Vitamina D nella pratica del pediatra: *certezze e prospettive*

Giuseppe Saggese

Napule è...

PEDIATRIA PREVENTIVA E SOCIALE

SOCIETÀ AFFILIATA ALLA SIP

LUCI OMBRE ABBAGLI

Prevenzione

Nutrizione

Allergologia

Dermatologia

Gastroenterologia

29 Aprile - 01 Maggio 2023

Evento Residenziale

Hotel Royal Continental, Napoli

Presidente del congresso: **Giuseppe Di Mauro**

fonti di approvvigionamento di Vitamina D

Vitamina D: fonti di approvigionamento

→ 90 - 95%

→ 5 - 10%

Sun exposure and vitamin D status

The NEW ENGLAND JOURNAL of MEDICINE

... exposure of arms and legs for 30 minutes (depending on time of day, season, latitude, and skin pigmentation) two-three times a week is often adequate.

(Holick MF. 2007)

stato vitaminico D
in bambini e adolescenti

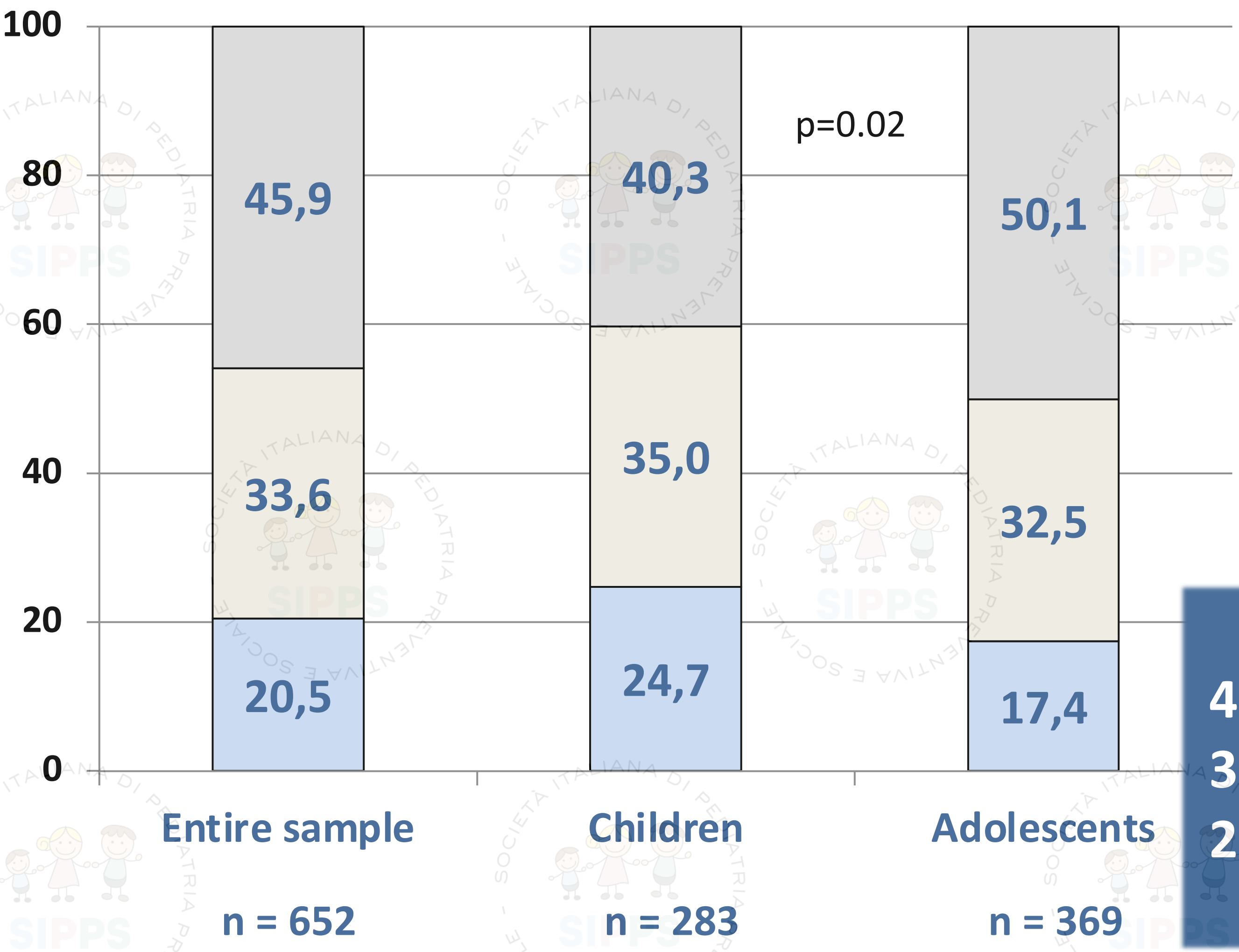
E' stata dimostrata un'elevata prevalenza di ipovitaminosi D (≤ 30 ng/ml = insufficienza + deficit) in età pediatrica (0-18 aa)

Si considerano ***sufficienti/normali*** i valori di Vitamina D (25-OH-D) ≥ 30 ng/ml (≥75 nmol/L), ***insufficienti*** i valori compresi tra 20 e 30 ng/ml (50 – 75 nmol/L) e come indicativi di ***deficit*** quelli ≤20 ng/ml (≤ 50 nmol/L), (deficit severo ≤ 12 ng/ml: ≤30 nmol/L)

** per convertire ng/ml in nmol/L si moltiplica per 2.5*

Vitamin D status in italian children and adolescents

Dept. of Pediatrics, University of Pisa (n = 652, 2-21 yrs)*



*not supplemented in the year preceding the study

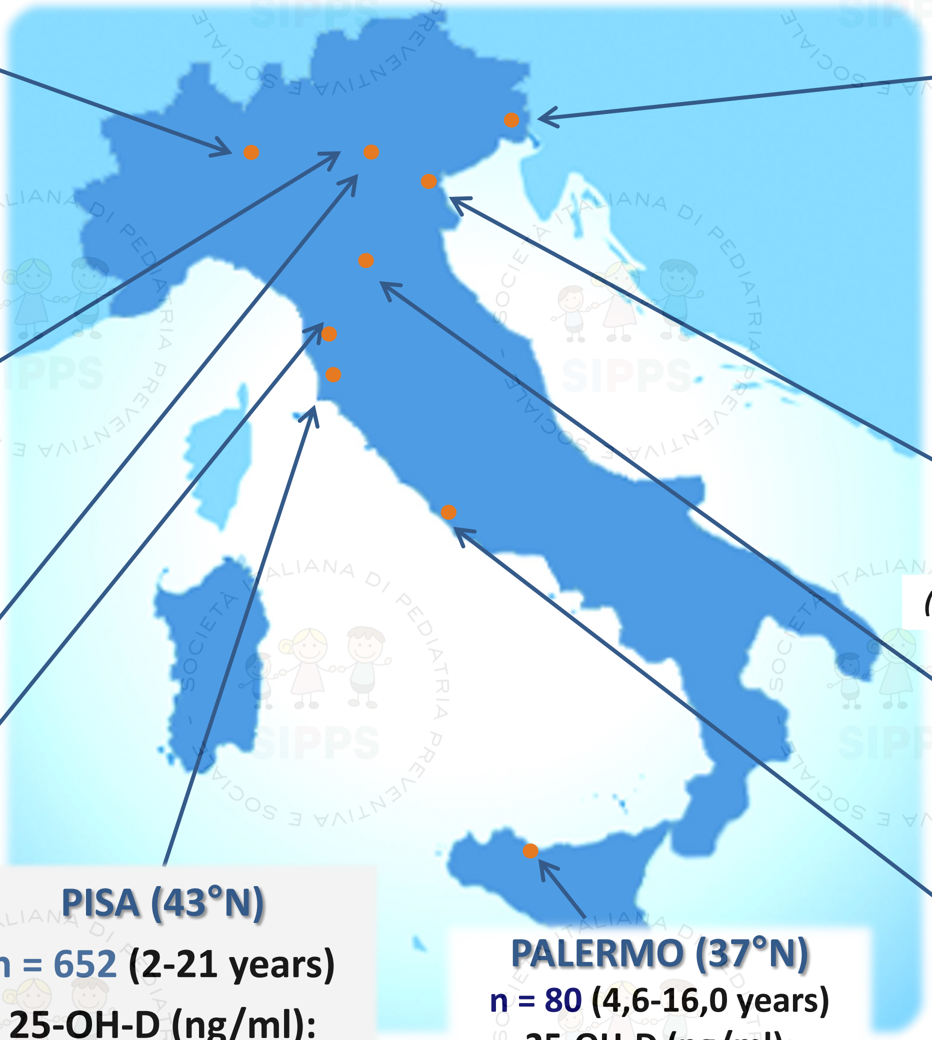
- ▨ **Deficiency** **(25-OH-D < 20 ng/ml)**
- ☐ **Insufficiency** **(25-OH-D: 20-30 ng/ml)**
- ☐ **Sufficiency** **(25-OH-D ≥ 30 ng/ml)**

30 ng/ml = 75 nmol/L
20 ng/ml = 50 nmol/L
10 ng/ml = 25 nmol/L

45,9% Vitamin D deficiency
33,6% Vitamin D insufficiency
20,5% Vitamin D sufficiency

(Saggese G et al, It J Ped, 2018)

Prevalence of hypovitaminosis D in Italy



NOVARA (45°N)

n = 62 (newborns)

25-OH-D (ng/ml):

75.6% < 20 ng/ml

(Cadario F et al. Ital J Pediatr 2013)

VERONA (45°N)

n = 59 (9-12 years)

25-OH-D (ng/ml):

- < 20 42.4%
- 20-30 45.8%

(Chinellato I et al. Eur Respir J 2011)

VERONA (45°N)

n = 192 (0-18 years)

25-OH-D (ng/ml):

< 11 6.2%

(Lippi G et al. CMAJ 2007)

FIRENZE (43°N)

n = 679 (0-18 years)

25-OH-D (ng/ml):

- < 20 55.4%
- 20-30 33.3%

(Stagi S et al. Italian J Pediatr In press)

UDINE (46°N)

n = 93 (0.2-18 years)

25-OH-D (ng/ml):

< 20 54.8%

(Marrone G et al. Eur J Nutr 2011)

PADOVA (45°N)

n = 58 (1.1-15.3 years)

25-OH-D (ng/ml):

- < 20 50.0%
- 20-30 27.0%

(Mazzoleni S et al. Int J Pediatr Endocr 2012)

PARMA (44°N)

n = 270 (12-21 years)

25-OH-D (ng/ml):

- < 20 19.3%
- 20-30 36.3%

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

ROMA (42°N)

HELENA study

n = 104 (12.6-17.4 years)

25-OH-D (ng/ml):

< 20 26.4%

(González-Gross M et al. Br J Nutr 2012;)

PISA (43°N)

n = 652 (2-21 years)

25-OH-D (ng/ml):

- < 20 20,5%
- 20-30 33.6%

(Saggese G et al. Eur J Pediatr2013)

PALERMO (37°N)

n = 80 (4,6-16,0 years)

25-OH-D (ng/ml):

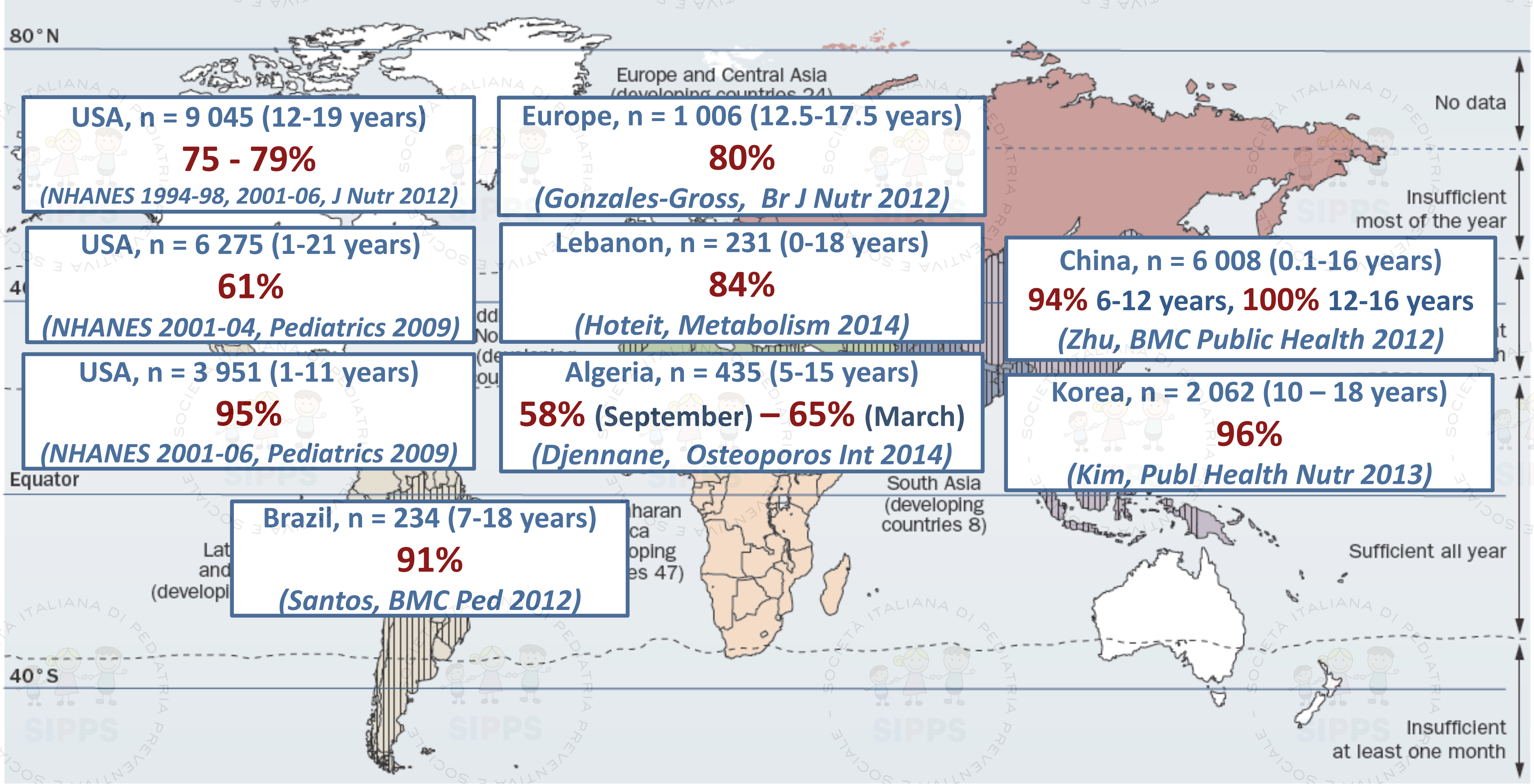
< 20 40%

20-30 35%

(Ciresi et al.)

Prevalence of hypovitaminosis D around the world

(% of pediatric subjects below 30 ng/ml: insufficient + deficient)



USA, n = 9 045 (12-19 years)
75 - 79%
(NHANES 1994-98, 2001-06, J Nutr 2012)

USA, n = 6 275 (1-21 years)
61%
(NHANES 2001-04, Pediatrics 2009)

USA, n = 3 951 (1-11 years)
95%
(NHANES 2001-06, Pediatrics 2009)

Europe, n = 1 006 (12.5-17.5 years)
80%
(Gonzales-Gross, Br J Nutr 2012)

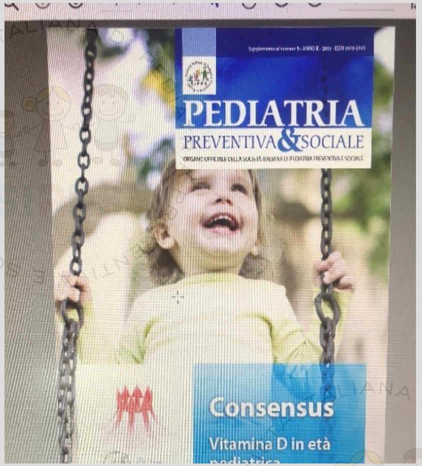
Lebanon, n = 231 (0-18 years)
84%
(Hoteit, Metabolism 2014)

Algeria, n = 435 (5-15 years)
58% (September) – **65%** (March)
(Djennane, Osteoporos Int 2014)

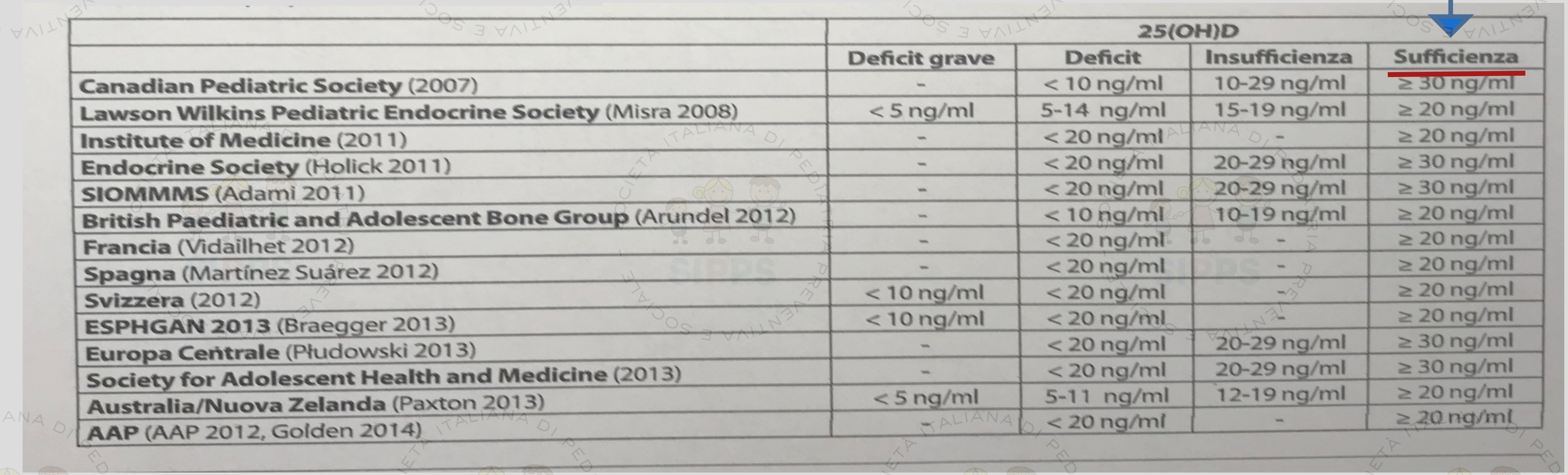
Brazil, n = 234 (7-18 years)
91%
(Santos, BMC Ped 2012)

China, n = 6 008 (0.1-16 years)
94% 6-12 years, **100%** 12-16 years
(Zhu, BMC Public Health 2012)

Korea, n = 2 062 (10 – 18 years)
96%
(Kim, Publ Health Nutr 2013)



Consensus SIPPS - SIP
Vitamina D in età pediatrica
2015

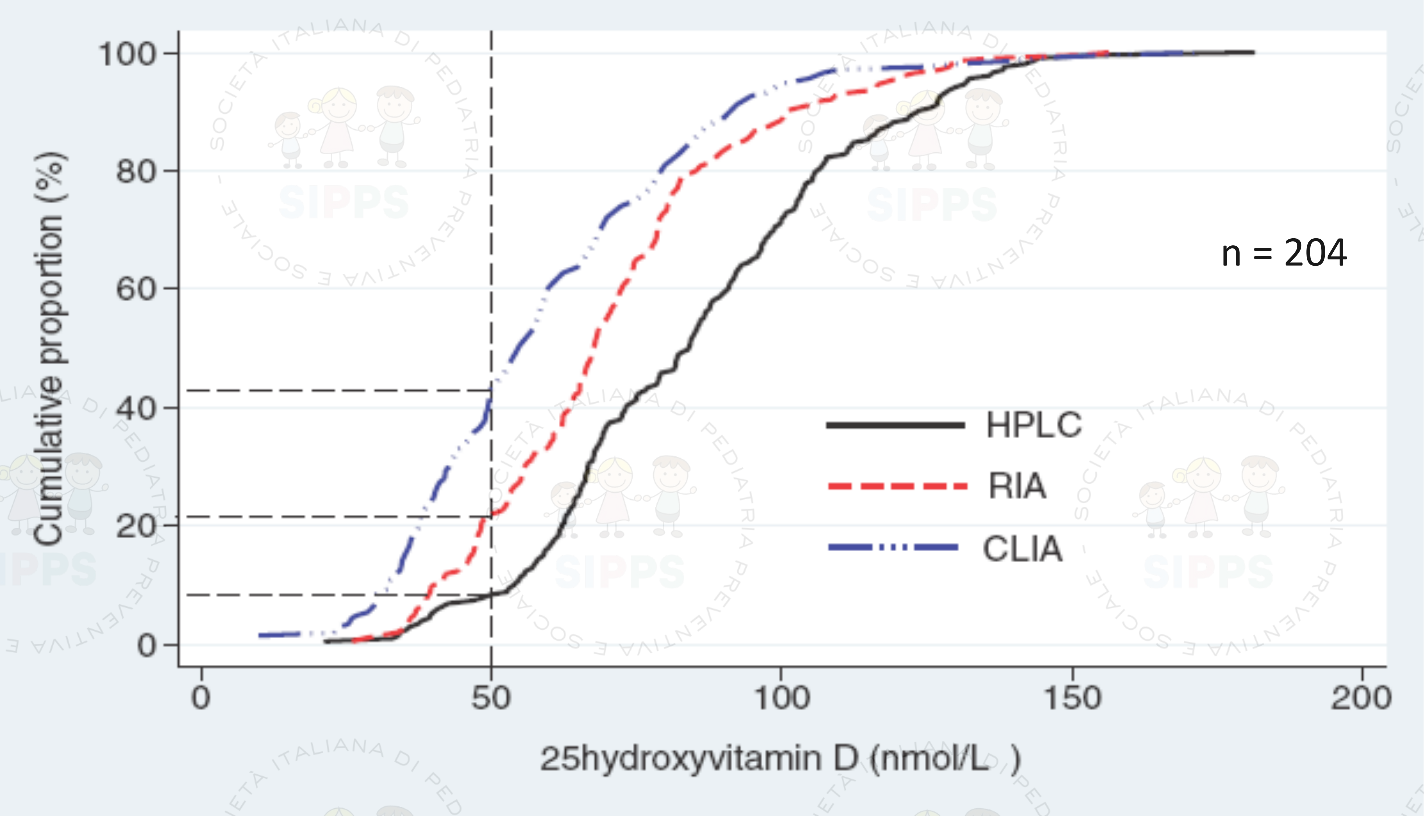


	25(OH)D			
	Deficit grave	**Deficit**	**Insufficienza**	**Sufficienza**
Canadian Pediatric Society (2007)	-	< 10 ng/ml	10-29 ng/ml	≥ 30 ng/ml
Lawson Wilkins Pediatric Endocrine Society (Misra 2008)	< 5 ng/ml	5-14 ng/ml	15-19 ng/ml	≥ 20 ng/ml
Institute of Medicine (2011)	-	< 20 ng/ml	-	≥ 20 ng/ml
Endocrine Society (Holick 2011)	-	< 20 ng/ml	20-29 ng/ml	≥ 30 ng/ml
SIOMMMS (Adami 2011)	-	< 20 ng/ml	20-29 ng/ml	≥ 30 ng/ml
British Paediatric and Adolescent Bone Group (Arundel 2012)	-	< 10 ng/ml	10-19 ng/ml	≥ 20 ng/ml
Francia (Vidailhet 2012)	-	< 20 ng/ml	-	≥ 20 ng/ml
Spagna (Martínez Suárez 2012)	-	< 20 ng/ml	-	≥ 20 ng/ml
Svizzera (2012)	< 10 ng/ml	< 20 ng/ml	-	≥ 20 ng/ml
ESPHGAN 2013 (Braegger 2013)	< 10 ng/ml	< 20 ng/ml	-	≥ 20 ng/ml
Europa Centrale (Płudowski 2013)	-	< 20 ng/ml	20-29 ng/ml	≥ 30 ng/ml
Society for Adolescent Health and Medicine (2013)	-	< 20 ng/ml	20-29 ng/ml	≥ 30 ng/ml
Australia/Nuova Zelanda (Paxton 2013)	< 5 ng/ml	5-11 ng/ml	12-19 ng/ml	≥ 20 ng/ml
AAP (AAP 2012, Golden 2014)	-	< 20 ng/ml	-	≥ 20 ng/ml

