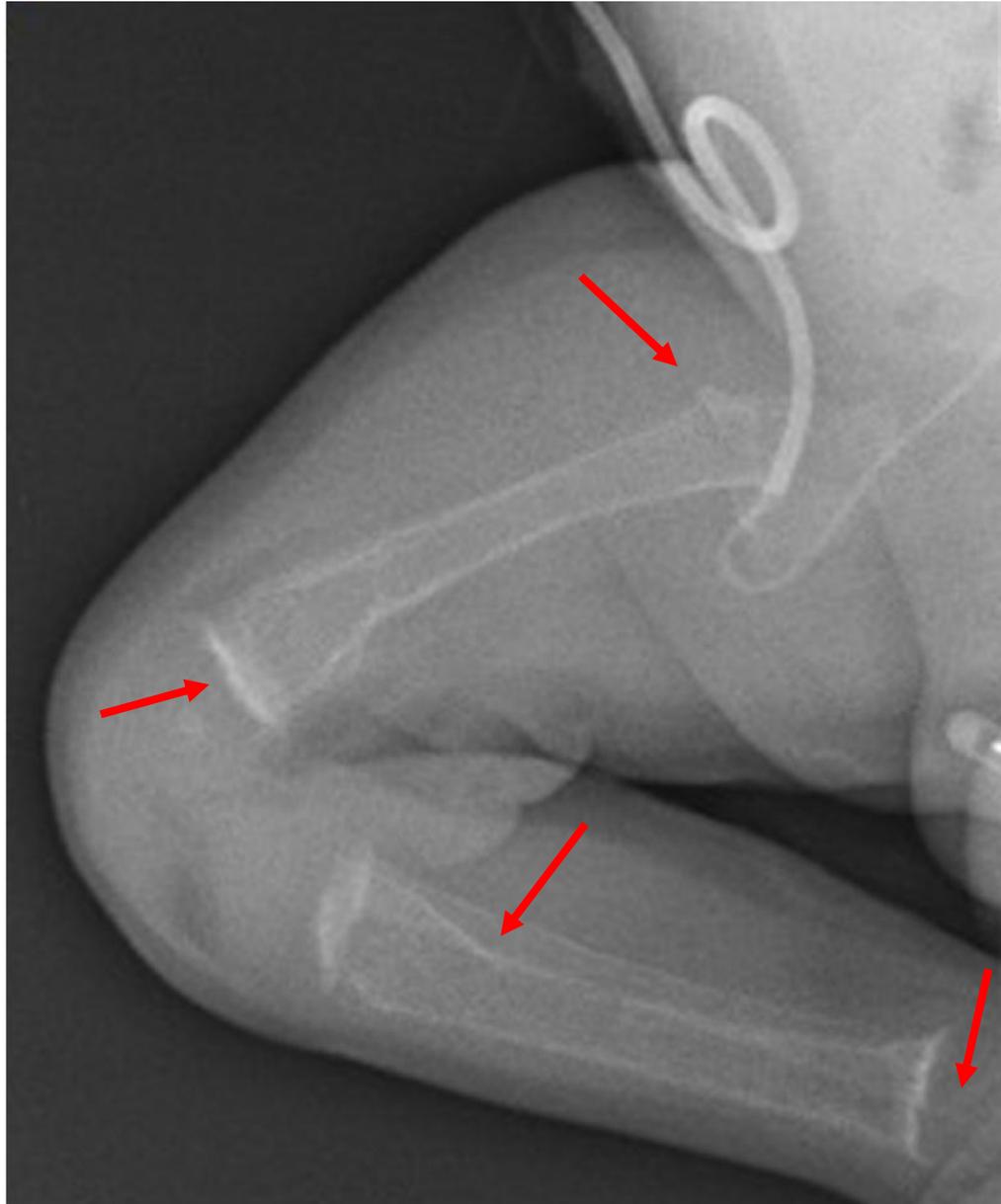
(Holick MF et al. JCEM 2011, July)

Physiological evolution of bone mineral density during the last trimester of gestation and during the first year of life in term and preterm infants



(Rigo J et al. J of Pediatrics 2006)