Determining Vitamin D status: comparison between available assays

- **High-performance liquid chromatography (HPLC, Tandem Mass)**
- **Radioimmunoassay (RIA)**
- **Chemiluminescent immunoassay (CLIA)**

Cumulative proportion of subjects classified as insufficient (25-OH-D < 20 ng/ml) by assay



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

(Snellman G et al. Plos One 2010)

“Choosing wisely”

American Academy of Pediatrics (2017)

thing not do do:

routinely prescribing vitamin D assay in healthy children

fattori di rischio per ipovitaminosi D

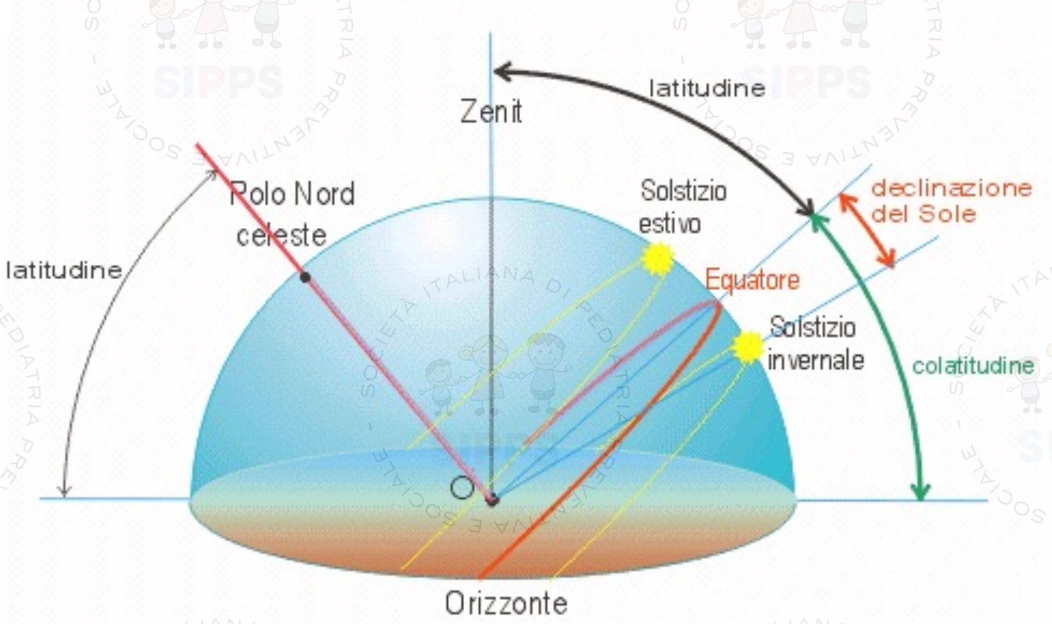
Fattori di rischio di ipovitaminosi D

- ridotta esposizione al sole (stili di vita, abbigliamento, abitudini socio-culturali e religiose)
- fattori che possono influenzare l’efficacia dei raggi solari
- elevata pigmentazione cutanea, etnia
- allattamento al seno esclusivo senza profilassi
- adolescenza
- obesità
- specifiche condizioni patologiche (es. malassorbimenti, insufficienza epatica o renale)
- farmaci interferenti con il metabolismo della vitamina D (antiepilettici, corticosteroidi)

Sunshine and vitamin D

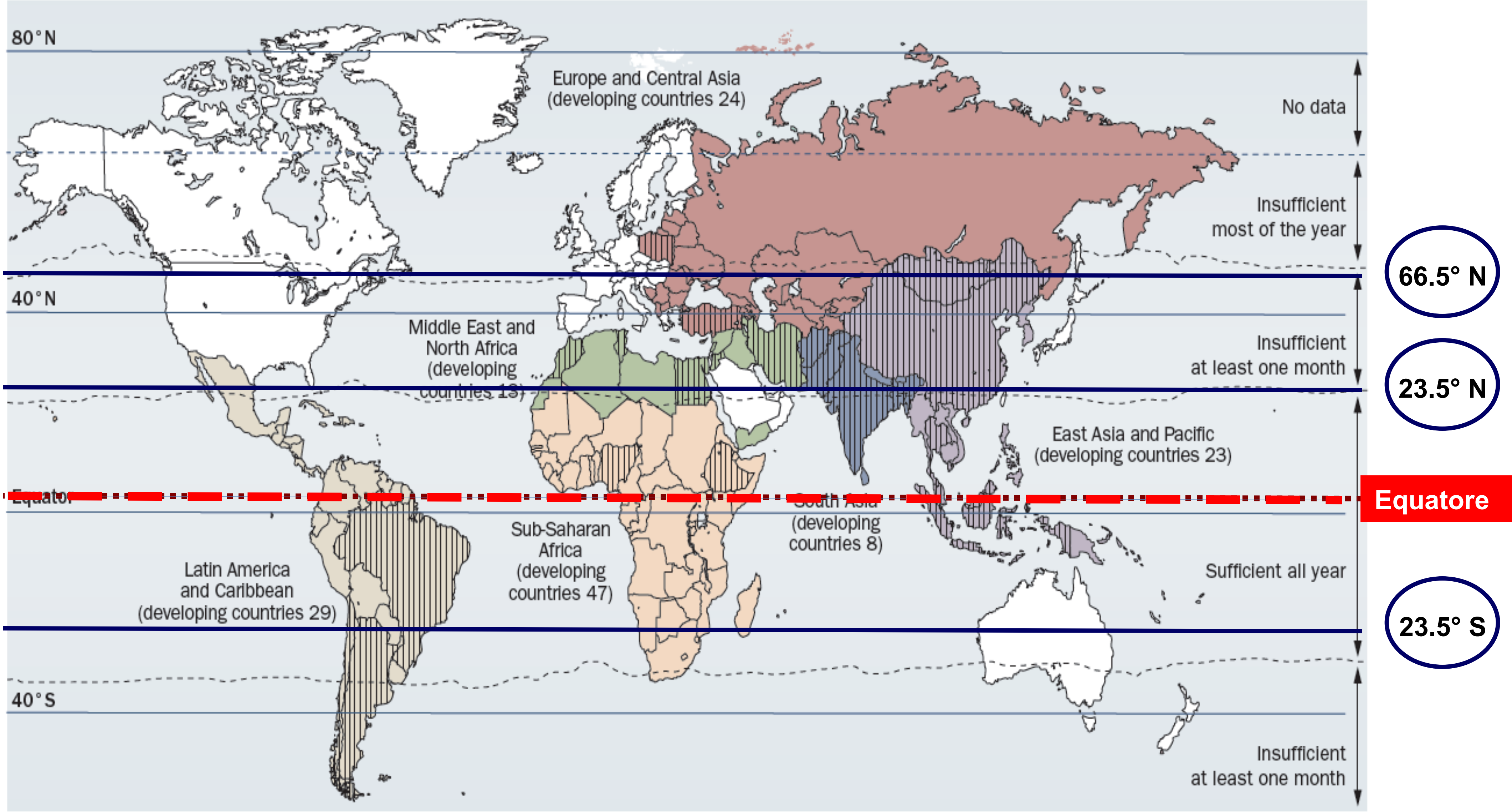
Factors influencing the amount of exposure to sun

- ➢ **solar zenith angle**
- ➢ **cloud cover**
- ➢ **atmospheric polluti**
- ➢ **ozone layer**



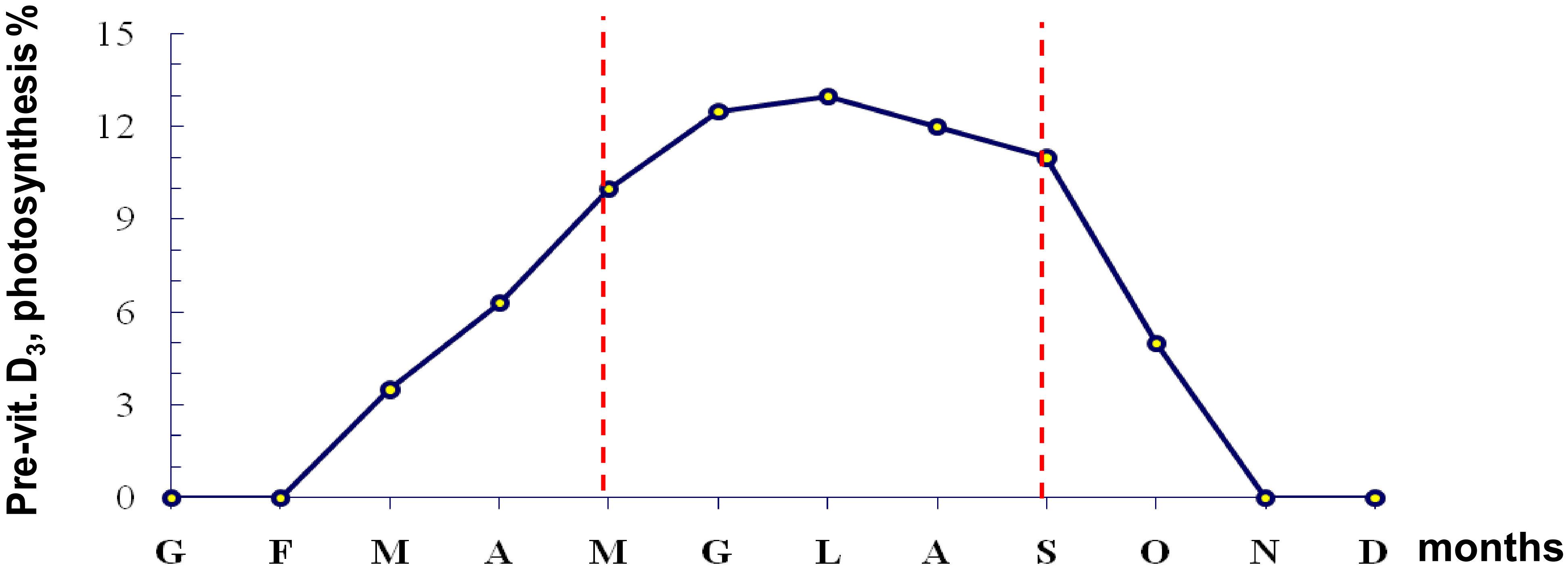
N. Shaw, Arch Dis Child, 2017

Latitude and cutaneous synthesis of Vitamin D



(Arabi A et al. Nat Rev Endocrinol 2010)

Photosynthesis of pre-vitamin D3 from 7-dehydrocholesterol during the year, *in vitro,*in Pisa (latitude 43°N)



During winter and early spring photosynthesis of vitamin D is low or absent; adequate vitamin D status can be assured by body vitamin D stores or supplementation.

(Saggese G et al. It J Ped 1992)

Fattori di rischio di ipovitaminosi D

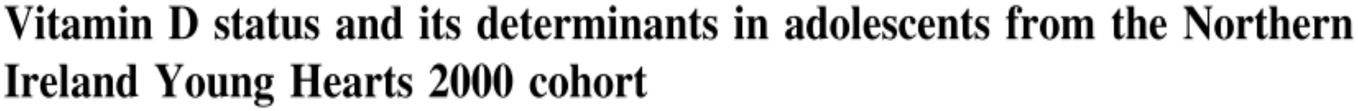
- ridotta esposizione al sole (stili di vita, abbigliamento, aabitudini socio-culturali e religiose)
- fattori che possono influenzare l'efficacia dei raggi solari
- **elevata pigmentazione cutanea, etnia**
- **allattamento al seno esclusivo senza profilassi**
- adolescenza
- obesità
- specifiche condizioni patologiche (es. malassorbimenti, ininsufficienza epatica o renale)
- farmaci interferenti con il metabolismo della vitamina DD (antiepilettici, corticosteroidi)

Fattori di rischio di ipovitaminosi D

- ridotta esposizione al sole (stili di vita, abbigliamento, aabitudini socio-culturali e religiose)
- fattori che possono influenzare l'efficacia dei raggi solari
- elevata pigmentazione cutanea, etnia
- allattamento al seno esclusivo senza profilassi
- **adolescenza**
- **obesità**
- specifiche condizioni patologiche (es. malassorbimenti, ininsufficienza epatica o renale)
- farmaci interferenti con il metabolismo della vitamina DD (antiepilettici, corticosteroidi)

Vitamin D status during adolescence

(Deficiency : 25-OH-D < 20 ng/ml)



Vitamin D status and its determinants in adolescents from the Northern Ireland Young Hearts 2000 cohort

(Hill TR et al, Br J Nutr 2008)

36%

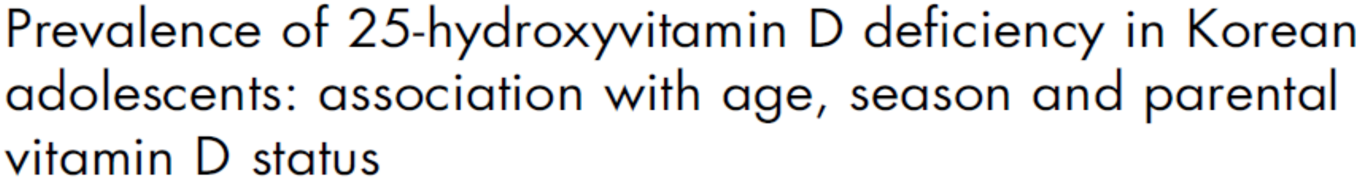
(N = 1,015)

Implications of a New Definition of Vitamin D Deficiency in a Multiracial US Adolescent Population: The National Health and Nutrition Examination Survey III

(Saintonge S et al, Pediatrics 2009)

14%

(N = 2,955)



Prevalence of 25-hydroxyvitamin D deficiency in Korean adolescents: association with age, season and parental vitamin D status

(Kim SH et al, Publ Health Nutr 2012)

54.7%

(N = 2,062)

Vitamin D deficiency in girls from South Brazil: a cross-sectional study on prevalence and association with vitamin D receptor gene variants

(Santos BR et al, BMC Pediatrics 2012)

36.3%

(N = 234)

Prevalence of hypovitaminosis D and predictors of vitamin D status in Italian healthy adolescents

(Saggese G et al, Ital J Pediatr, 2014)

49.9%

(N = 427)

Stato vitaminico D negli adolescenti

- stili di vita: ridotta esposizione alla luce solare per il ridotto tempo passato all'aperto, ridotta attività fisica e aumento della sedentarietà (eccessivo uso di smartphone e computer)
- obesità/sovrappeso (30% degli adolescenti)
- malattie croniche (20% degli adolescenti)
- aumentate richieste di calcio e fosforo per lo spurt puberale

Clinical presentation of Vitamin D deficiency (25-OH-D < 20 ng/ml) in children and adolescents

Clinical findings	1-3 yrs (n=118) n (%)	4-6 yrs (n=103) n (%)	7-11 yrs (n=193) n (%)	12-17 yrs (n=129) n (%)
Low weight gain (failure to thrive)	106 (89)	70 (68)	20 (10.4)	0 (0)
Muscle weakness	108 (91)	79 (76)	30 (15.5)	1 (0.8)
Head deformity (frontal bossing)	42 (35.6)	1 (1)	–	0 (0)
Enlarged fontanel	27 (22.9)	–	–	–
Rachitic rosary	2 (1.6)	–	–	–
Harrison groove	5 (4.5)	–	–	–
Respiratory infections and atelectasis	28 (23.7)	9 (8.7)	4 (2.1)	–
Enlargement of wrist and ankles	35 (29.7)	–	–	–
Bowing of tibia and femur	20 (16.9)	–	–	–
Leg pain	4 (3.4)	30 (29.1)	110 (57)	34 (26.4)
Seizures	4 (3.4)	–	–	–
Chest pain	–	2 (1.9)	54 (28)	71 (55)
Obesity	–	6 (5.8)	60 (31)	82 (63)

in older children and adolescents, low vitamin D levels mostly result in nonspecific subtle complaints.

(Torun E et al. JPEM 2015)

frontiers in Endocrinology **2019**

(I. Zakharova et al)

Vitamin D Insufficiency in Overweight and Obese Children and Adolescents

	Vitamin D insufficiency level	Prevalence of vitamin D insufficiency among overweight/obese children	Reference number
AMERICA			
Canada	<50 nmol/L (<20 ng/mL)	5.6% (77.0%–consumption of vitamin D-fortified milk)	(85)
Canada	<75 nmol/L (<30 ng/mL)	**93.0%**	(86)
Canada	<75 nmol/L (<30 ng/mL)	**76.0%**	(87)
Mexico	<75 nmol/L (<30 ng/mL)	36.0%	(88)
USA, *New York*	<50 nmol/L (<20 ng/mL)	55.0%	(89)
USA, *Brooklyn*	<50 nmol/L (<20 ng/mL)	55.2%	(90)
USA, *Alabama*	<50 nmol/L (<20 ng/mL)	78.4%	(91)
USA, Pennsylvania	<75 nmol/L (<30 ng/mL)	**27.8% (5–9 years)** **35.4% (10–14 years)** **50.9% (↑ 15 years)**	(92)
USA, *Wisconsin*	<50 nmol/L (<20 ng/mL)	32.3%	(93)
AFRICA			
Ethiopia	<50 nmol/L (<20 ng/mL)	42.0%	(94)

EUROPE			
Denmark	*Deficiency* <30 nmol/L (<12 ng/mL)	16.5%	(95)
Germany	<75 nmol/L (<30 ng/mL)	**96.0%**	(5)
Greece	<50 nmol/L (<20 ng/mL)	**obesity–60.5%** overweight–51.6	(96)
Norway	<75 nmol/L (<30 ng/mL)	50.0%	(97)
Spain	<75 nmol/L (<30 ng/mL)	morbid obesity–81.1% **obesity–68.2%** **overweight–55.0%**	(98)
Sweden	<50 nmol/L (<20 ng/mL)	33.2%	(99)
The Netherlands	<50 nmol/L (<20 ng/mL)	24.5%	(100)
The Russian Federation, *Arkhangelsk*	<75 nmol/L (<30 ng/mL)	90.0%	(101)
The Russian Federation, *Saint Petersburg*	<75 nmol/L (<30 ng/mL)	**92.0%**	(102)
ASIA			
Iran	<75 nmol/L (<30 ng/mL)	**95.6%**	(103)
Malaysia	<50 nmol/L (<20 ng/mL)	obesity–19.2% overweight–17.4%	(104)
Turkey	25–50 nmol/L (<20 ng/mL)	23.0%	(105)
China	<75 nmol/L	48.6%	(106)

EUROPE			
Denmark	*Deficiency* <30 nmol/L (<12 ng/mL)	16.5%	(95)
Germany	<75 nmol/L (<30 ng/mL)	**96.0%**	(5)
Greece	<50 nmol/L (<20 ng/mL)	**obesity–60.5%** overweight–51.6	(96)
Norway	<75 nmol/L (<30 ng/mL)	50.0%	(97)
Spain	<75 nmol/L	morbid obesity–81.1%	(98)
Sweden			
The Nethe	(<20 ng/mL)		
The Russian Federation, *Arkhangelsk*	<75 nmol/L (<30 ng/mL)	90.0%	(101)
The Russian Federation, *Saint Petersburg*	<75 nmol/L (<30 ng/mL)	**92.0%**	(102)
ASIA			
Iran	<75 nmol/L (<30 ng/mL)	**95.6%**	(103)
Malaysia	<50 nmol/L (<20 ng/mL)	obesity–19.2% overweight–17.4%	(104)
Turkey	25–50 nmol/L (<20 ng/mL)	23.0%	(105)
China	<75 nmol/L	48.6%	(106)

l’aumento dell’1% del BMI determina una diminuzione del 5% dei livelli di 25-OH-D

Fattori di rischio di ipovitaminosi D

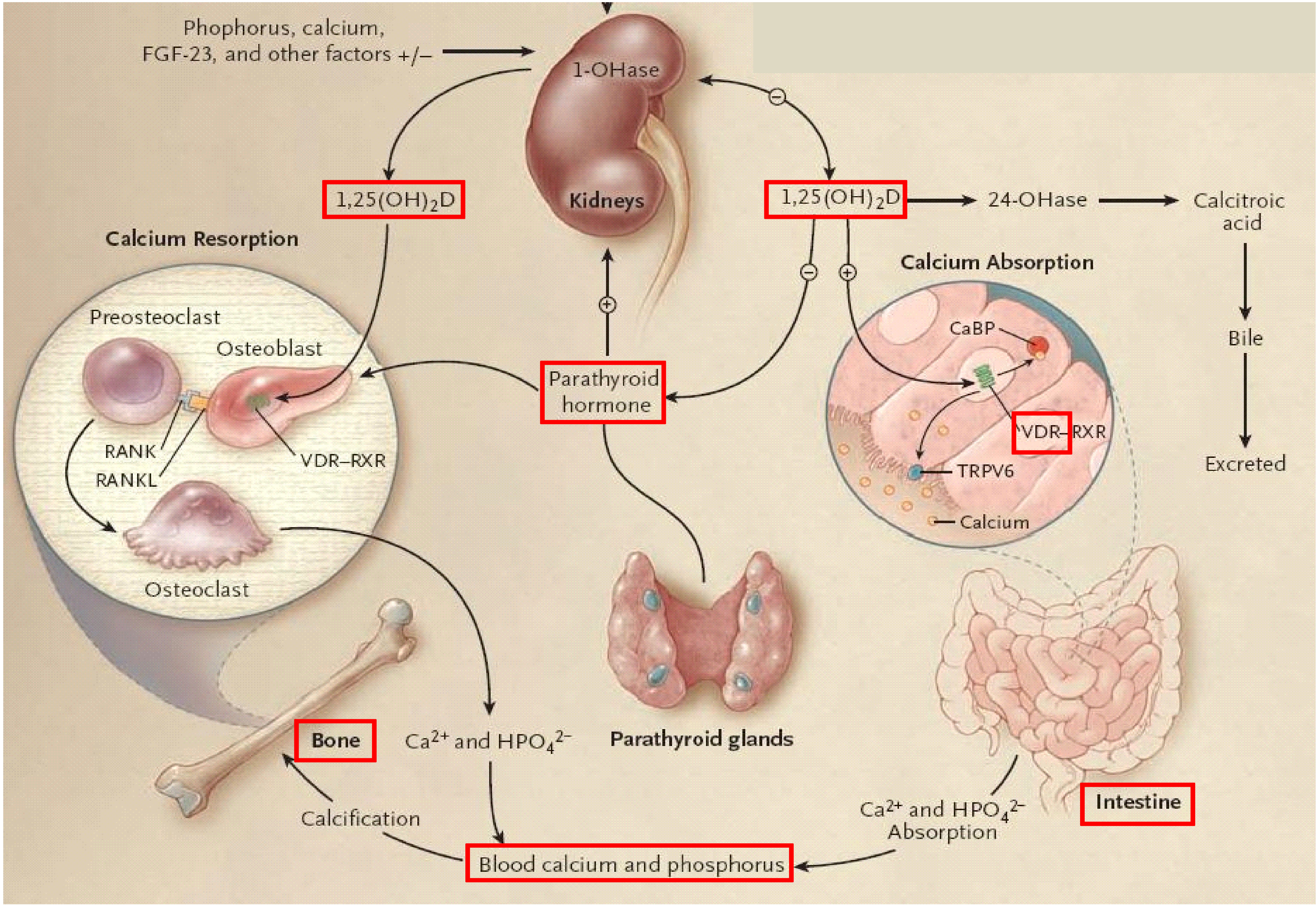
- ridotta esposizione al sole (stili di vita, abbigliamento, aabitudini socio-culturali e religiose)
- fattori che possono influenzare l’efficacia dei raggi solari
- elevata pigmentazione cutanea, etnia
- allattamento al seno esclusivo senza profilassi
- adolescenza
- obesità
- specifiche condizioni patologiche (es. malassorbimenti, ininsufficienza epatica e renale)
- farmaci interferenti con il metabolismo della vitamina DD (antiepilettici, corticosteroidi)

condizioni cliniche associate/correlate con ipovitaminosi D

Condizioni cliniche correlate con le azioni scheletriche della vitamin D

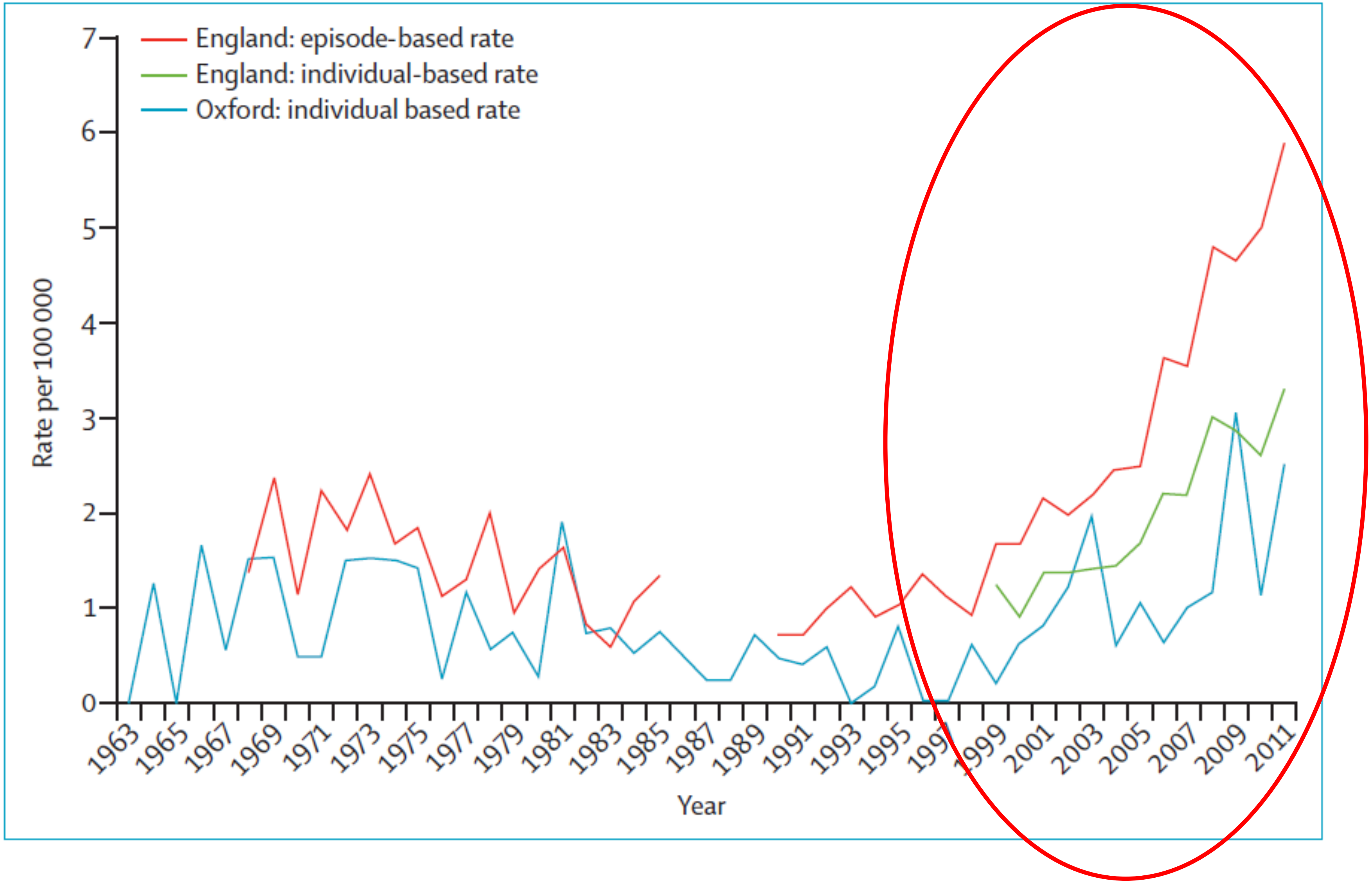
1) *rachitismo*
2) *inadeguata acquisizione della massa ossea*

Vitamin D skeletal actions



(MF Holick. NEJM)

Hospitalization for children with rickets in England: a historical perspective



(*Goldacre et al. Lancet 2014)*

ADC Online First, published on April 16, 2018 as 10.1136/archdischild-2018-314826

Review

Prevention of rickets and osteomalacia in the UK: political action overdue

Suma Uday,[1,2] Wolfgang Högler[1,2]

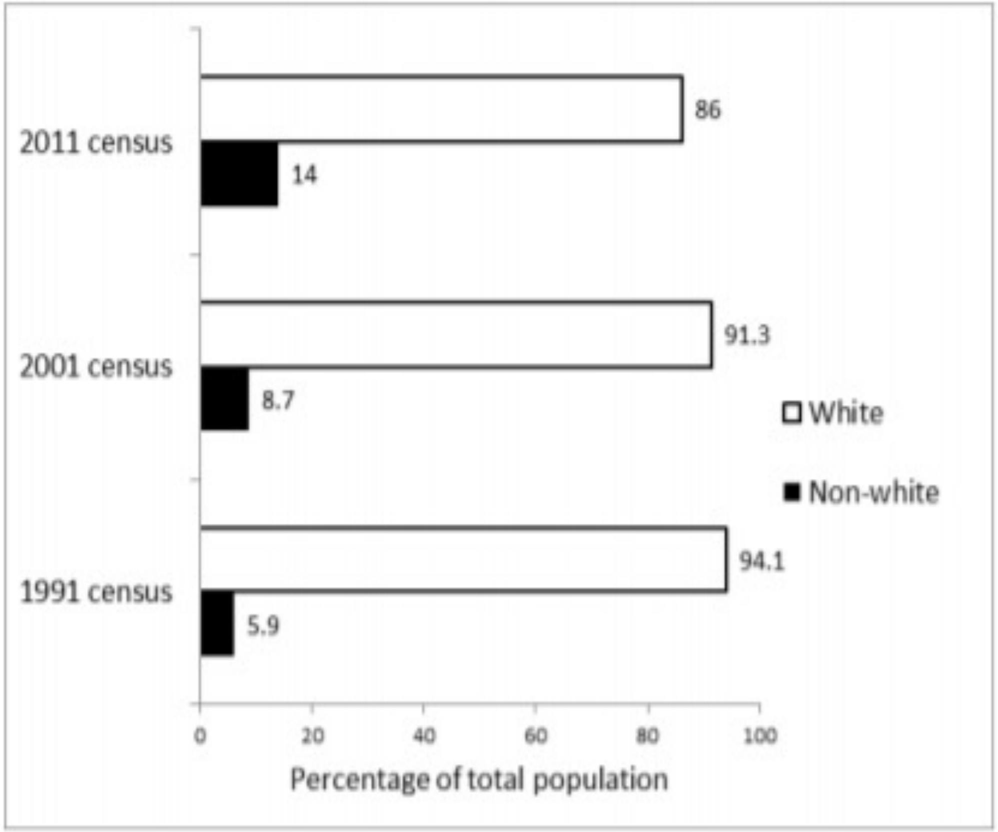


Figure 1 Census data (1991–2011) demonstrating an upward trend in the proportion of non-white population and a downward trend in the proportion of white population. Data from national statistics.[10]

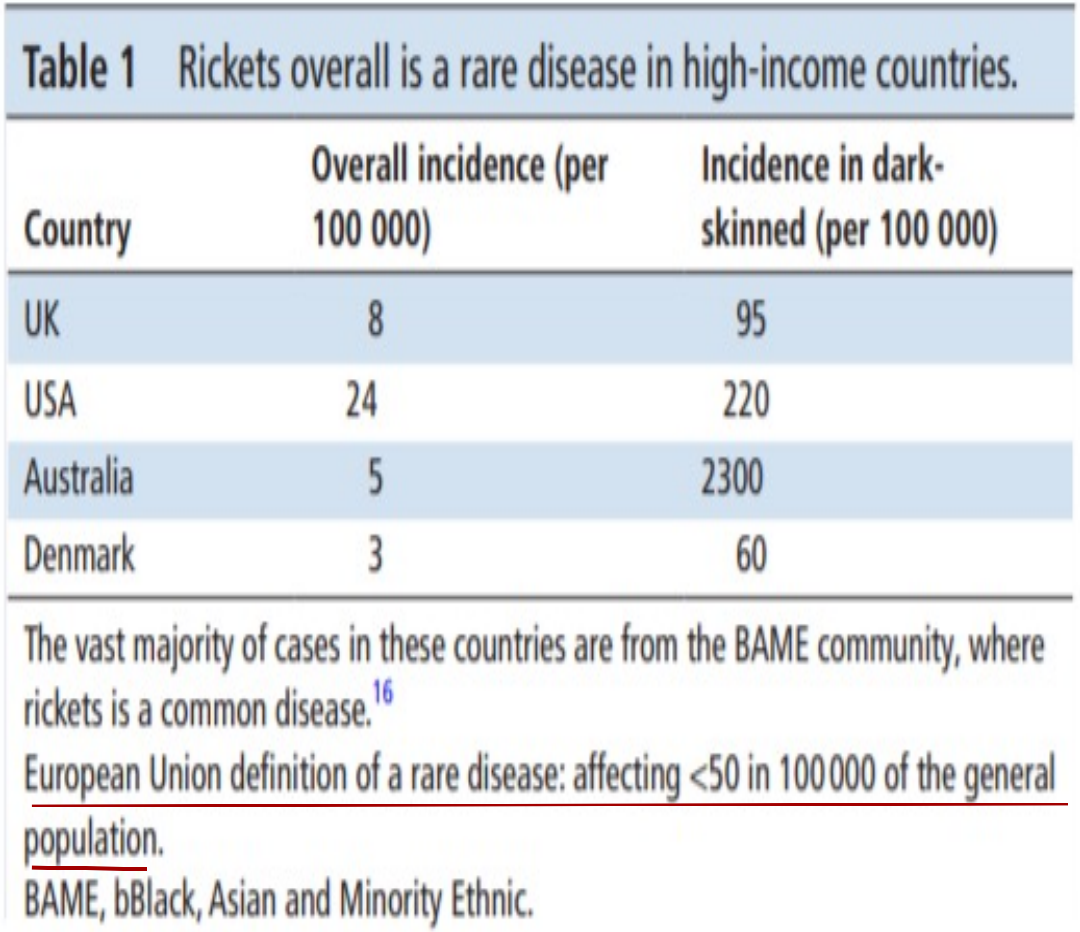


Table 1 Rickets overall is a rare disease in high-income countries.

Country	Overall incidence (per 100 000)	Incidence in dark-skinned (per 100 000)
UK	8	95
USA	24	220
Australia	5	2300
Denmark	3	60

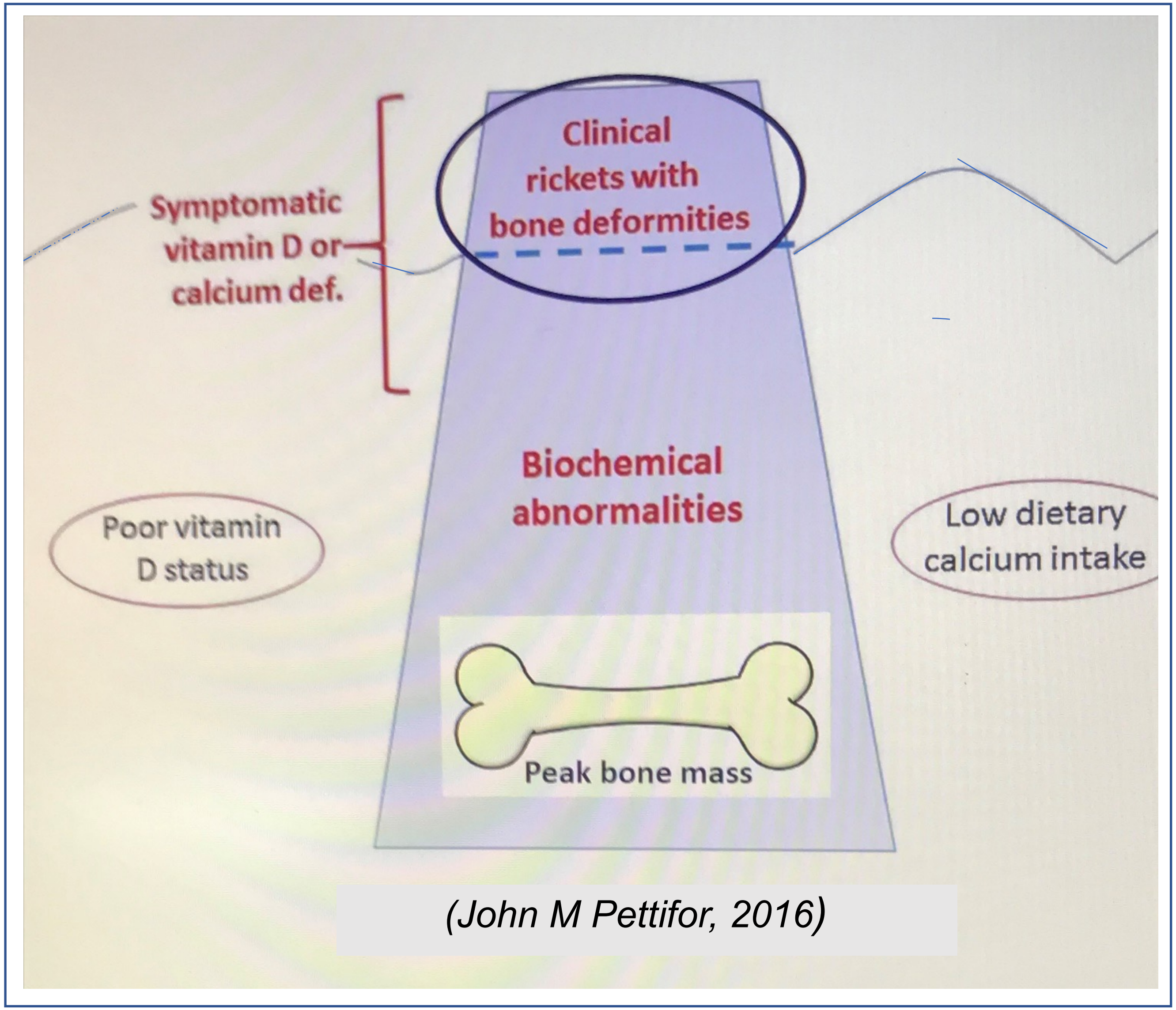
The vast majority of cases in these countries are from the BAME community, where rickets is a common disease.[16]

European Union definition of a rare disease: affecting <50 in 100 000 of the general population.

BAME, bBlack, Asian and Minority Ethnic.

(Uday S, Hogler W, Arch Dis Chid 2018)

The rickets «iceberg»

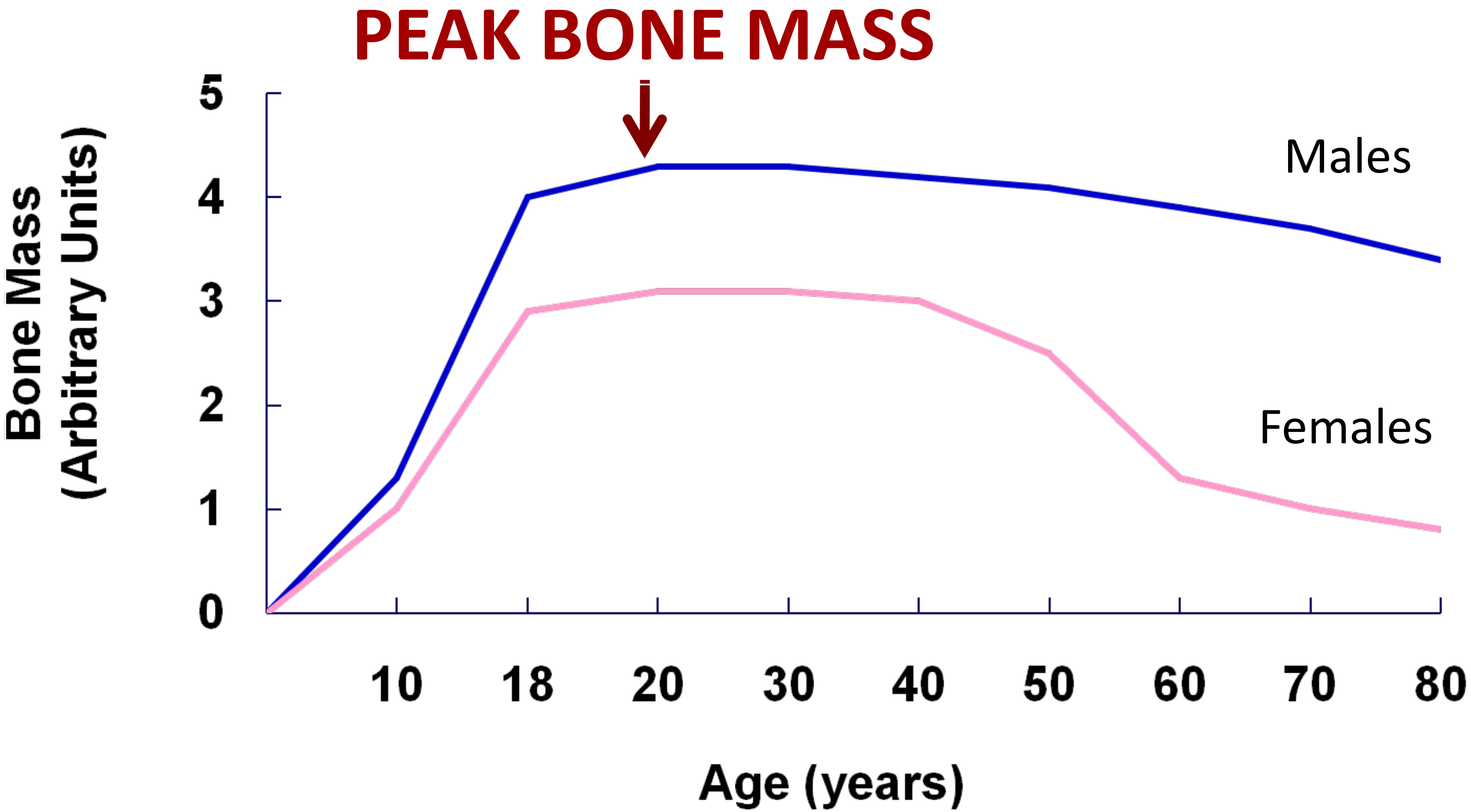


(John M Pettifor, 2016)

Condizioni cliniche correlate con le azioni scheletriche della vitamin D

1) *rachitismo*
2) *inadeguata acquisizione della massa ossea*

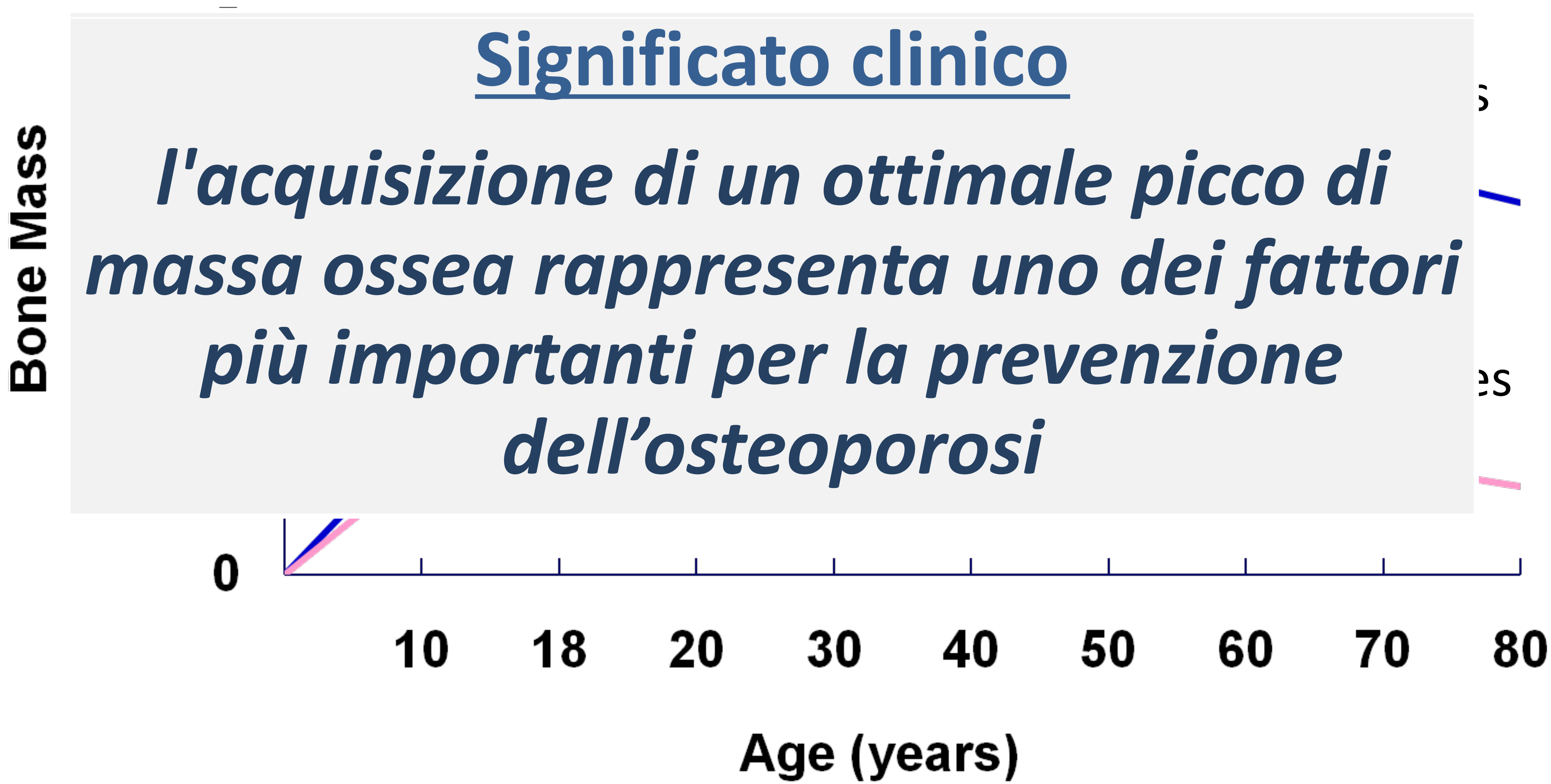
Changes in bone mass with age



PEAK BONE MASS

(Cooper C. 1990)

Changes in bone mass with age



Significato clinico

l'acquisizione di un ottimale picco di massa ossea rappresenta uno dei fattori più importanti per la prevenzione dell’osteoporosi

(Cooper C. 1990)

Vitamin D status as a determinant of peak bone mass

Relationship between peak bone mass and 25-OH-D levels in young Finnish men

(n = 220, age 18.3 - 20.6 y)

(Valimaki et al. JCEM 2014)

Skeletal site	***p***
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

The relation between 25-hydroxyvitamin-D with peak bone mineral density in healthy young adults (n = 464, age 17-31 yrs)

25-OH-D levels were related to the achievement of peak bone mass.