Osteopenia del pretermine

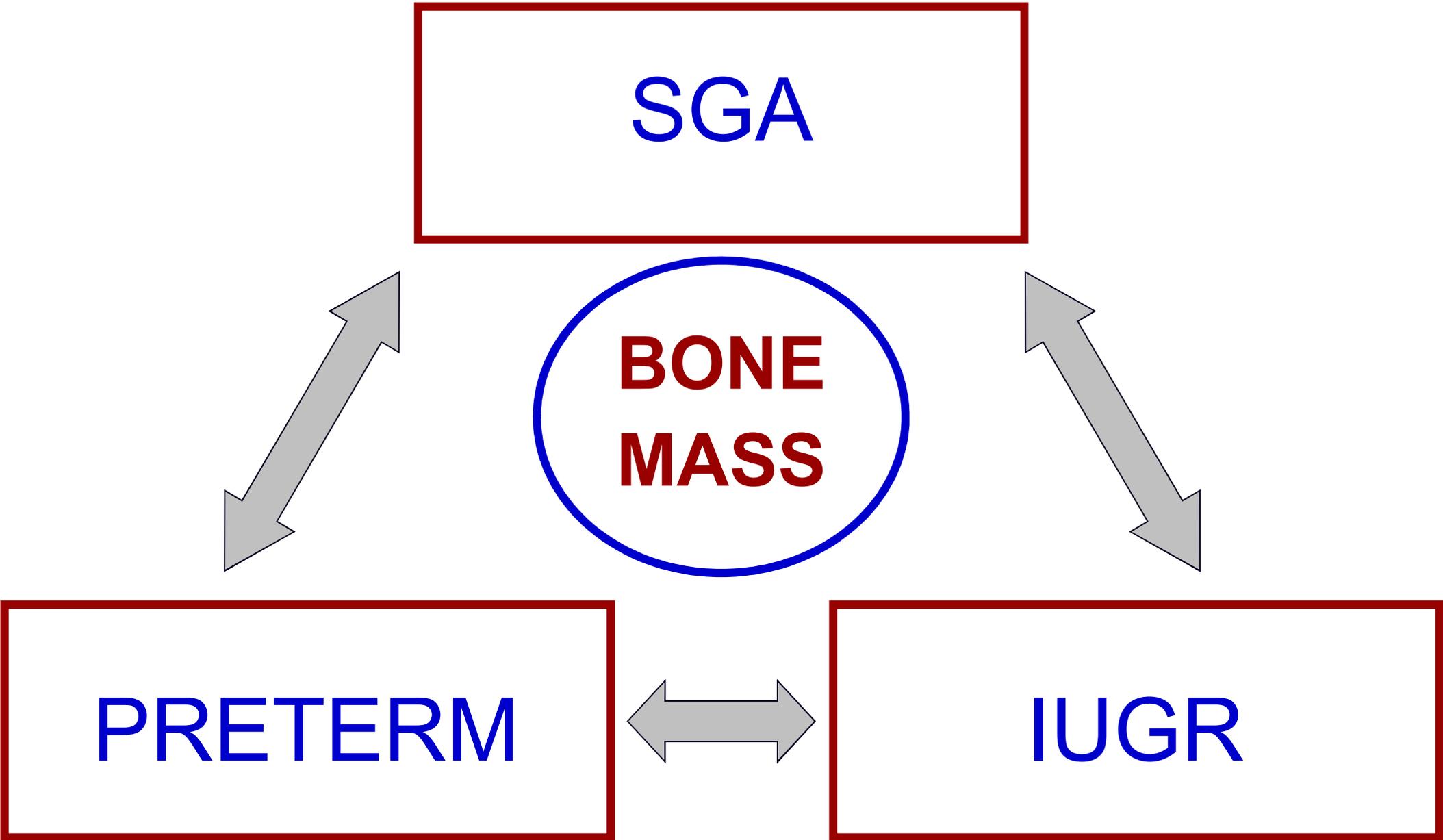


Minerals and vitamin D recommended intakes in preterm infants

REQUIREMENTS	LSRO (2002)	Atkinson (2005)	Rigo (2007)	ESPGHAN (2010)
Calcium (mg/kg/day)	150 - 220	120 - 200	100 - 160	120- 140
Phosphorus (mg/kg/day)	100 - 130	60 - 140	60 - 90	65 - 90
Vitamin D (IU=day)		200 - 1000	800 - 1000*	800 - 1000
(IU/kg/day)	90 - 225	150 - 400		

**until the theoretical term
(40 weeks)*

- LSRO: Life Sciences Research Office
- ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology And Nutrition



Bone Mineral Content (BMC) in newborns SGA

SGA: 56 (■)

AGA: 129 (□)