(Boot AM et al. J Pediatr Endocr Met 2011)

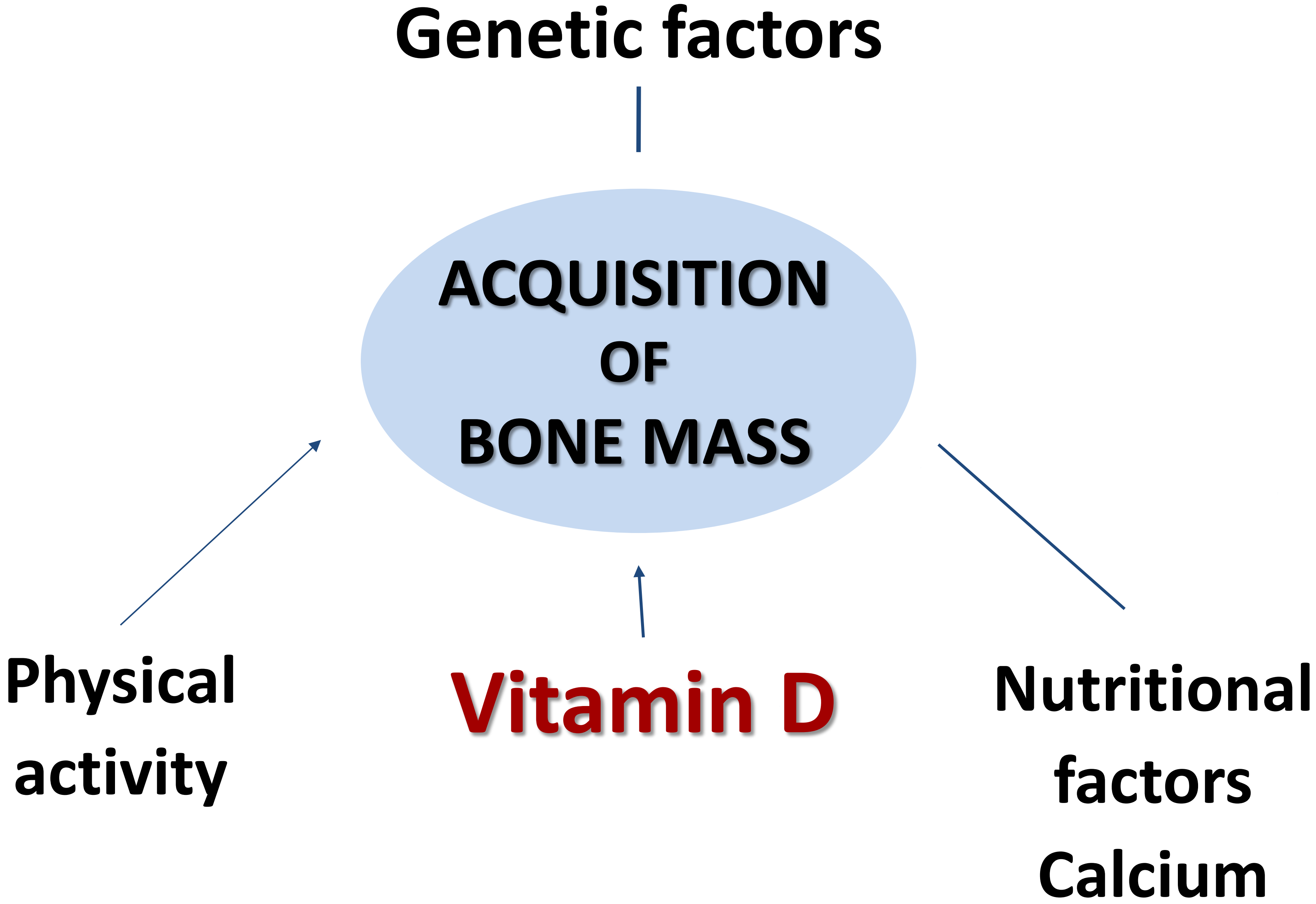
"Mechanostat theory" (Frost, 1994)

muscolo

- *livelli intracellulari di calcio*
- *proteine contrattili*

Vitamin D

massa ossea



Genetic factors

ACQUISITION
OF
BONE MASS

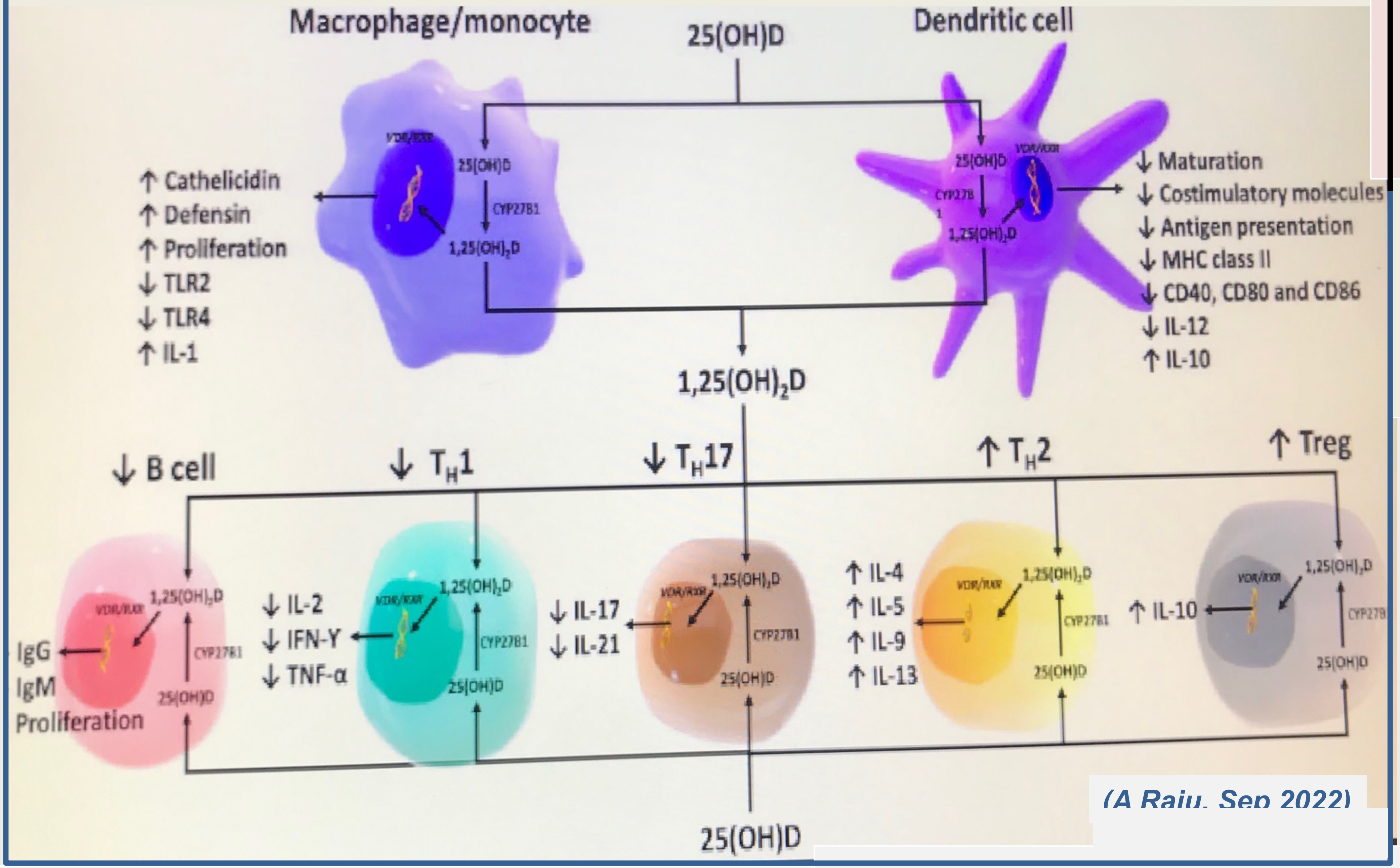
Physical
activity

Vitamin D

Nutritional
factors
Calcium

Condizioni cliniche associate/correlate con le azioni extra-scheletriche delle Vitamina D

1) ***infezioni, infezioni respiratorie***
2) ***asma***
3) ***malattie allergiche***
4) ***patologie autoimmuni***
5) ***obesità***



(A Raju, Sep 2022)

Vitamin D & extraskeletal actions – association studies

D Zissi, Hormones. 2019; 18(4): 353-363

The association between vitamin D status and infectious diseases of the respiratory system in infancy and childhood: a systematic review.

The review included studies on tuberculosis, OM, URTI, rhinosinusitis, URTI, LRTI, influenza. Most studies agree in that decreased vitamin D concentrations are prevalent among most infants and children with RTIs. However, studies with vitamin D supplementation revealed conflicting results.

A Raju et al. Cureus. 2022 Sep;14(9)

Role of Vitamin D Deficiency in Increased Susceptibility to Respiratory Infections Among Children: A Systematic Review.

This systematic review concluded that children with low vitamin D levels are prone to developing respiratory infections. But a conclusive association between the severity of respiratory infections and low vitamin D levels was not found.

Vitamin D & extraskeletal actions - association studies

Association between serum Vitamin D levels and asthma severity and control in children and adolescents. *AP Malhero et al. Pediatric Asthma, Febr 2023*

There is no evidence of association between serum vit D levels and asthma control in children and adolescents. However, vit D and lung function were positively correlated and the group with vit D insufficiency had a higher prevalence of severe asthma

Pre- and postnatal vitamin D status and allergy outcomes in early childhood. *K Reuter et al. Biomedicines, 2022*

This review indicates that there are inconsistent results in observational studies regarding associations between 25(OH)D and allergy outcomes in childhood. Furthermore, to date, no sufficiently powered intervention studies have investigated the effect of vitamin D supplementation and status in the prenatal nor early postnatal period on allergic disease development in early childhood.

Association of 25-hydroxy vitamin D with asthma and its severity in children: a case–control study. *A. Sharif et al. Clinical and Molecular Allergy 2020*

Lower level of 25(OH) vit. D correlated with the higher severity of asthma manifestations. Therefore, it is recommended that 25(OH) vit. D levels get routinely checked especially in severe asthma cases and if the deficiency presents, appropriate therapeutic measures be used to reduce the asthma severity

Six-Year Follow-up of a Trial of Antenatal Vitamin D for Asthma Reduction

Litonjua et al 2020

We previously reported (VDAART Study) that prenatal vitamin D supplementation to prevent asthma and recurrent wheeze in young children, provided a protective effect ***at the age of 3 yrs****., mainly iin mothers with baseline 25-OH-D > 30 ng/mL*

This follow-up study, was aimed to determine whether children born to mothers who had received 4,400 IU of vitamin D_3 per day during pregnancy (vitamin D group) would have a lower incidence of asthma and recurrent wheeze **at the age of 6 years** than would those born to mothers who had received 400 IU of vitamin D_3 per day (control group). **There was no effect of maternal vitamin D supplementation on asthma and recurrent wheeze at the age of 6 yrs with stratification according to the maternal 25-hydroxyvitamin D level during pregnancy.**

nutrients **Thorsteinsdottir V et al 2020**

Neonatal Vitamin D Status and Risk of Asthma in Childhood: Results from the *D-Tect Study*

Case (911) - cohort (1424) study. **Results suggest that higher neonatal vitamin D concentration may reduce the risk of developing childhood asthma at ages 3–9 years**, indicating that neonatal vitamin D status as a proxy of vitamin D status during the prenatal period is important for normal immune- and lung development.

Vitamin D & extraskeletal actions - positive effect

- **Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised and controlled trials.** *Jolliffe DA et al, Lancet Diabetes Endocrinol, 2021*

- **Vitamin D supplementation and lower respiratory tract infection in infants: a case-control study.** *Hong M et al. Infection May 2022*

- **Vitamin D can safely reduce exacerbations among corticosteroid-using children and adults with asthma: a systematic review and meta-analysis***. Chen Z et al Nutrition Research, 2021.*

- **Serum Vitamin D level and efficacy of Vitamin D supplementation in children with atopic dermatitis: a systematic rewiev and meta-analysis**. *Hongo Fu et al. Hindawi 2022*

- **Neonatal Vitamin D and risk of asthma in childhood: results from the D-Tect study.***Thorsteinsdottir V et al. Nutrients 2020*

- **Low gestational vitamin D level and childhood asthma are related to impaired lung function in high-risk children**. *Knihtila HM et al J Allergy Clin Immunol, 2021*

Vitamin D & extra-skeletal actions - no/uncertain effect

The Effect of Vitamin D Supplementation in Children With Asthma: A Meta-Analysis

M Hao et al, Front Pediatr Jun 2022

Vitamin D supplementation significantly increased patients' serum vitamin D levels, but it had no benefit for asthma control. It is essential to systemically search for more large-scale, rigorous, and well-designed RCTs to fully confirm these conclusions

Vitamin D supplementation in pregnant women or infants for preventing allergic diseases: a systematic review and meta-analysis of randomized controlled trials. *C Luo et al. Clin Med J, 2022*

Supplementation of vitamin D in pregnant women or infants does not have an effect on the primary prevention of allergic diseases

Vitamin d supplementation and allergic diseases during childhood: a systematic review and meta-analysis. *Q Li et al. Nutrients, October 2022*

Vit D supplementation did not reduce asthma exacerbation risk in children overall, but may reduce asthma exacerbation risk in children with serum 25(OH)D concentration < 10 ng/mL. Vit D supplementation reduces the severity of atopic dermatitis and symptoms of allergic rhinitis in children.

Vitamin D supplementation in primary allergy prevention: Systematic review of randomized and non-randomized studies. *J.J. Ypes-Nunez et al. Allergy, 2018*

Limited information is available addressing primary prevention of allergic diseases after vitamin D supplementation, and its potential impact remains uncertain

Vitamin D & extra-skeletal actions - uncertain/no effect

- **Vitamin D supplementation for the prevention of childhood acute respiratory infections: a systematic revue of RCT.** *L Xiao et al. Br J Nutr 2016*
- **Vitamin D supplementation for preventing infections in children under five years of age.** *MY Yakoob et al. Cochrane Database, 2016*
- **25-hydroxyvitamin D supplementation and health-service utilization for upper respiatory tract infection in young children.** *Omand JA et al. Public Health Nutrition, 2019*
- **Vitamin D and asthma in children: a systematic review and meta-analysis of observational studies.** *Jat KR et al. Lung 2017*
- **Effect of Vitamin D supplementation to reduce respiratory infections in children and adolescents. A randomized controlled trial.** *M Loeb et al Influenza, 2019*
- **Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study).** *Litonjua A. et al. NEJM 2020*
- **Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life.** *Loo El et al. Pediatric Allergy and Immunology, 2018*
- **The role of Vitamin D in respiratory allergies prevention. Why the effect is so difficult to disentangle?** *Sikorska-Szaflik H et al, Nutrients, 2022*
- **Prevention of recurrent respiratory infections: intersociety Consensus.** *E. Chiappini et al. Ital J Pediatr, 2021*

Is vitamin D deficiency a risk factor for Covid-19 in children ?

(K Yilmaz, V Sen , Dec 2020 , Pediatr Pulmonol)

45 controls, mean age 6.3 years Vit. D 34,8 ng/ml

40 Covid-19, mean age 8,5 years Vit. D 13,1 ng/ml

-vitamin D levels were significantly lower in Covid-19 vs controls

-vitamin D ilevels were in range of severe deficiency (≤ 12 ng/ml) in Covid-19 with symptoms (fever, cough)

<u>The causal role of Vitamin D deficiency has to be demontrated</u>

Association of vitamin D and severity of COVID-19 in children

(Karimian P et al. Eur J Transl Myol , 2022)

Cross-sectional study performed on **101 COVID 19 infected children** (average age 2.85 ± 0.85 year)

Clinical signs in cases with deficient vitamin D levels were more severe in terms of tachypnea and tachycardia (p = 0.01) and gastrointestinal symptoms; children with vitamin D lower than 10 ng/ml showed more frequency (p = 0.02). .

Vitamin D extra-skeletal actions

remarks

- Results from studies (most observational) on Vitamin D in pediatric extra-scheletal conditions gave mixed results.
- At present caution must be given in attributing a causative role to Vitamin D and in recommending the routine use of vitamin D in such conditions
- Neverthless data of studies emphasize the importance of mantaining normal levels of Vitamin D in such conditions.

(Saggese G. Congresso Naz. Farmacologia, Roma 16-19 novembre 2022)

CONSENSUS SIPPS 2023

Azioni extra-scheletriche della Vitamina D in età pediatrica

Consensus azioni extra-scheletriche Vitamina D

Gruppo EBM (C. Verga, M. Bergamini, G. Simeone, L. Terracciano)

TOPICS

- Infezioni respiratorie e altre malattie infettive
  (infezioni alte e basse vie respiratorie, infezioni respiratorie ricorrenti, polmoniti, bronchioliti, influenza, OMA).
- Asma
- Patologie allergiche *(dermatite atopica, rinite, allergie alimentari)*
- Patologie autoimmuni *(diabete tipo 1, artrite idiopatica giovanile, endocrinopatie, ecc.).*
- Obesità, sindrome metabolica: *(resistenza all'insulina, profilo lipidico, rischio cardiovascolare).*
- Malattie intestinali *(malattia celiaca, malattie croniche intestinali-MICI)*

Vitamina D:
dosi, modi di somministrazione

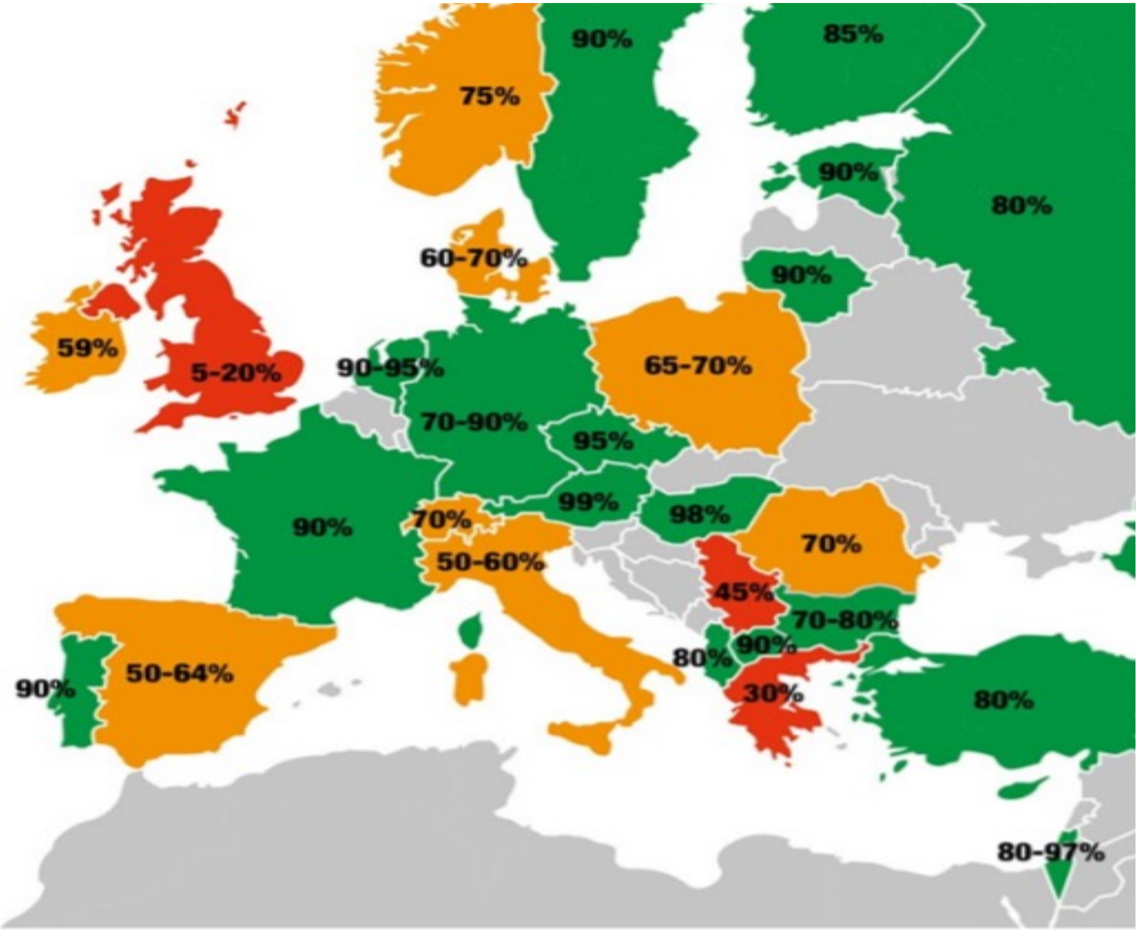
Vitamina D nella pratica del Pediatra
primo anno di vita

Tutti i bambini devono ricevere la profilassi con Vitamina D alla dose di 400 UI al giorno, indipendentemente dal tipo di allattamento (materno o formula).

ADC Online First, published on April 16, 2018 as 10.1136/archdischild-2018-314826

Prevention of rickets and osteomalacia in the UK: political action overdue

Suma Uday,[1,2] Wolfgang Högler[1,2]



Adherence rates for infant vitamin D supplementation in the first year of life in Europe, with UK reporting the lowest rates.[13] Good adherence (≥80% of infants supplemented) is indicated in green, moderate adherence (79%–50%) in orange and low adherence (<50%) in red.

Vitamina D nella pratica del Pediatra
dopo il primo anno, fino al 18° anno

- ☐ **Deve essere garantito un approvvigionamento di 600 UI di Vitamina D al giorno.**
- ☐ **La profilassi deve essere individualizzata in ciascun bambino, con una particolare attenzione alla presenza di fattori di rischio come la scarsa esposizione alla luce solare, l'etnia, l'adolescenza, l'obesità e specifiche patologie croniche.**
- ☐ **Il "mandato" del Pediatra è dunque quello di valutare clinicamente (anamnesi, stili di vita, esame clinico) l'opportunità della supplentazione, in modo particolare da novembre ad aprile.**

Profilassi con Vitamina D dopo il 1° anno nei bambini e negli adolescenti

modo di somministrazione

- ☐ **giornaliero = 600 UI**
- ☐ settimanale = 4.000 UI

- **nei bambini e adolescenti obesi = 1.000-1.500 UI al giorno (sec. BMI)**

- **non utilizzare i metaboliti attivi della Vitamina D**

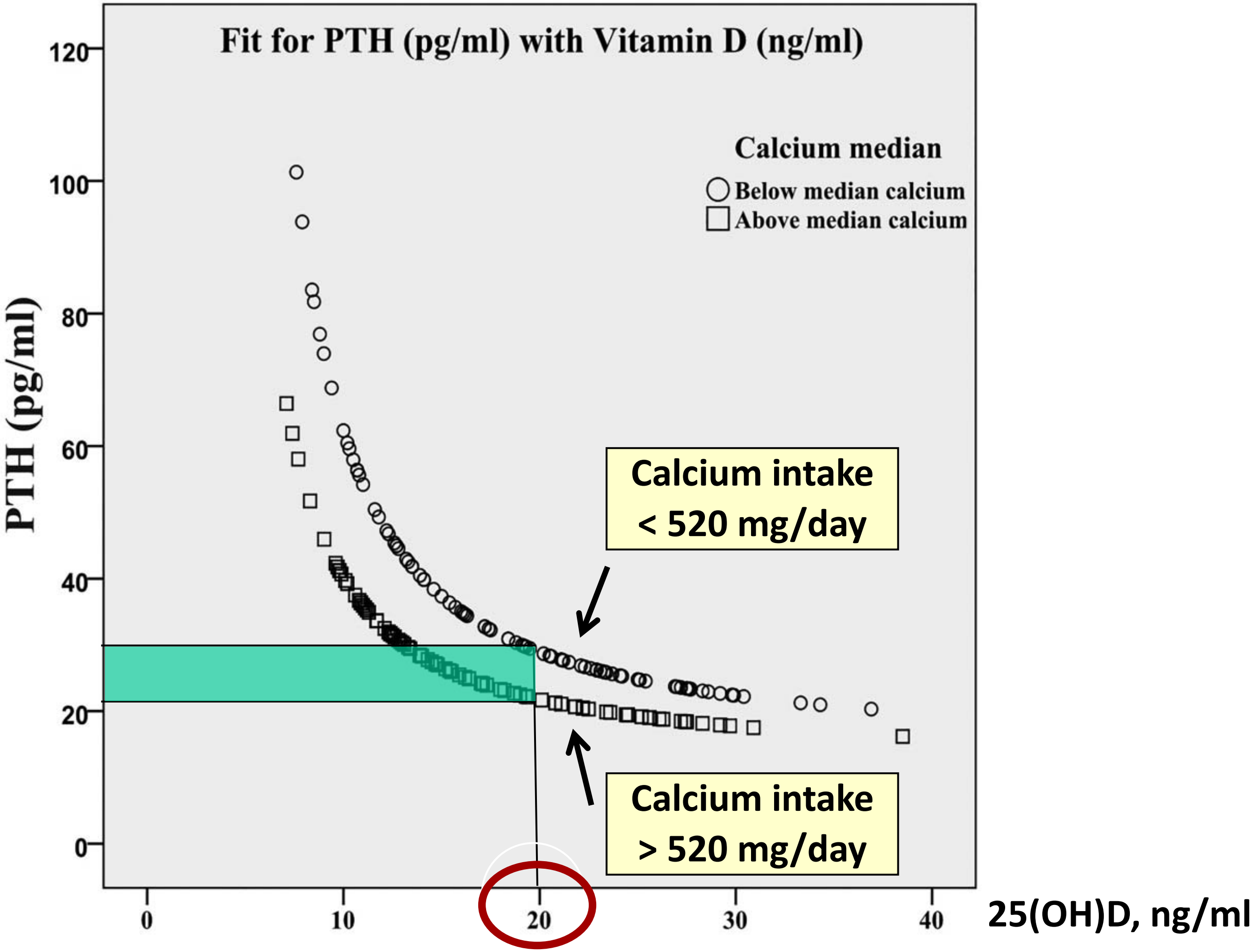
Calcio

Calcio

insieme alla Vitamina D è essenziale per la salute ossea di bambini e adolescenti

Dietary calcium intake, serum 25(OH)D and PTH concentration

(n = 181, 10-14 yr)



Calcium intake < 520 mg/day

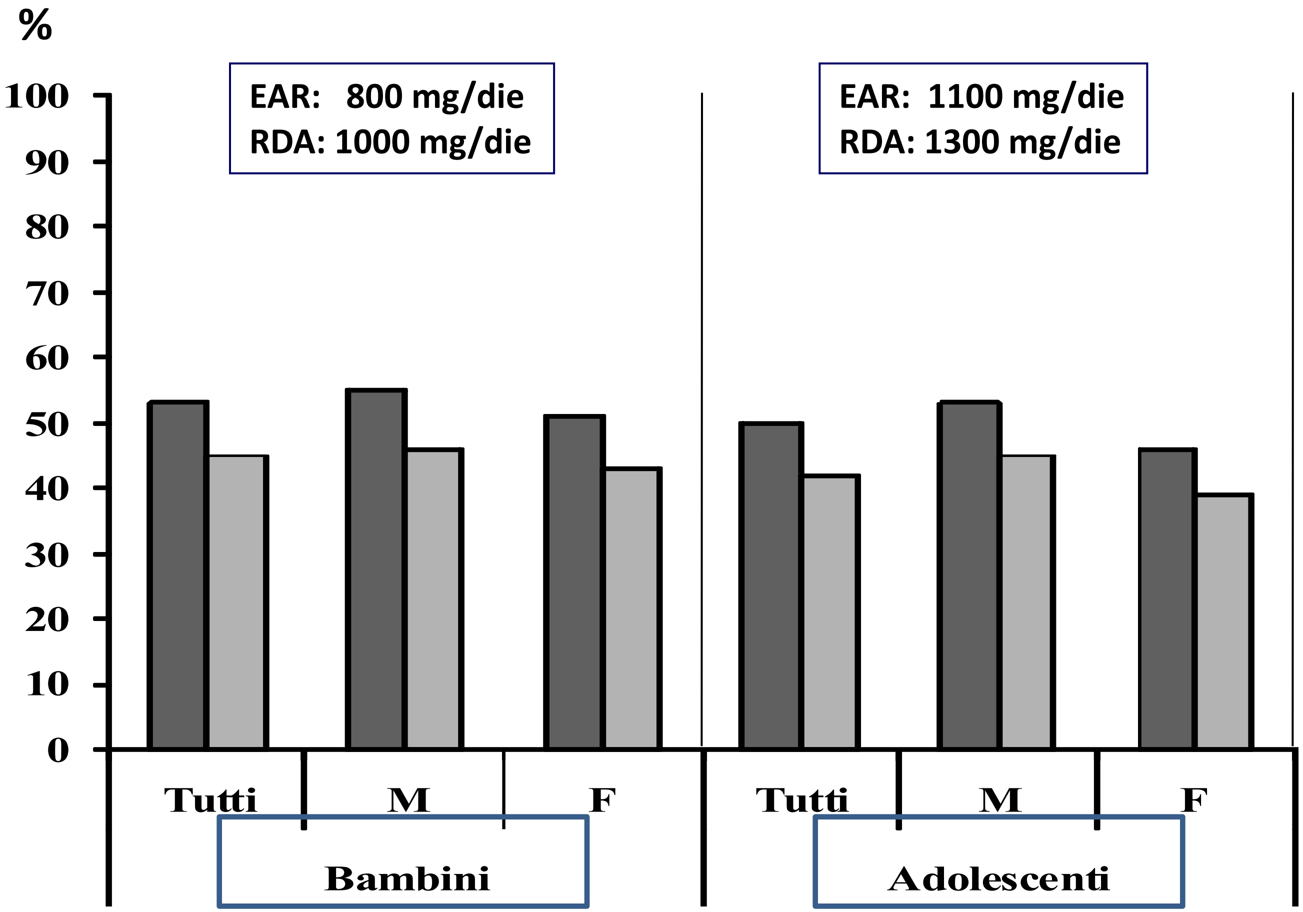
Calcium intake > 520 mg/day

- Dietary calcium intake modifies the relationship between 25(OH)D and PTH concentrations.
- Dietary calcium intake should be taken into account when assessing an individual's vitamin D status.

(Patel et al. Arch Dis Child 2016)

Calcium intake as percentage of recommended needs (IOM 2010)

Dept. of Pediatrics, Pisa University (n = 742; M = 384; F = 358))



n = 117 (4.0-8.9 aa)

n = 225 (9.0-18.0 aa)

● EAR % (Estimated Average Requirement)

● RDA % (Recommended Dietary Allowance)

Vitamin D deficiency rickets treatment (1)

Vitamin D

- Daily administration of 1.000 - 10.000 IU of vitamin D for a 2- to 3-month period:
    - 1.000 IU/day for infants <1 month old
    - 1.000 to 5.000 IU/day for infants 1 to 12 months old
    - > 5.000 IU/day for children >12 months old.

  Once radiologic evidence of healing is observed, the dose of vitamin D can be reduced to 400 IU/day.

- In case of poor compliance, high single dose of vitamin D: 100.000–200.000 IU (either intramuscular injection or as oral dose) which can be repeated every 1-3 months, until radiological healing of rachitic lesions and then followed by vitamin D supplementation at 400 IU/day

Vitamin D deficiency rickets treatment (3)
Management

What to expect

1 – 2 weeks	Normalization of **calcium** and **phosphorus**
1 – 2 months	Normalization of **25-OH-D and PTH**
2 – 3 months	**Complete radiological healing** • Changes may be seen in 1 week • Evidence of healing already present within 4 weeks • First sign is the appearance of the provisional zone of calcification

What to monitor

1 month	**Calcium, phosphorus, ALP**
3 months	• **Calcium, phosphorus, magnesium, ALP, PTH, 25-OH-D** • Repeat **X-rays** • Consider urine sample → **calcium/creatinine ratio**
1 year and yearly	**25-OH-D**

- ALP is a convenient biochemical marker: always ↑in vitamin D deficiency rickets + slow ↓to normal with therapy. Remember ALP may actually initially ↑ during therapy as bone formation rates increase.
- If no radiographic evidence of healing by 3 months, consider malabsorption, liver disease or lack of compliance.

(Pettifor JM et al, Clin Endocrinol and Metab 2011)
(Misra M, Pediatrics 2008)

Vitamin D deficiency rickets treatment (2)
Calcium

- **Latent hypocalcemia**:

oral calcium therapy (35-75 mg/Kg/day over 2-3 doses).

- **Symptomatic hypocalcemia**:

5-20 mg of elemental calcium/kg (0.5-2 ml/kg if using calcium gluconate 10%) e.v. in 5-10 minutes (repeatable, if necessary, every 4-6 hours).

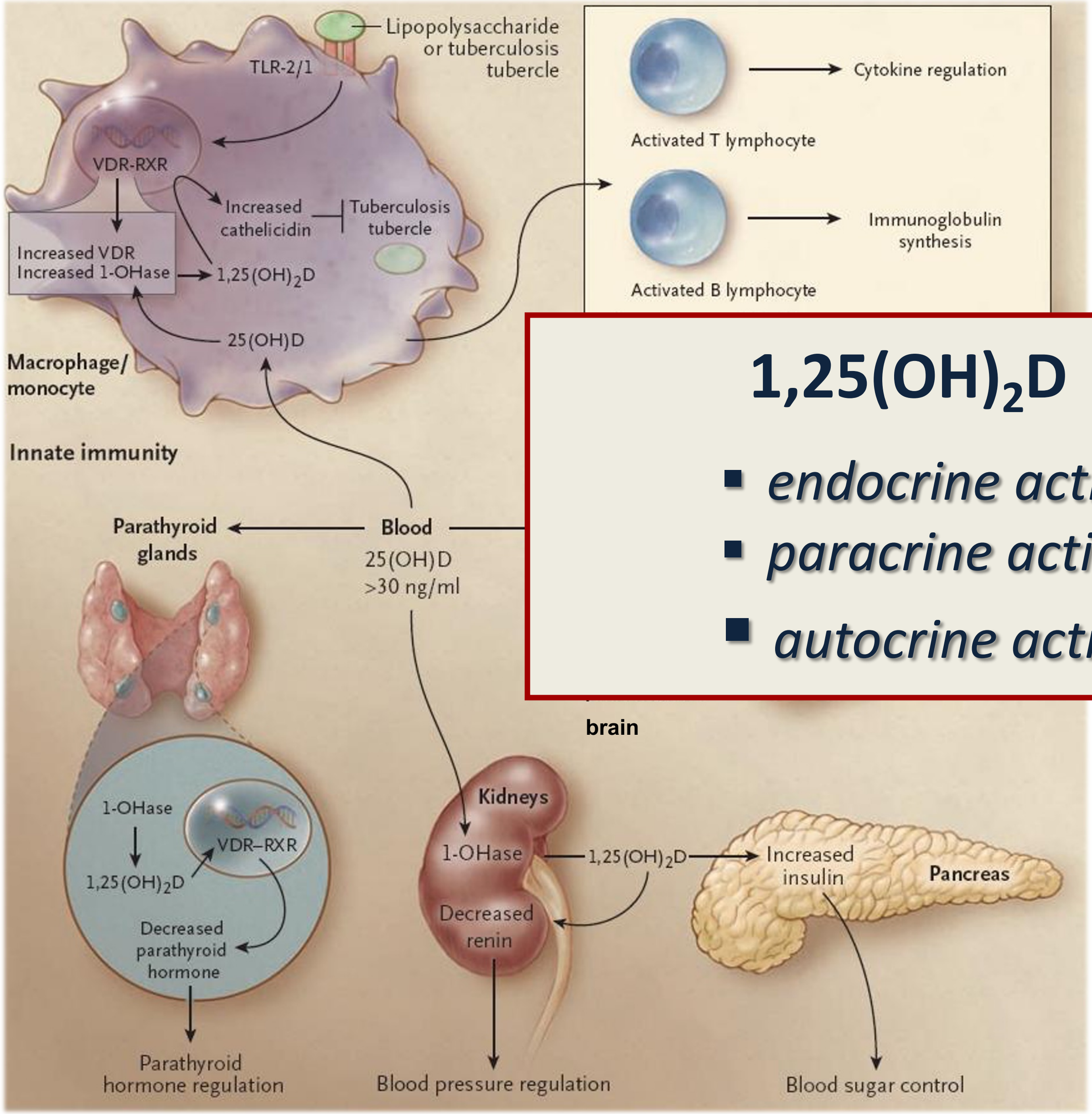
After normalization of serum calcium, oral calcium (35-75 mg/kg/day over 2-3 doses).

Oral calcium supplementation may be useful even in presence of normocalcemia, in order to prevent the "hungry bone syndrome", until the normalization of serum PTH and 25-OH-D .

Quando richiedere il dosaggio della Vitamina D

- sospetto deficit di Vitamina D in presenza di sintomi (es. segni di rachitismo, storia di fratture)
- patologie croniche (malassorbimento: MICI, celiachia, malattie epatiche e renali)
- terapie croniche interferenti con il metabolismo della Vitamina D (antiepilettici, corticosteroidi)

Vitamin D extra-skeletal actions



$1,25(OH)_2D$

- *endocrine action*
- *paracrine action*
- *autocrine action*

$1,25(OH)_2D$:

- controls directly or indirectly up to 1,250 genes;
- regulates cellular proliferation differentiation; induces ptosis and inhibits ogenesis (reducing risk of er);
- ts an immunomodulatory n, reducing risk of autoimmune diseases;
- promotes innate immunity, reducing risk of recurrent infections.

(Holick MF, NEJM)

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Global Consensus on Recommendations on Vitamin D in Children and Adolescents

Vitamin D deficiency is a preventable global public health problem in infants, children and adolescents. Vitamin D supplement should be incorporated into childhood primary health care programs along with immunization.

(Munns C.F. et al. J Clin Endocrinol Metab, 2016)

Journal of Paediatrics and Child Health 2015

Jason KG Tan,[1,2] Paula Kearns,[3] Andrew C Martin[1] and Aris Siafarikas[1]

Randomised controlled trial of daily versus stoss vitamin D therapy in children

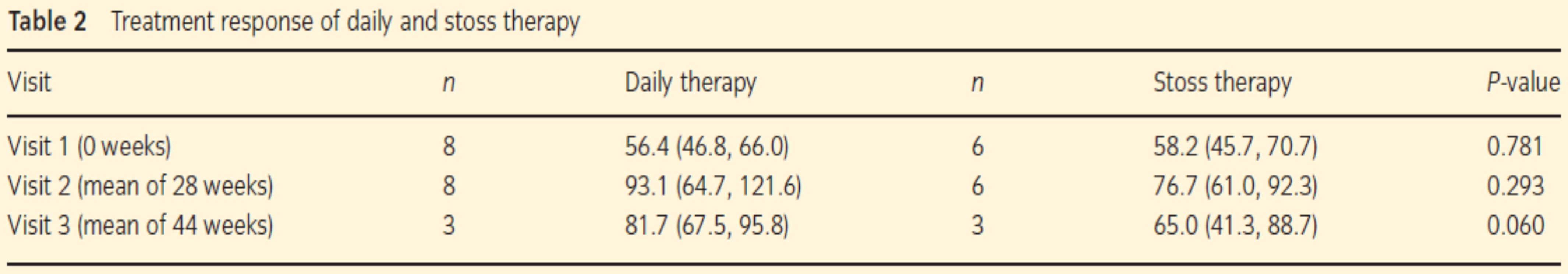


Table 2 Treatment response of daily and stoss therapy

Visit	*n*	Daily therapy	*n*	Stoss therapy	*P*-value
Visit 1 (0 weeks)	8	56.4 (46.8, 66.0)	6	58.2 (45.7, 70.7)	0.781
Visit 2 (mean of 28 weeks)	8	93.1 (64.7, 121.6)	6	76.7 (61.0, 92.3)	0.293
Visit 3 (mean of 44 weeks)	3	81.7 (67.5, 95.8)	3	65.0 (41.3, 88.7)	0.060

- **Participants with a 25(OH)D level less than 78 nmol/L were randomised to receive daily (2.500-5.000 IU) or stoss (100.000-200.000 IU) vitamin D therapy with follow-up at 4–6 months and 9–12 months.**
- **73 participants were enrolled**
- **25(OH)D levels were less than 78 nmol/L in 43/73 (59%) participants. Of these, 34/43 (79%) were insufficient (50–78 nmol/L), 8/43 (19%) mildly deficient (27.5–50 nmol/L) and 1/43 (2%) deficient (<27.5 nmol/ L).**
- **Daily vitamin D therapy had a higher average increase in 25(OH)D levels from baseline than stoss therapy; however, this was not significant.**

Authors propose that oral stoss therapy could be used to treat vitamin D deficiency; however, research to evaluate the optimal dose and schedule is required before widespread use.

Efficacy and safety of a single monthly dose of cholecalciferol in healthy school children

Kuchay MS, et al.

J Pediatr Endocrinol Metab. 2016

- 118 children received vitamin D supplementation in the form of oral cholecalciferol 60,000 IU monthly.
- Serum calcium and 25-hydroxyvitamin D (25OHD) levels were estimated at 0 and 12 months.
- The proportion of subjects achieving vitamin D sufficiency was assessed.

The mean 25OHD levels increased significantly from 12.04±5.27 ng/mL at baseline to 32.6±7.05 ng/mL after 12 months of supplementation (p<0.001). None developed hypercalcemia.

Vitamin D supplementation in the doses of 60,000 IU monthly is a reasonable, safe and cost-effective regimen for children to attain and maintain vitamin D sufficiency.

Consensus azioni extra-scheletriche Vitamina D

TOPICS

- Gruppo EBM (C. Verga, M. Bergamini, G. Simeone)
- Infezioni respiratorie e altre malattie infettive
- *(infezioni alte e basse vie respiratorie, infezioni respiratorie ricorrenti, polmoniti, bronchioliti, influenza, OMA).*
- Asma
- Patologie allergiche *(dermatite atopica, rinite, allergie alimentari)*
- Patologie autoimmuni *(diabete tipo 1, artrite idiopatica giovanile, endocrinopatie, ecc.).*
- Obesità, sindrome metabolica: *(resistenza all'insulina, profilo lipidico, rischio cardiovascolare).*
- Malattie intestinali *(malattia celiaca, malattie croniche intestinali-MICI)*

Consensus azioni extra-scheletriche Vitamina D

Topics / Working group experts

Gruppo EBM: *Carmen Verga, Marcello Bergamini, Giovanni Simeone*

Infezioni respiratorie e altre malattie infettive (alte e basse vie respiratorie, infezioni respiratorie ricorrenti, polmoniti, bronchioliti, influenza, OMA).

Fabio Cardinale, Elena Chiappini, Susanna Esposito, Alfredo Guarino, Michele Miraglia del Giudice , Nicola Principi.

Asma

Carlo Caffarelli, Luciana Indinnimeo, Giorgio Piacentini, Luigi Terracciano (qui?)

Patologie allergiche (dermatite atopica, rinite, allergie alimentari)

Roberto Berni Canani (?), Iride Dello Iacono, Alessandro Fiocchi, Daniele Ghiglioni, Diego Peroni

Patologie autoimmuni (diabete tipo 1, artrite idiopatica giovanile).

Dario Iafusco, Lucia Leonardi, Ravelli Angelo

Obesità, sindrome metabolica: effetti della supplementazione con Vitamina D sulle conseguenze metaboliche dell'obesità infantile (resistenza all'insulina, profilo lipidico e rischio cardiovascolare).

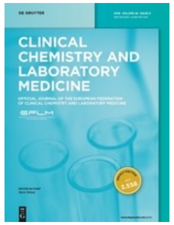
Gianni Bona, Margherita Caroli, Maffeis Claudio (?), Emanuele Miraglia del Giudice

Malattie intestinali (malattia celiaca, malattie croniche intestinali-MICI):

Lionetti Paolo, Strisciuglio Caterina, Troncone Riccardo

Factors influencing 25-OH-D levels

- *ethnicity*
- *body mass index (BMI)*
- *latitude*
- *season*
- *UVB radiation*
- *vitamin D supplementation*
- *genetic factors (DBP polymorphisms)*
- *25-OH-D epimers*
- *assay method (CLIA, RIA, Tandem Mass)*



CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Assessment of vitamin D status - a changing landscape.
Herrmann M et al Clin Chem Lab Med, 2017
Concerning vitamin D reference range: pre-analytical and analytical variability of vitamin D measurement. Ferrari D et al, Biochem Med 2017

Vitamin D & extra-skeletal actions - uncertain/no effect

- **Vitamin D supplementation for the prevention of childhood acute respiratory infections: a systematic revue of RCT.** *L Xiao et al. Br J Nutr 2016*
- **Vitamin D supplementation for preventing infections in children under five years of age.** *MY Yakoob et al. Cochrane Database, 2016*
- **25-hydroxyvitamin D supplementation and health-service utilization for upper respiratory tract infection in young children.** *Omand JA et al. Public Health Nutrition, 2019*
- **Vitamin D ans asthma in children: a systematic review and meta-analysis of observational studies.** *Jat KR et al. Lung 2017*
- **Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study).** *Litonjua A. et al. NEJM 2020*
- **Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life.** *Loo El et al. Pediatric Allergy and Immunology, 2018*
- **The role of Vitamin D in respiratory allergies prevention. Why the effect is so difficult to disentangle?** *Sikorska-Szaflik H et al, Nutrients, 2022*
- **Prevention of recurrent respiratory infections: intersociety Consensus.** *E. Chiappini et al. Ital J Pediatr, 2021*

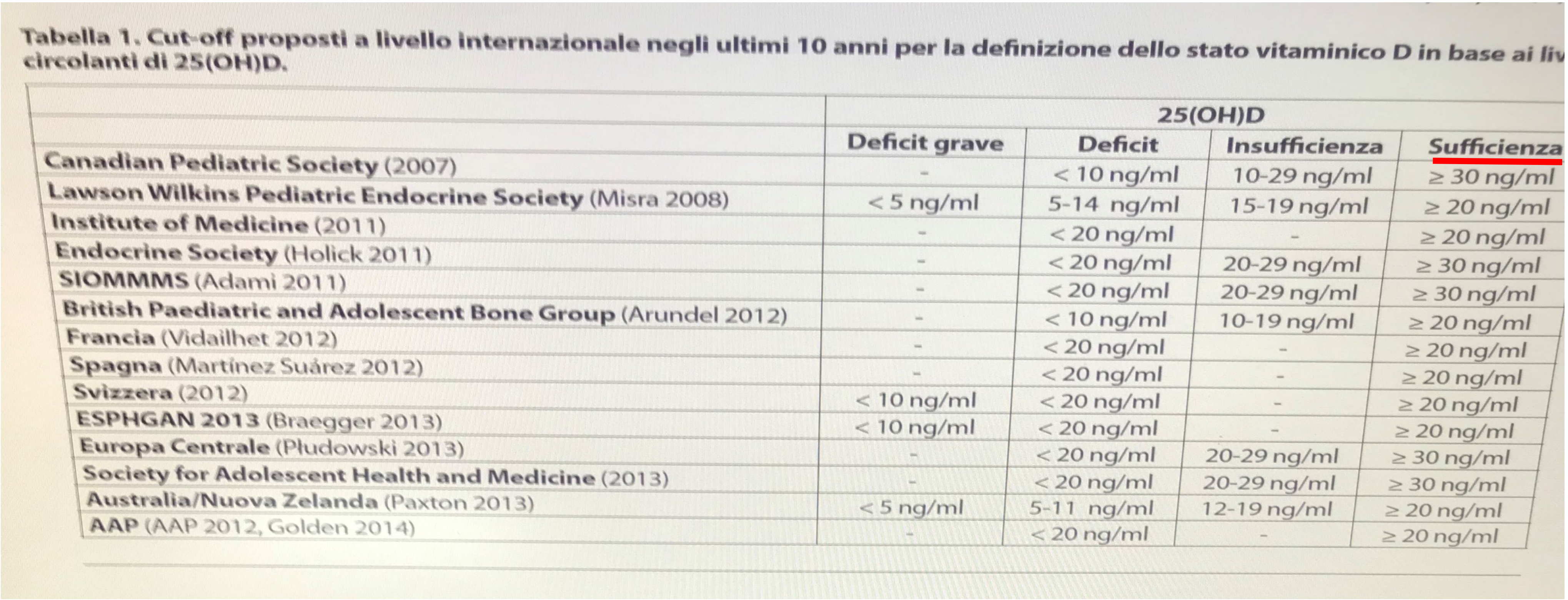


Tabella 1. Cut-off proposti a livello internazionale negli ultimi 10 anni per la definizione dello stato vitaminico D in base ai liv circolanti di 25(OH)D.

	25(OH)D			
	Deficit grave	Deficit	Insufficienza	Sufficienza
Canadian Pediatric Society (2007)	-	< 10 ng/ml	10-29 ng/ml	≥ 30 ng/ml
Lawson Wilkins Pediatric Endocrine Society (Misra 2008)	< 5 ng/ml	5-14 ng/ml	15-19 ng/ml	≥ 20 ng/ml
Institute of Medicine (2011)	-	< 20 ng/ml	-	≥ 20 ng/ml
Endocrine Society (Holick 2011)	-	< 20 ng/ml	20-29 ng/ml	≥ 30 ng/ml
SIOMMMS (Adami 2011)	-	< 20 ng/ml	20-29 ng/ml	≥ 30 ng/ml
British Paediatric and Adolescent Bone Group (Arundel 2012)	-	< 10 ng/ml	10-19 ng/ml	≥ 20 ng/ml
Francia (Vidailhet 2012)	-	< 20 ng/ml	-	≥ 20 ng/ml
Spagna (Martínez Suárez 2012)	-	< 20 ng/ml	-	≥ 20 ng/ml
Svizzera (2012)	< 10 ng/ml	< 20 ng/ml	-	≥ 20 ng/ml
ESPHGAN 2013 (Braegger 2013)	< 10 ng/ml	< 20 ng/ml	-	≥ 20 ng/ml
Europa Centrale (Płudowski 2013)	-	< 20 ng/ml	20-29 ng/ml	≥ 30 ng/ml
Society for Adolescent Health and Medicine (2013)	-	< 20 ng/ml	20-29 ng/ml	≥ 30 ng/ml
Australia/Nuova Zelanda (Paxton 2013)	< 5 ng/ml	5-11 ng/ml	12-19 ng/ml	≥ 20 ng/ml
AAP (AAP 2012, Golden 2014)	-	< 20 ng/ml	-	≥ 20 ng/ml

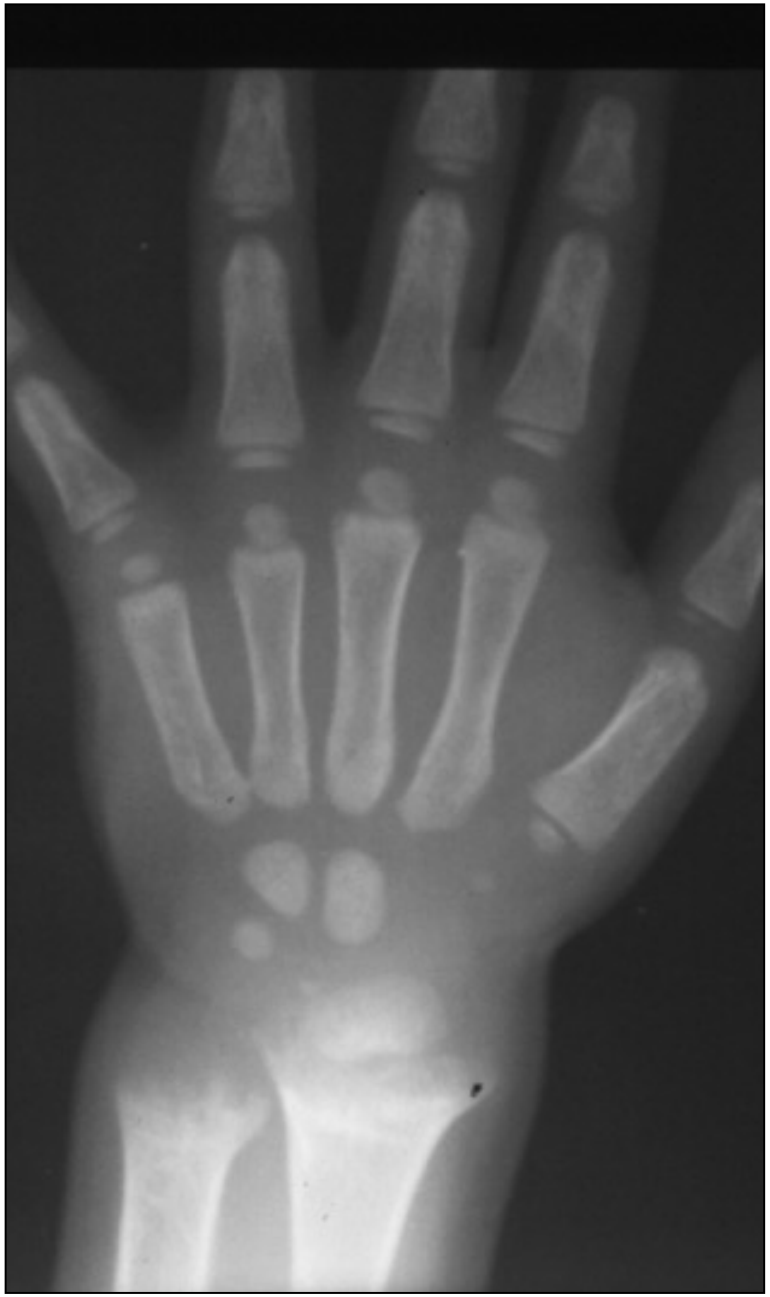
PEDIATRIA
PREVENTIVA & SOCIALE
ORGANO UFFICIALE DELLA SOCIETÀ ITALIANA DI PEDIATRIA PREVENTIVA E SOCIALE

Consensus
Vitamina D in età pediatrica

Consensus SIPPS - SIP
Vitamina D in età pediatrica
2015


ENTE
OSPEDALIE

Rachitismo



Congenital rickets in a term newborn

- Medhi: born at term from cesaean section, algerian origin.
- wide anterior and posterior fontanelle
- platibasia, rachitic rosary.