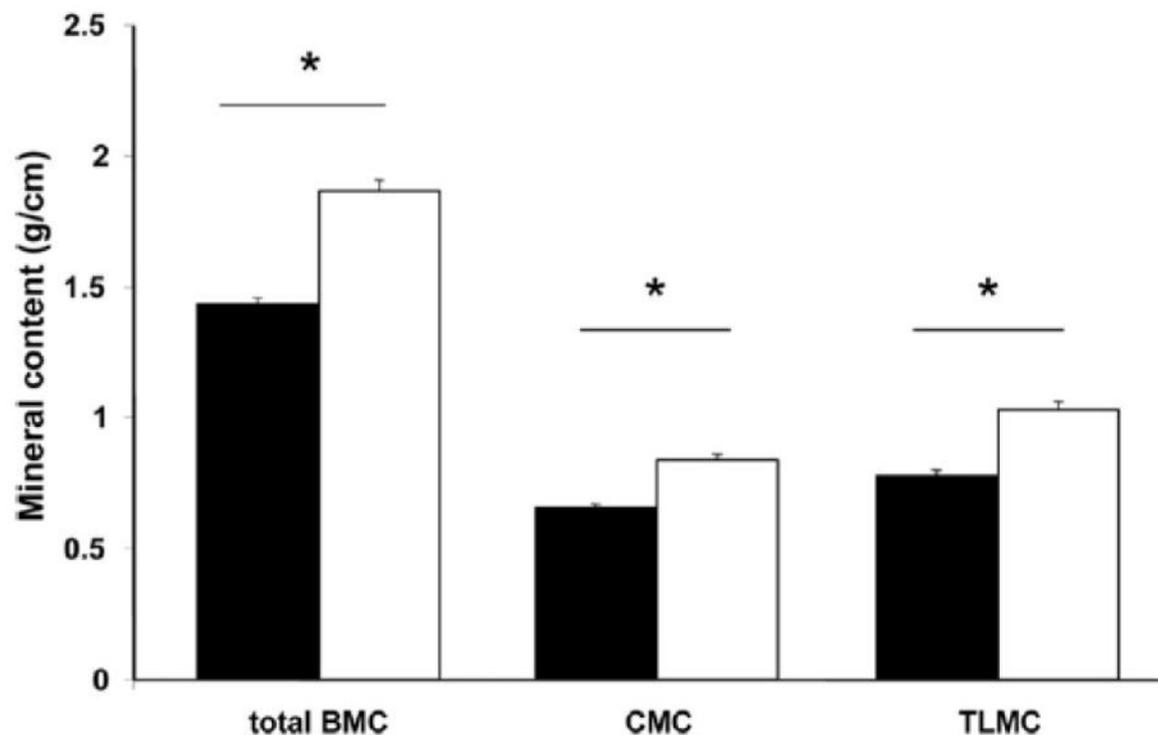
IUGR: 112 (71 AGA e 41 SGA)

total BMC: total bone mineral content

CMC: cranium mineral content

TLMC: trunk and limbs mineral content

* $p < 0.05$



Bone mineral content is significantly lower in SGA than in AGA.

IUGR is an additional, independent factor responsible of BMC reduction.

SGA plus IUGR newborns are those at higher risk to present a reduced bone mineralization.

(Beltrand et al. Pediatric Research 2008)

Le nuove e le vecchie indicazioni della vitamina D

Conclusioni (1)

- **Gli studi effettuati nell'ultima decade da una parte hanno permesso di caratterizzare meglio le azioni classiche della vitamina D sul metabolismo osseo, dall'altra hanno aperto un nuovo scenario per quanto riguarda le "nuove" azioni della vitamina D a livello extrascheletrico.**
- **La conoscenza di queste nuove azione ha sottolineato la necessità di definire lo stato vitaminico ottimale in età pediatrica.**
- **La deficienza di vitamina D viene definita dalla presenza di livelli circolanti di 25-OH-D inferiori ai 20 ng/ml.
Mentre livelli di 25-OH-D superiori a 30 ng/ml caratterizzano uno stato vitaminico ottimale, livelli tra compresi tra 20-30 ng/ml richiedono una attenta valutazione dei fattori di rischio.**

Conclusioni (2)

- **Il rachitismo carenziale è ancora presente, anche nei paesi sviluppati, in particolare in gruppi a rischio (immigrati/adottati).**
- **Per quanto riguarda le azioni extrascheletriche, recenti studi suggeriscono che la deficienza di vitamina D si può associare ad un aumentato rischio di infezioni, allergia e patologie autoimmuni, suggerendo al pediatra l'importanza di assicurare uno stato vitaminico ottimale.**
- **La profilassi con vitamina D è indicata, fin dai primi giorni di vita, in tutti i bambini, con particolare attenzione al periodo adolescenziale.**
- **La gravidanza è un periodo particolarmente delicato, per le possibili conseguenze della deficienza di vitamina D sia sulla gestante che sulla salute futura del bambino.**
- **I neonati pretermine e/o SGA sono particolarmente a rischio di presentare deficienza di vitamina D ed osteopenia.**