[redacted]

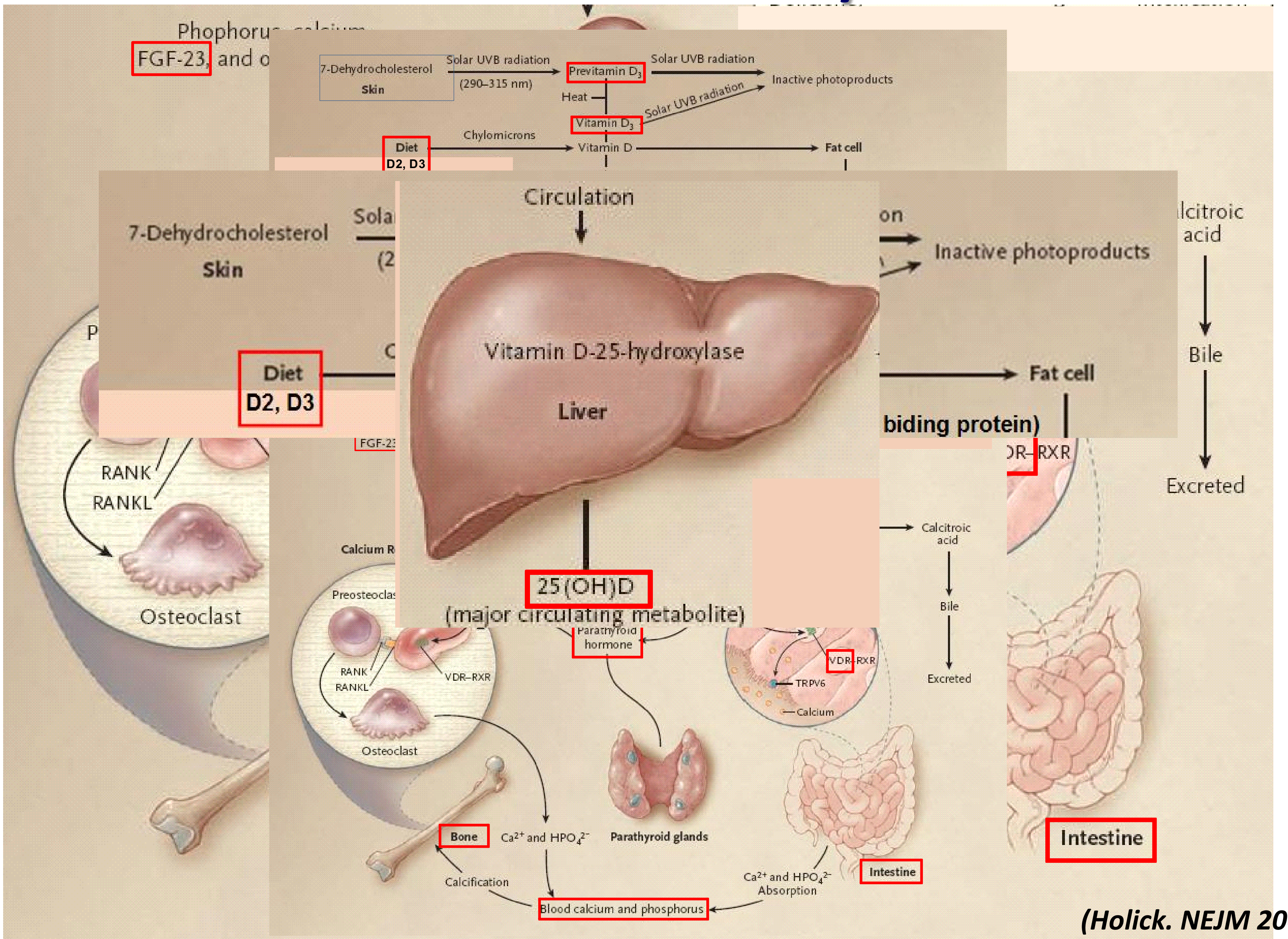
- *veiled mother*
- *no vit. D supplem. in pregnancy*
- *conceived in winter*

☐ **Mehdi : 25-OH-D: 9 ng/ml**

☐ **Mother : 25-OH-D : 8 ng/ml**

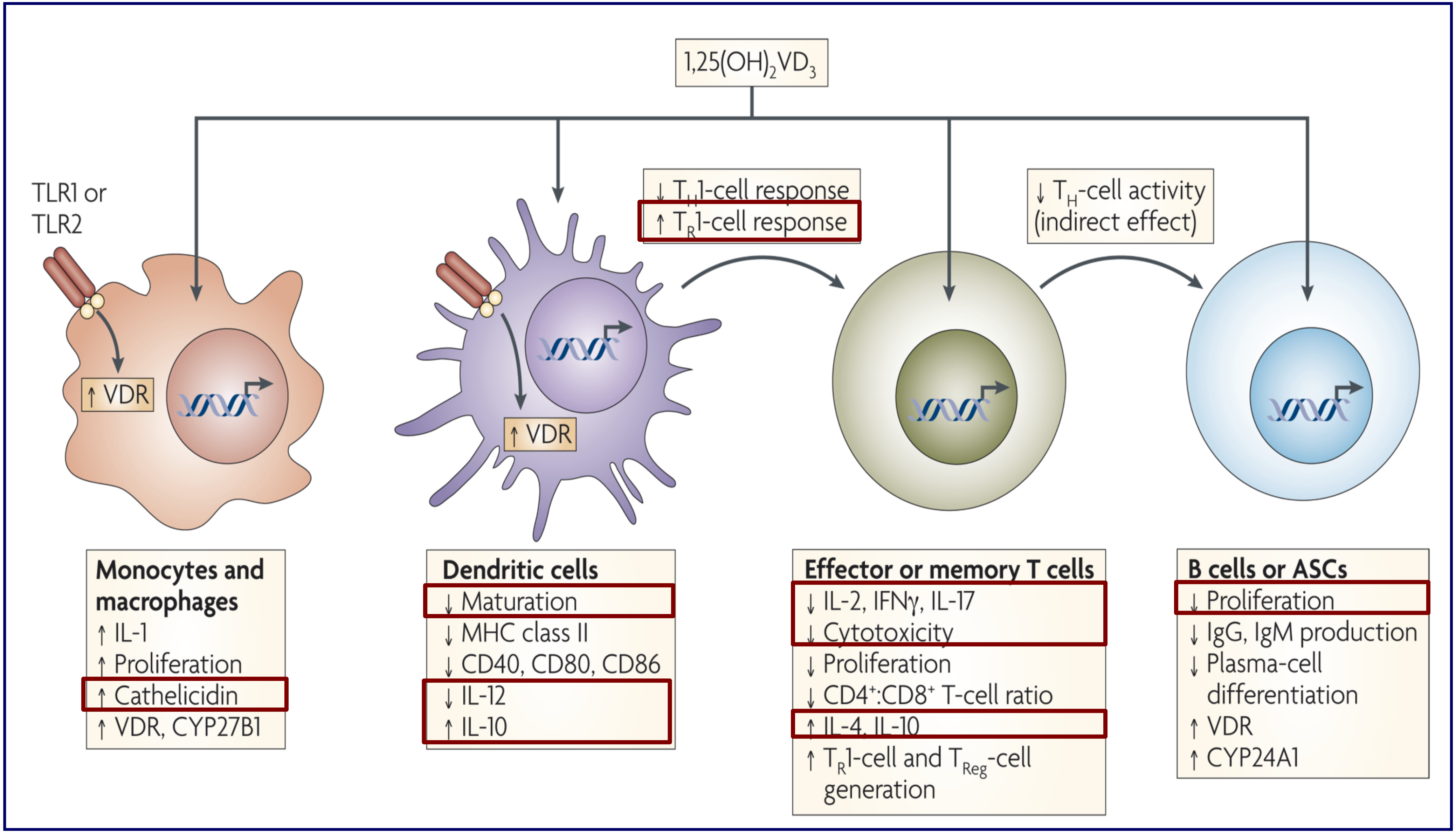
(Medico e Bambino, 2011)

Vitamin D endocrine system



(Holick. NEJM 2007)

Vitamin D effects on the immune system



Monocytes and macrophages
- ↑ IL-1
- ↑ Proliferation
- ↑ Cathelicidin
- ↑ VDR, CYP27B1

Dendritic cells
- ↓ Maturation
- ↓ MHC class II
- ↓ CD40, CD80, CD86
- ↓ IL-12
- ↑ IL-10

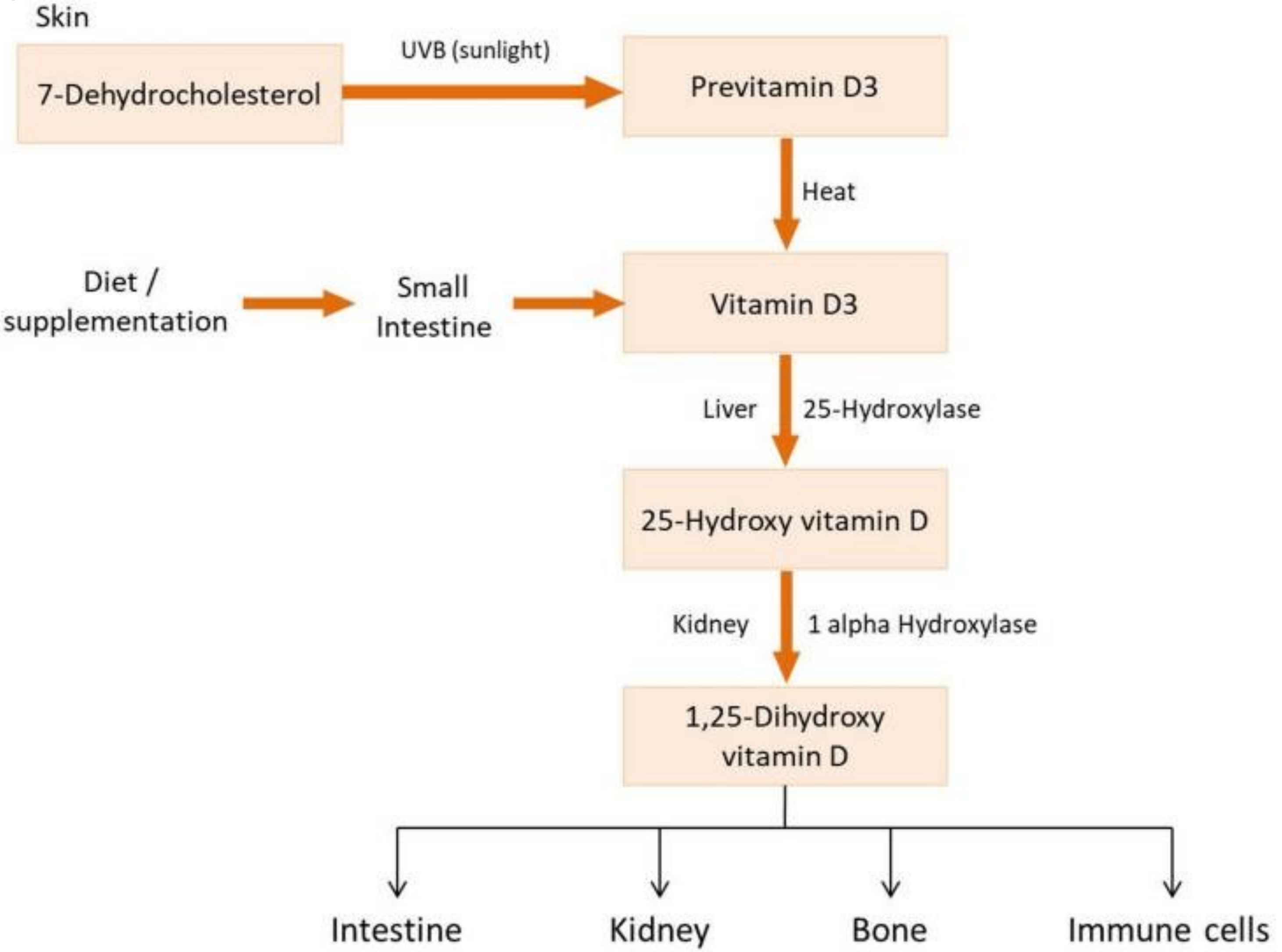
Effector or memory T cells
- ↓ IL-2, IFNγ, IL-17
- ↓ Cytotoxicity
- ↓ Proliferation
- ↓ $CD4^+$:$CD8^+$ T-cell ratio
- ↑ IL-4, IL-10
- ↑ T_R1-cell and T_{Reg}-cell generation

B cells or ASCs
- ↓ Proliferation
- ↓ IgG, IgM production
- ↓ Plasma-cell differentiation
- ↑ VDR
- ↑ CYP24A1

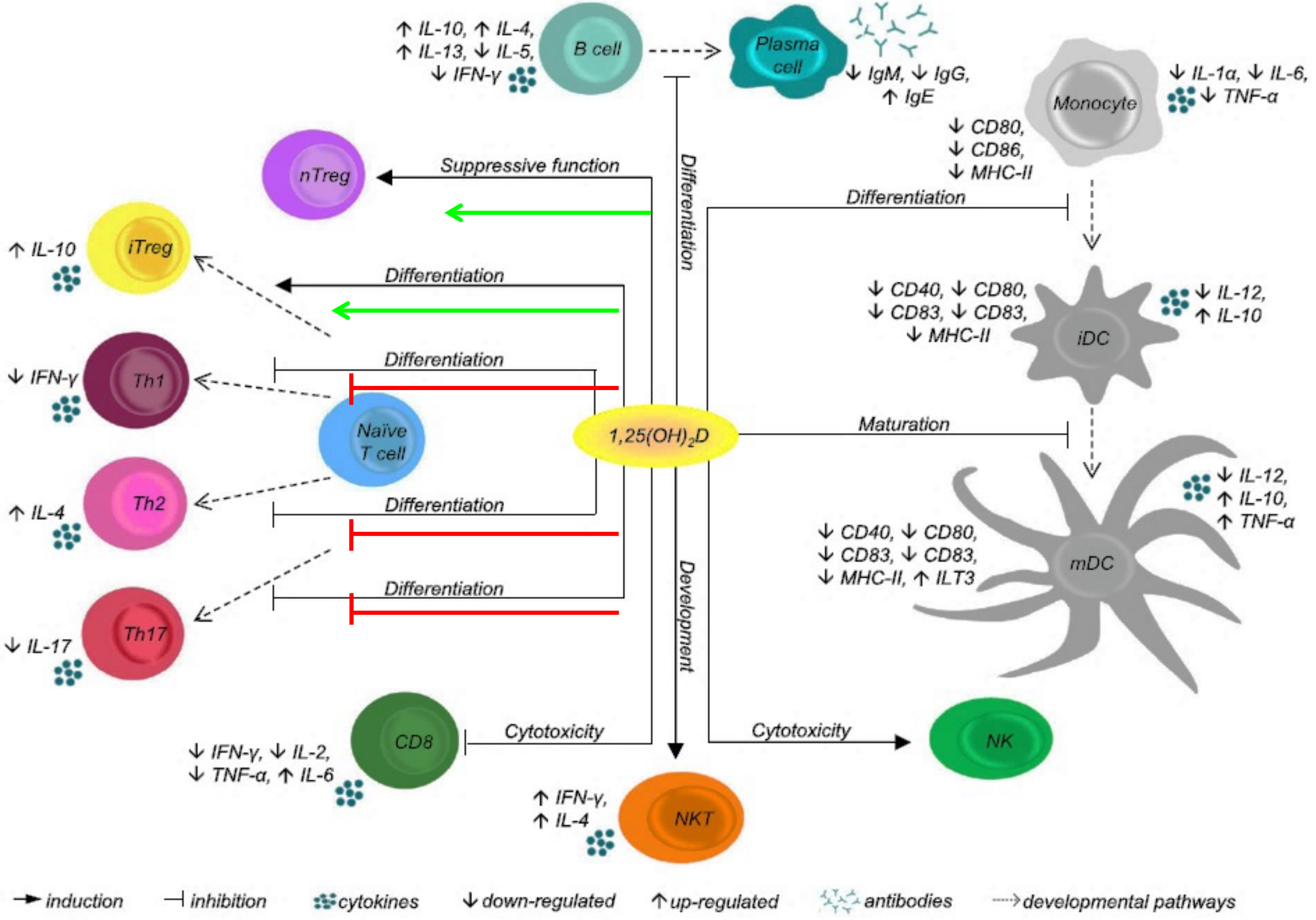
(Mora JR et al. Nat Rev Immunol 2008)

Synthesys and metabolism of Vitamin D

The synthesis and metabolism of vitamin D



(((A. Raju Cureus sept 2022)A. Ra

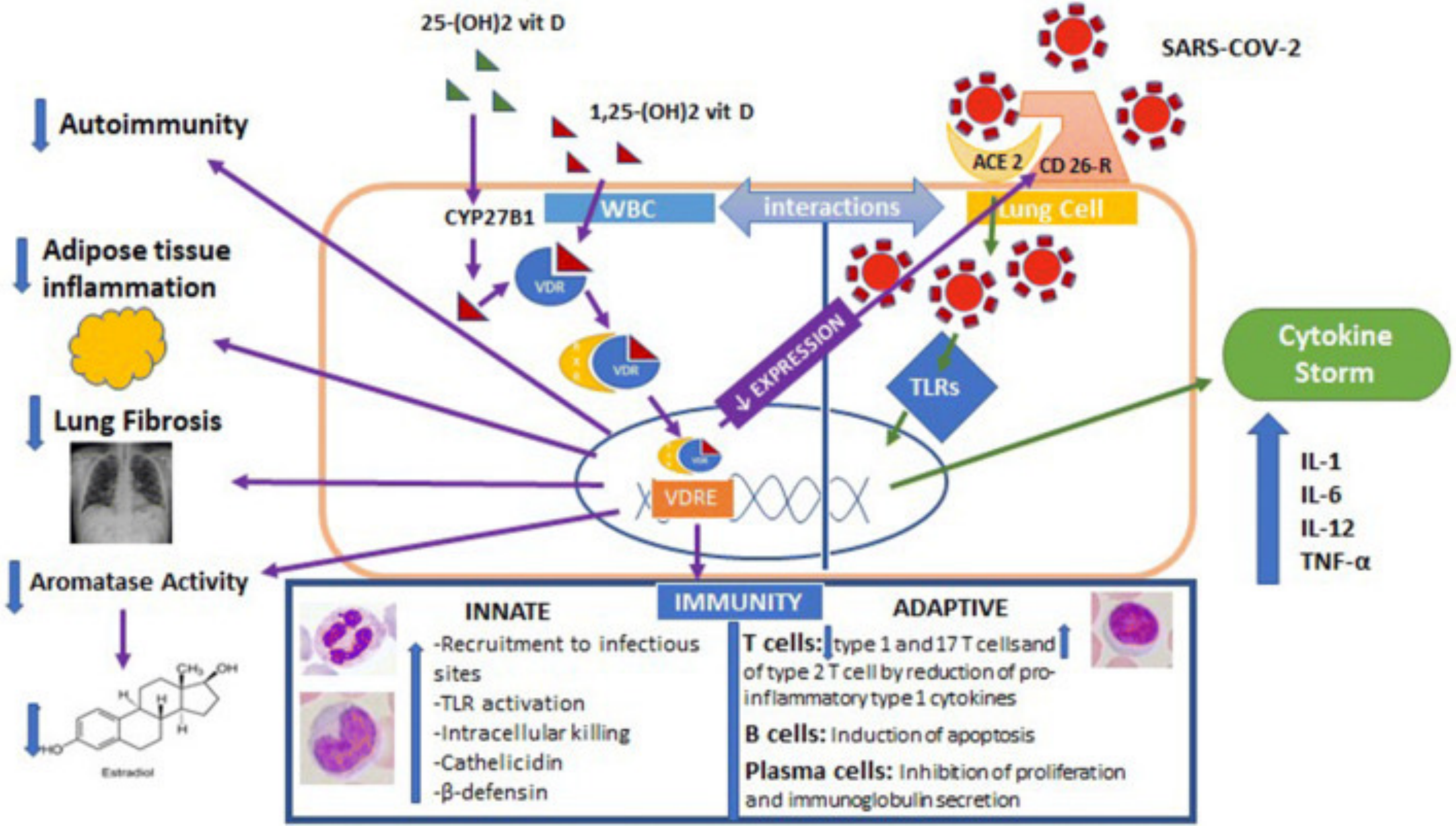


(Peelen E. Autoimmunity Reviews 2019)

Nature Public Health Emergency Collection
Public Health Emergency COVID-19 Initiative

Panfili FM et al
J Endocrinol Invest Jun 2020

Possible role of vitamin D in Covid-19 infection In pediatric population



INNATE

↑
- -Recruitment to infectious sites
- -TLR activation
- -Intracellular killing
- -Cathelicidin
- -β-defensin

ADAPTIVE

T cells: ↓ type 1 and 17 T cells and ↑ of type 2 T cell by reduction of pro-inflammatory type 1 cytokines

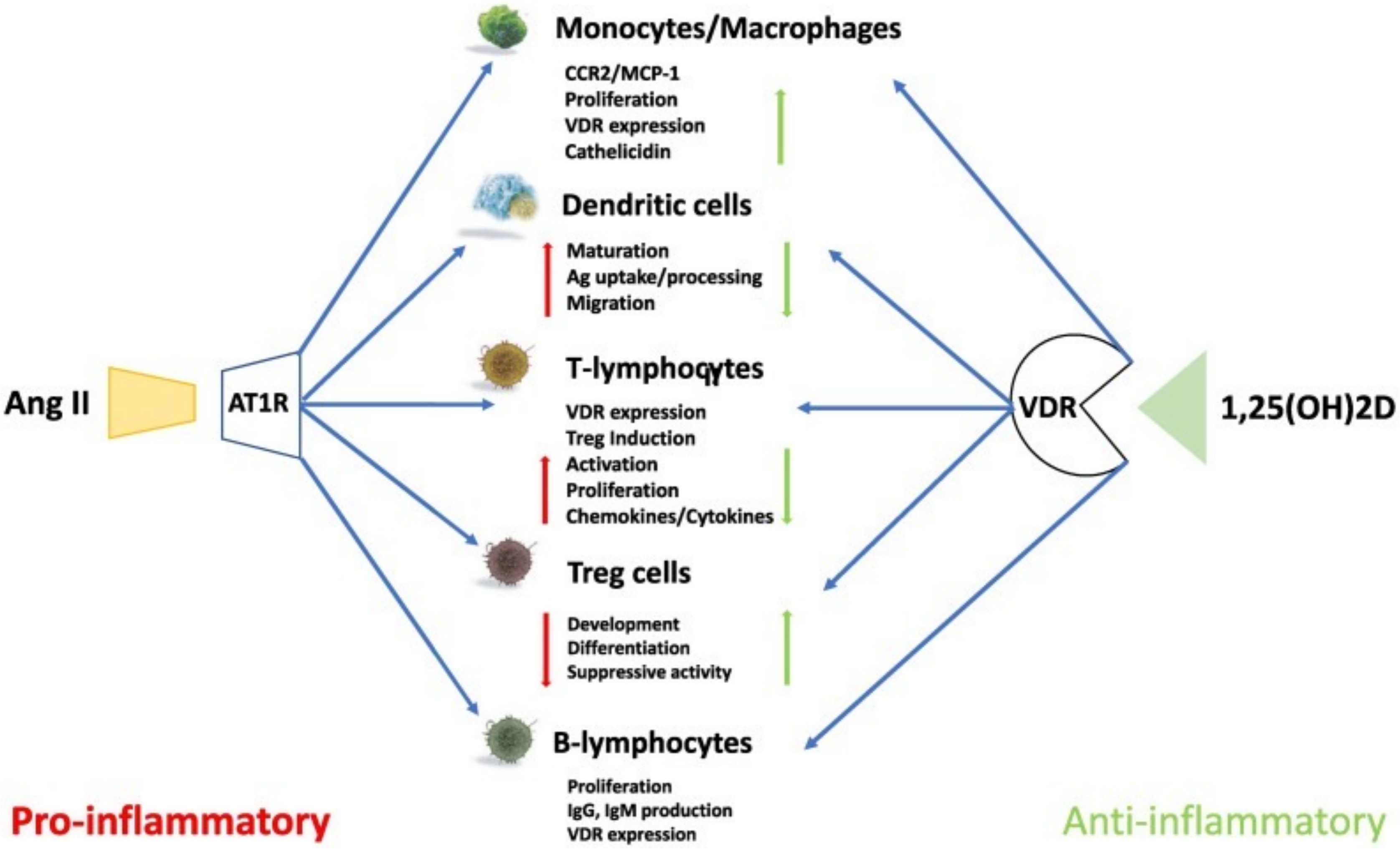
B cells: Induction of apoptosis

Plasma cells: Inhibition of proliferation and immunoglobulin secretion

Elsevier Public Health Emergency Collection
Public Health Emergency COVID-19 Initiative

Biesalski H K
Nfs Journal Aug 2020

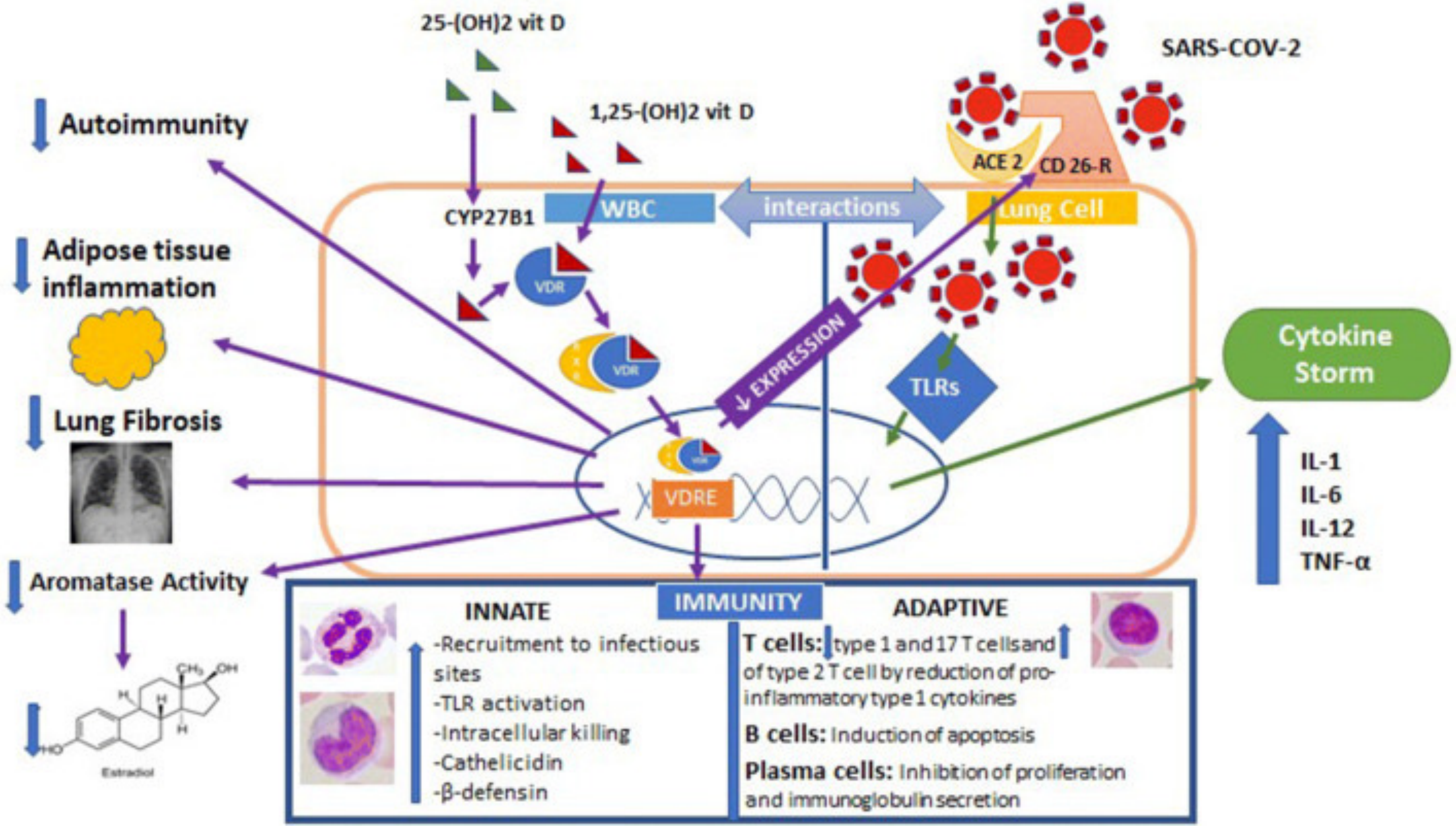
Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship?



Nature Public Health Emergency Collection
Public Health Emergency COVID-19 Initiative

Panfili FM et al
J Endocrinol Invest Jun 2020

Possible role of vitamin D in Covid-19 infection In pediatric population



IMMUNITY

INNATE

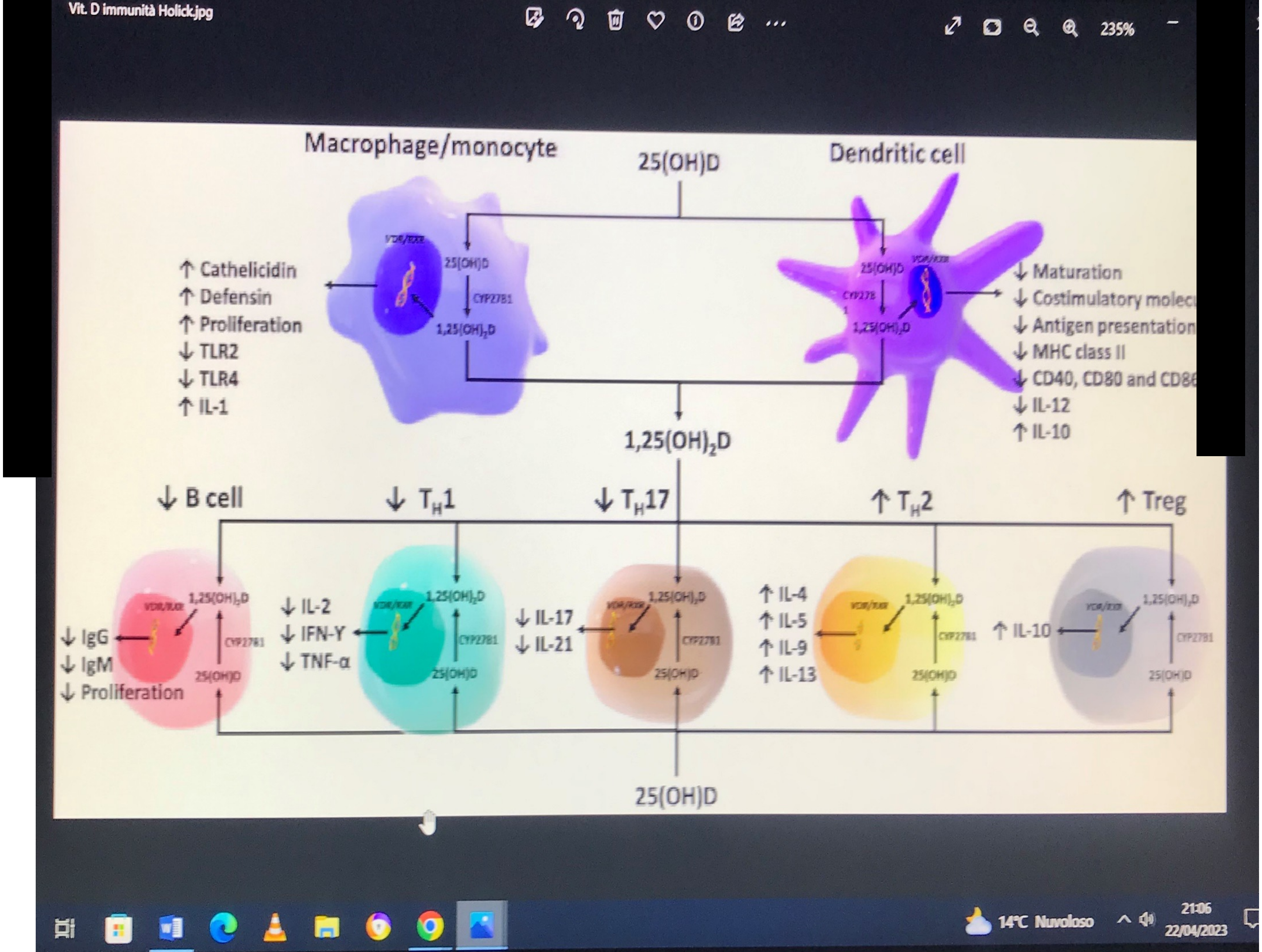
- -Recruitment to infectious sites
- -TLR activation
- -Intracellular killing
- -Cathelicidin
- -β-defensin

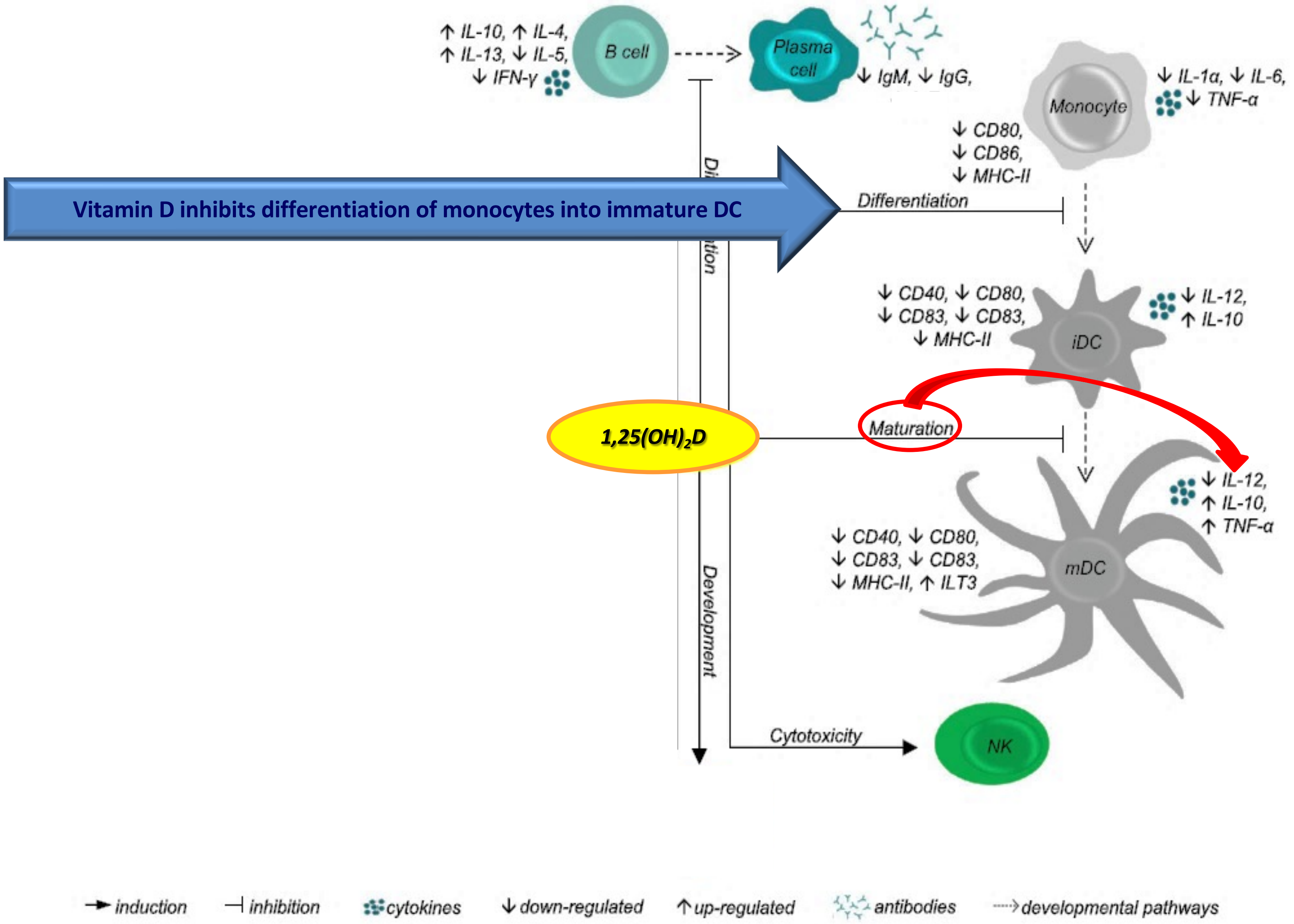
ADAPTIVE

T cells: ↓ type 1 and 17 T cells and ↑ of type 2 T cell by reduction of pro-inflammatory type 1 cytokines

B cells: Induction of apoptosis

Plasma cells: Inhibition of proliferation and immunoglobulin secretion

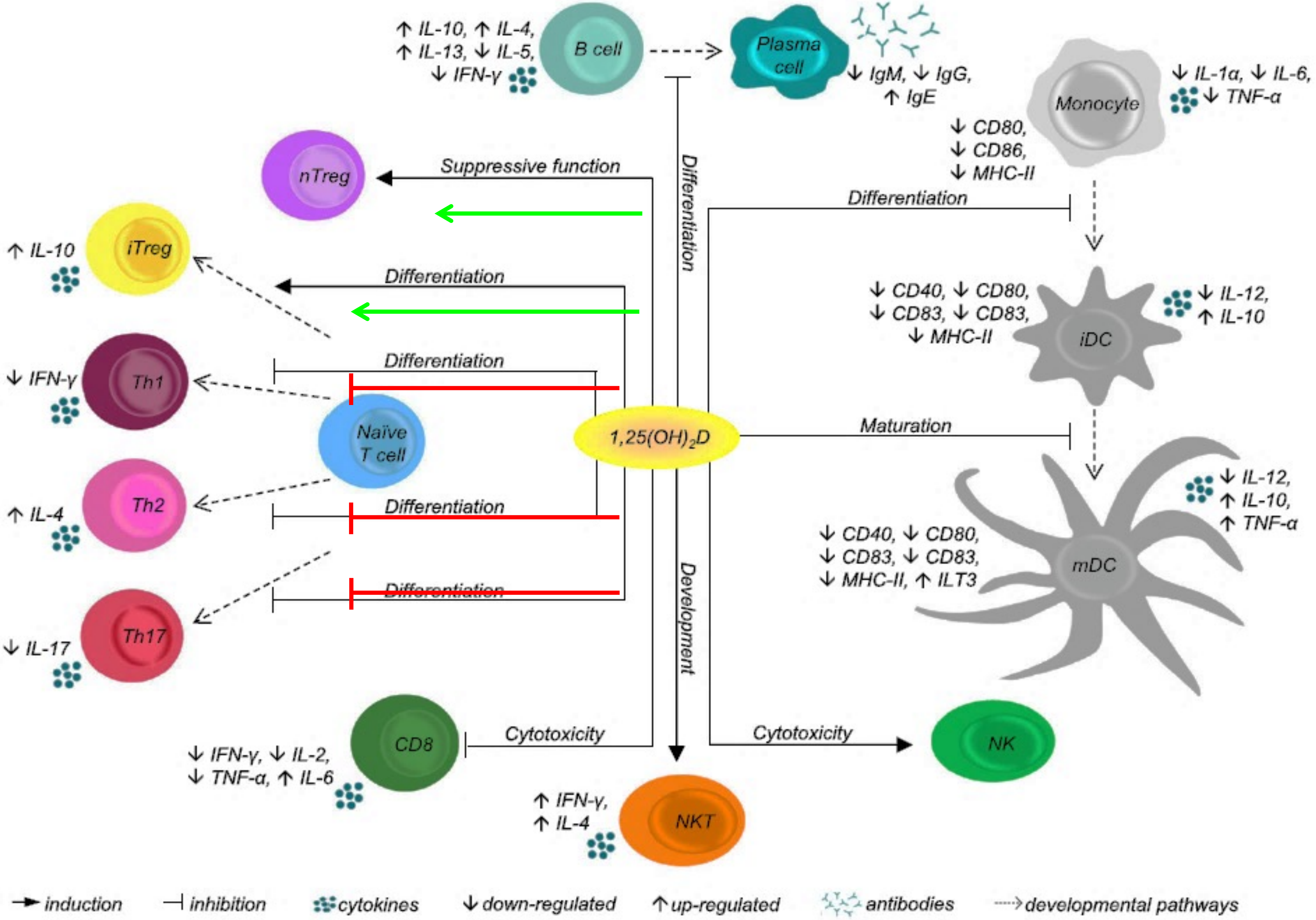

Vit. D immunità Holick.jpg
235%
Macrophage/monocyte
25(OH)D
Dendritic cell
VDR/RXR
25(OH)D
CYP27B1
$1,25(OH)_2D$
↑ Cathelicidin
↑ Defensin
↑ Proliferation
↓ TLR2
↓ TLR4
↑ IL-1
↓ Maturation
↓ Costimulatory molec
↓ Antigen presentation
↓ MHC class II
↓ CD40, CD80 and CD8
↓ IL-12
↑ IL-10
$1,25(OH)_2D$
↓ B cell
↓ T_H1
↓ T_H17
↑ T_H2
↑ Treg
↓ IgG
↓ IgM
↓ Proliferation
↓ IL-2
↓ IFN-Y
↓ TNF-α
↓ IL-17
↓ IL-21
↑ IL-4
↑ IL-5
↑ IL-9
↑ IL-13
↑ IL-10
25(OH)D
14°C Nuvoloso
21:06
22/04/2023



Vitamin D inhibits differentiation of monocytes into immature DC

$1,25(OH)_2D$

Peelen E. Autoimmunity Reviews 2011

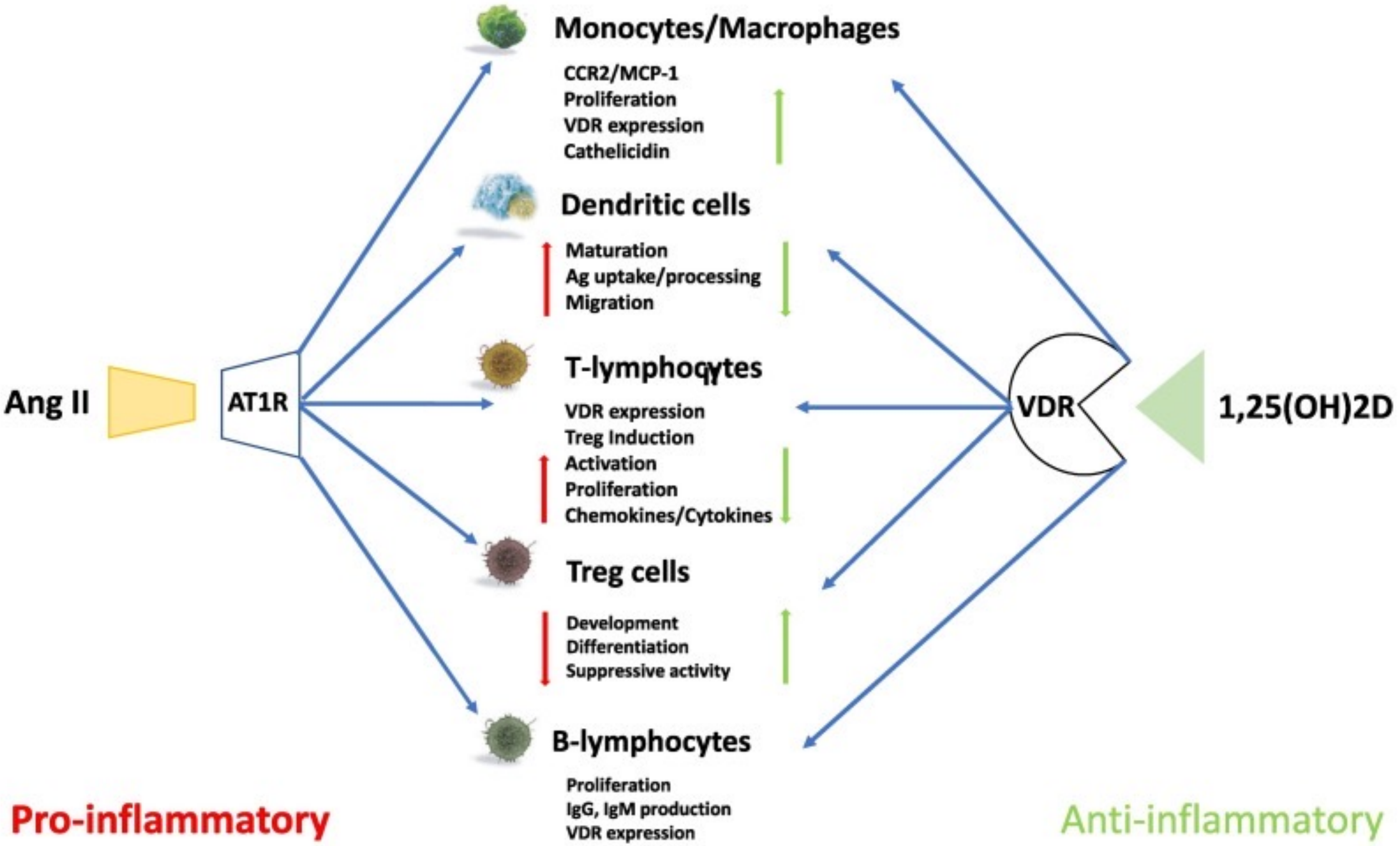


(Peelen E. Autoimmunity Reviews 2019)

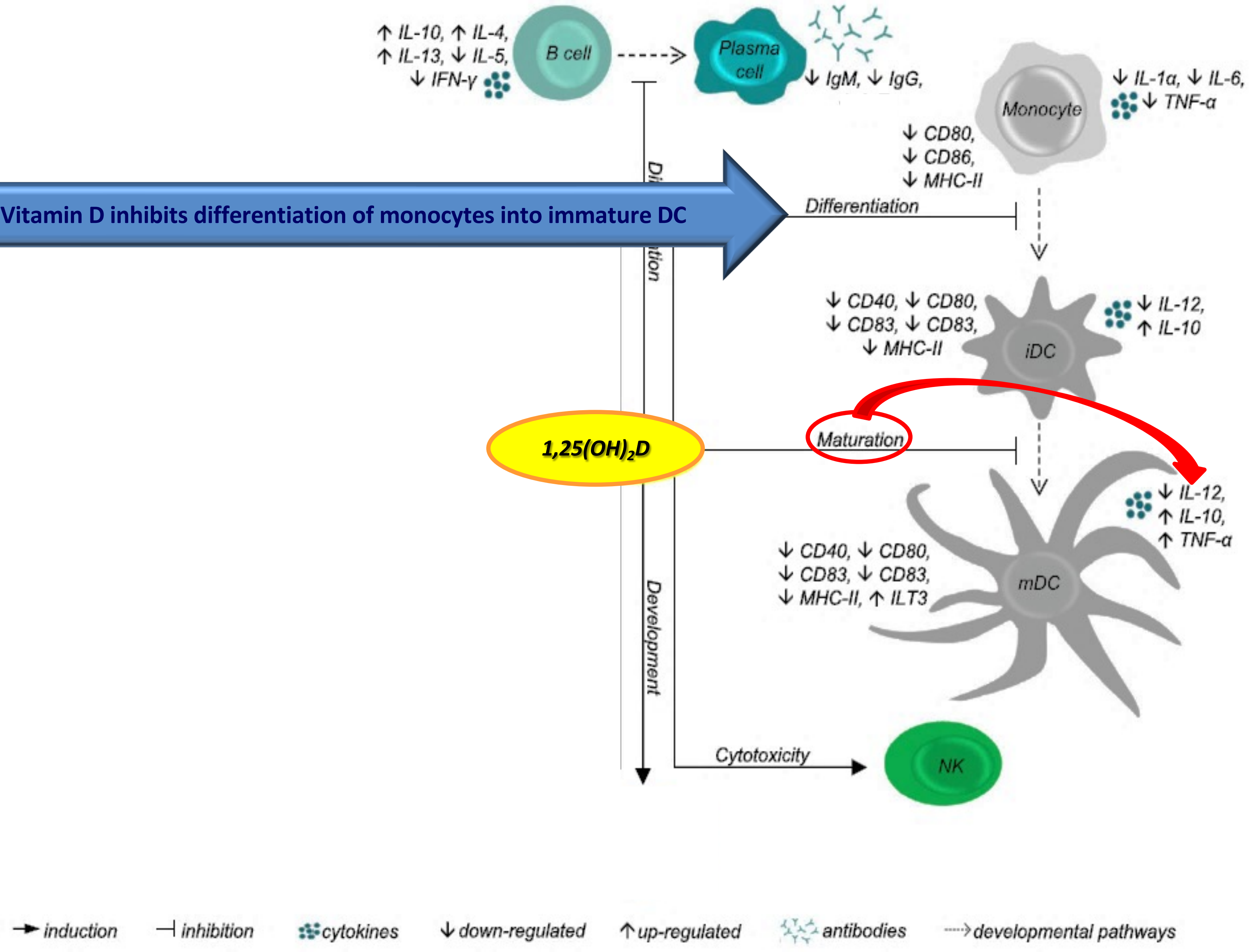
Elsevier Public Health Emergency Collection
Public Health Emergency COVID-19 Initiative

Biesalski H K
Nfs Journal Aug 2020

Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship?



Vitamin D inhibits differentiation of monocytes into immature DC



Peelen E. Autoimmunity Reviews 2011

Vitamin D & extra-skeletal actions - uncertain/no effect

- **Vitamin D supplementation for the prevention of childhood acute respiratory infections: a systematic revue of RCT.** *L Xiao et al. Br J Nutr 2016*
- **Vitamin D supplementation for preventing infections in children under five years of age.** *MY Yakoob et al. Cochrane Database, 2016*
- **25-hydroxyvitamin D supplementation and health-service utilization for upper respiratory tract infection in young children.** *Omand JA et al. Public Health Nutrition, 2019*
- **Vitamin D ans asthma in children: a systematic review and meta-analysis of observational studies.** *Jat KR et al. Lung 2017*
- **Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study).** *Litonjua A. et al. NEJM 2020*
- **Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life.** *Loo EI et al. Pediatric Allergy and Immunology, 2018*
- **The role of Vitamin D in respiratory allergies prevention. Why the effect is so difficult to disentangle?** *Sikorska-Szaflik H et al, Nutrients, 2022*
- **Prevention of recurrent respiratory infections: intersociety Consensus.** *E. Chiappini et al. Ital J Pediatr, 2021*

endocrine reviews

August 2019

Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions

Roger Bouillon ✉, Claudio Marcocci, Geert Carmeliet, Daniel Bikle, John H White, Bess Dawson-Hughes, Paul Lips, Craig F Munns, Marise Lazaretti-Castro, Andrea Giustina

- **A wealth of human cross-sectional and long-term prospective studies have linked a poor vitamin D status with a variety of human diseases as predicted on the basis of the preclinical data, including higher risk of cancer, infections, autoimmune diseases, cardiovascular and metabolic risk factors and events, and muscle dysfunction and falls**

- **This has generated an intense interest and even irrational enthusiasm about the possible health effects of vitamin D supplements.**

- **Most governmental and scientific societies are more prudent and await further proof of causality before formulating optimal thresholds for serum 25OHD or optimal dosages beyond what is needed for skeletal effects.**

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

n. 312 with lower initial levels of 25 (OH)D = 17,6 ng/ml

n. 400 with initial levels of 25 (OH)D = 27,1 ng/ml

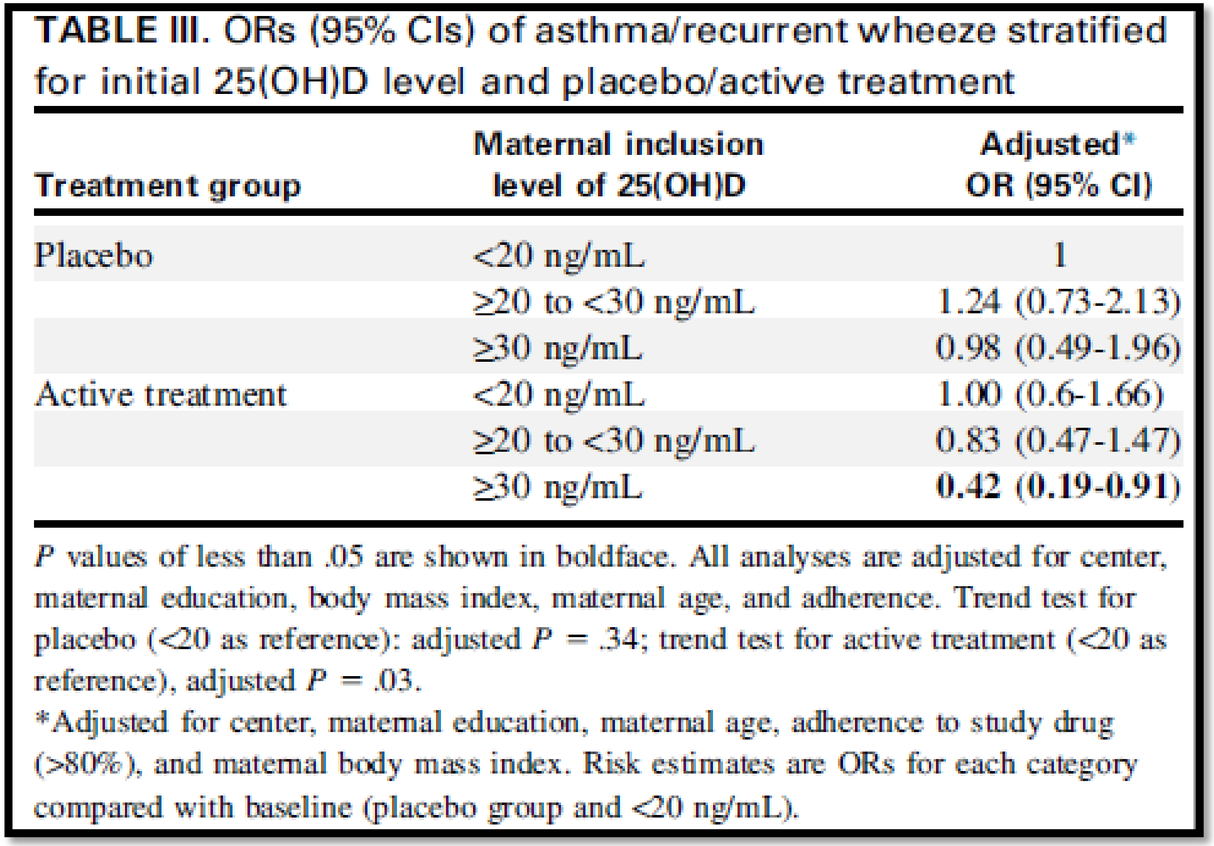


TABLE III. ORs (95% CIs) of asthma/recurrent wheeze stratified for initial 25(OH)D level and placebo/active treatment

Treatment group	Maternal inclusion level of 25(OH)D	Adjusted* OR (95% CI)
Placebo	<20 ng/mL	1
	≥20 to <30 ng/mL	1.24 (0.73-2.13)
	≥30 ng/mL	0.98 (0.49-1.96)
Active treatment	<20 ng/mL	1.00 (0.6-1.66)
	≥20 to <30 ng/mL	0.83 (0.47-1.47)
	≥30 ng/mL	**0.42 (0.19-0.91)**

P values of less than .05 are shown in boldface. All analyses are adjusted for center, maternal education, body mass index, maternal age, and adherence. Trend test for placebo (<20 as reference): adjusted *P* = .34; trend test for active treatment (<20 as reference), adjusted *P* = .03.

*Adjusted for center, maternal education, maternal age, adherence to study drug (>80%), and maternal body mass index. Risk estimates are ORs for each category compared with baseline (placebo group and <20 ng/mL).

Maternal supplementation of vitamin D, particularly in mothers with initial 25(OH)D levels of greater than 30 ng/mL, reduced asthma/recurrent wheeze in the offspring through age 3 years, suggesting that higher vitamin D status beginning in early pregnancy is necessary for asthma/recurrent wheeze prevention in early life.

(Wolsk HM et al. J Allergy Clin Immunol 2017)

Vitamin D & extraskeletal actions - no/uncertain effect

- Vitamin D supplementation for the prevention of childhood acute respiratory infections: a systematic revue of RCT. *L Xiao et al. Br J Nutr 2016*
- Vitamin D supplementation for preventing infections in children under five years of age. *MY Yakoob et al. Cochrane Database, 2016*
- 25-hydroxyvitamin D supplementation and health-service utilization for upper respiatory tract infection in young children. *Omand JA et al. Public Health Nutrition, 2019*
- Vitamin D ans asthma in children: a systematic review and meta-analysis of observational studies. *Jat KR et al. Lung 2017*
- Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study). *Litonjua A. et al. NEJM 2020*
- Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life. *Loo El et al. Pediatric Allergy and Immunology, 2018*
- The role of Vitamin D in respiratory allergies prevention. Why the effect is so difficult to disentangle? *Sikorska-Szaflik H et al, Nutrients, 2022*

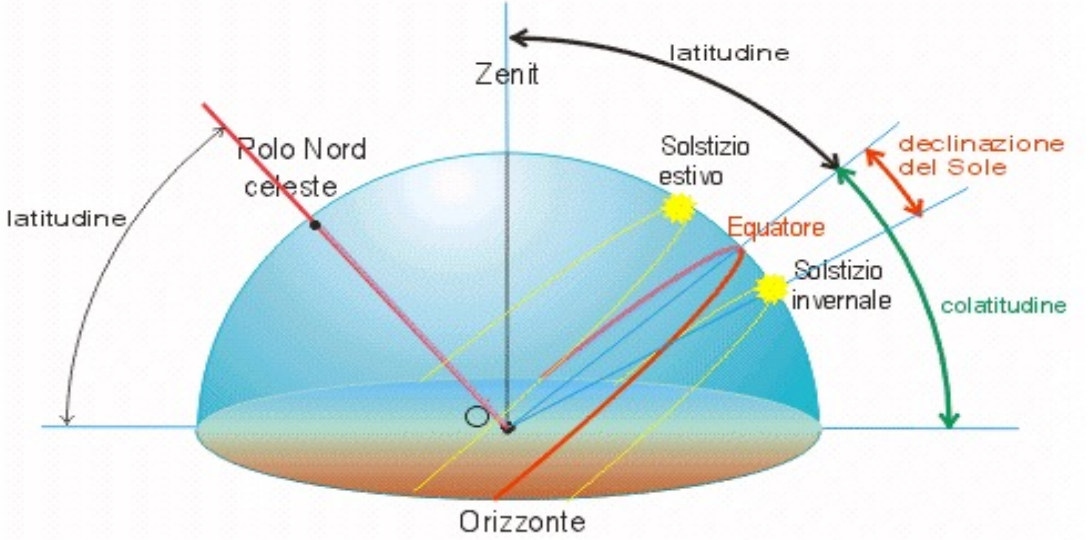
Vitamin D sources

Sunshine and vitamin D

factors influencing the amount of exposure to sun

Nick Shaw, Arch Dis Child, 2017

- solar zenith angle
- cloud cover
- atmospheric pollution
- ozone layer
- minute suspended particles in the atmosphere



Content of Vitamin D (IU/100 g) in foods

whole milk	3 - 40 / L
yogurt	89
cheese	28 - 44
egg	120
butter	35
margarine	60/spoon
liver beef	40 - 70
meat	40 - 50

- *fish: cod* 250, *tuna* 250, *herring* 300, *salmon* 450

~~(100 UI = 2,5 microg)~~

Vitamin D status during adolescence

Deficiency : 25-OH-D < 20 ng/ml

Vitamin D status and its determinants in adolescents from the Northern Ireland Young Hearts 2000 cohort

(Hill TR et al, Br J Nutr 2008)

36%

(N = 1,015)

Implications of a New Definition of Vitamin D Deficiency in a Multiracial US Adolescent Population: The National Health and Nutrition Examination Survey III

(Saintonge S et al, Pediatrics 2009)

14%

(N = 2,955)

Prevalence of 25-hydroxyvitamin D deficiency in Korean adolescents: association with age, season and parental vitamin D status

(Kim SH et al, Publ Health Nutr 2012)

54.7%

(N = 2,062)

Prevalence of hypovitaminosis D and predictors of vitamin D status in Italian healthy adolescents

(Saggese G et al, Ital J Pediatr, 2014)

49.9%

(N = 427)

Vitamin D status during adolescence

Deficiency : 25-OH-D < 20 ng/ml

Risk factors for hypovitaminosis D during adolescence

- **lifestyle: reduced sun exposure due to reduced time spent outdoor and sedentary lifestyle (excessive smartphone, computer use)**
- **obesity/overweight (30% of adolescents)**
- **chronic diseases (20% of adolescents)**
- **increased demand for calcium and phosphorus for the growth spurt**

(Santos BR et al, BMC Pediatrics 2012)

Prevalence of hypovitaminosis D and predictors of vitamin D status in Italian healthy adolescents

(Saggese G.et al Il J Pediatr 2014)

49.9%

(N = 427)

Risk factors for hypovitaminosis D

- reduced sun exposure (lifestyle, clothing habit)
- darker skin color (higher melanin)
- exclusive breastfeeding without Vitamin D prophylaxis
- adolescence
- obesity
- pathological conditions (malabsorption, kidney and liver diseases, etc.)
- drugs interfering with Vitamin D metabolism (antiepileptic, corticosteroids)

Vitamin D actions

skeletal

extrascheletal

Vitamin D actions

Vitamin D - skeletal actions

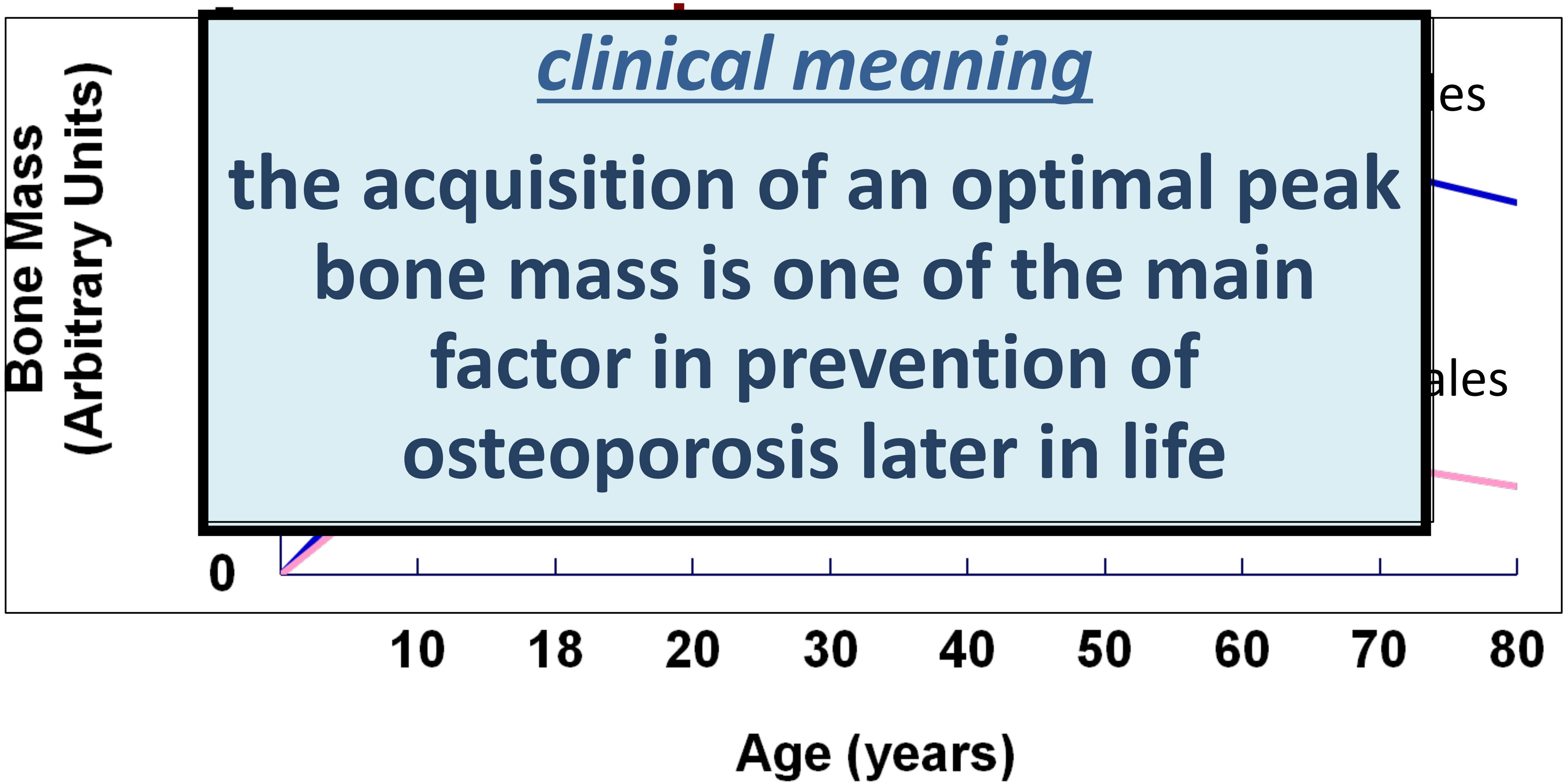
1) *prevention of rickets*
2) *promotion of the acquisition of bone mass*

Vitamin D - skeletal actions

1) *prevention of rickets*
2) ***promotion of the acquisition of bone mass***

Changes in bone mass with age

PEAK BONE MASS



clinical meaning

the acquisition of an optimal peak bone mass is one of the main factor in prevention of osteoporosis later in life

(Cooper C. 1990)

Azioni extra-scheletriche della Vitamina D

Condizioni pediatriche che possono essere associate a ipovitaminosi D

- **Infezioni** (***influenza, bronchiolite, polmonite, TBC***)
- **Asma**
- **Dermatite atopica**
- **Allergia alimentare**

- **Malattie autoimmuni** (***diabete mellito tipo 1, artrite idiopatica giovanile***)
- **Obesità**
- **Sindrome Metabolica, Diabete Mellito Tipo 2**

Vitamin D extraskeletal actions

Hypovitaminosis D has been associated with some extraskeletal pathological conditions in childhood and adolescence; particularly with an increased risk of respiratory infections, a worse asthma control and occurrence af allergic outcomes.

Vitamin D & extraskeletal actions - no/uncertain effect

- **25-hydroxyvitamin D supplementation and health-service utilization for upper respiatory tract infection in young children.** *Omand JA et al. Public Health Nutrition, 2019*
- **The role of Vitamin D in respiratory allergies prevention. Wy the effect is so difficult to disentagle?** *Sikorska-Szaflik H et al, Nutrients, 2022.*
- **Vitamin D ans asthma in children: a systematic review and meta-analysis of observational studies**. *Jat KR et al. Lung 2017*
- **Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study).** *Litonjua A. et al. NEJM 2020*
- **Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life.** *Loo EI et al. Pediatric Allergy and Immunology, 2018*

Vitamin D & extraskeletal actions - no/uncertain effect

- **25-hydroxyvitamin D supplementation and health-service utilization for upper respiatory tract infection in young children.** *Omand JA et al. Public Health Nutrition, 2019*
- **The role of Vitamin D in respiratory allergies prevention. Wy the effect is so difficult to disentagle?** *Sikorska-Szaflik H et al, Nutrients, 2022.*
- **Vitamin D ans asthma in children: a systematic review and meta-analysis of observational studies**. *Jat KR et al. Lung 2017*
- **Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study).** *Litonjua A. et al. NEJM 2020*
- **Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life.** *Loo El et al. Pediatric Allergy and Immunology, 2018*

Vitamin D & extraskeletal actions - no/uncertain effect

- **25-hydroxyvitamin D supplementation and health-service utilization for upper respiatory tract infection in young children.** *Omand JA et al. Public Health Nutrition, 2019*
- **The role of Vitamin D in respiratory allergies prevention. Wy the effect is so difficult to disentagle?** *Sikorska-Szaflik H et al, Nutrients, 2022.*
- **Vitamin D ans asthma in children: a systematic review and meta-analysis of observational studies**. *Jat KR et al. Lung 2017*
- **Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study).** *Litonjua A. et al. NEJM 2020*
- **Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life.** *Loo El et al. Pediatric Allergy and Immunology, 2018*

Vitamin D & extraskeletal actions - no/uncertain effect

- **25-hydroxyvitamin D supplementation and health-service utilization for upper respiatory tract infection in young children.** *Omand JA et al. Public Health Nutrition, 2019*
- **The role of Vitamin D in respiratory allergies prevention. Wy the effect is so difficult to disentagle?** *Sikorska-Szaflik H et al, Nutrients, 2022.*
- **Vitamin D ans asthma in children: a systematic review and meta-analysis of observational studies**. *Jat KR et al. Lung 2017*
- **Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study).** *Litonjua A. et al. NEJM 2020*
- **Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life.** *Loo El et al. Pediatric Allergy and Immunology, 2018*

Vitamin D & extraskeletal actions - no/uncertain effect

- **25-hydroxyvitamin D supplementation and health-service utilization for upper respiatory tract infection in young children.** *Omand JA et al. Public Health Nutrition, 2019*
- **The role of Vitamin D in respiratory allergies prevention. Wy the effect is so difficult to disentagle?** *Sikorska-Szaflik H et al, Nutrients, 2022.*
- **Vitamin D ans asthma in children: a systematic review and meta-analysis of observational studies**. *Jat KR et al. Lung 2017*
- **Six-year follow-up of a trial of antenatal Vitamin D for asthma reduction (VDAART Study).** *Litonjua A. et al. NEJM 2020*
- **Association between maternal Vitamin D levels during pregnany and allergic outcomes in the offspring in the first 5 years of life.** *Loo EI et al. Pediatric Allergy and Immunology, 2018*

Vitamin D extraskeletal actions

remarks

►Results from studies (most observational) on Vitamin D in pediatric extrascheletal conditions gave mixed results and at present suggest caution in attributing a causative role to Vitamin D.

►Neverthless data obtained emphasize the importance of mantaining normal levels of Vitamin D in such conditions.

Fattori di rischio di ipovitaminosi D

- **<u>ridotta esposizione al sole</u> (stili di vita, abbigliamento, abitudini socio-culturali e religiose)**
- **elevata pigmentazione cutanea, etnia**
- **creme solari**
- **allattamento al seno esclusivo senza profilassi**
- **adolescenza**
- **obesità**
- **condizioni patologie (es. malassorbimenti, insufficienza epatica o renale)**
- **farmaci interferenti con il metabolismo della vitamina D (antiepilettici, corticosteroidi)**

Vitamin D status during adolescence

Risk factors

- lifestyle: reduced sun exposure due to reduced time spent outdoor (reduced physical activity) and sedentary lifestyle (excessive smartphone, computer use)
- obesity/overweight (30% of adolescents)
- chronic diseases (20% of adolescents)
- increased demand for calcium and phosphorus for the growth spurt

%
,015)

%
,955)

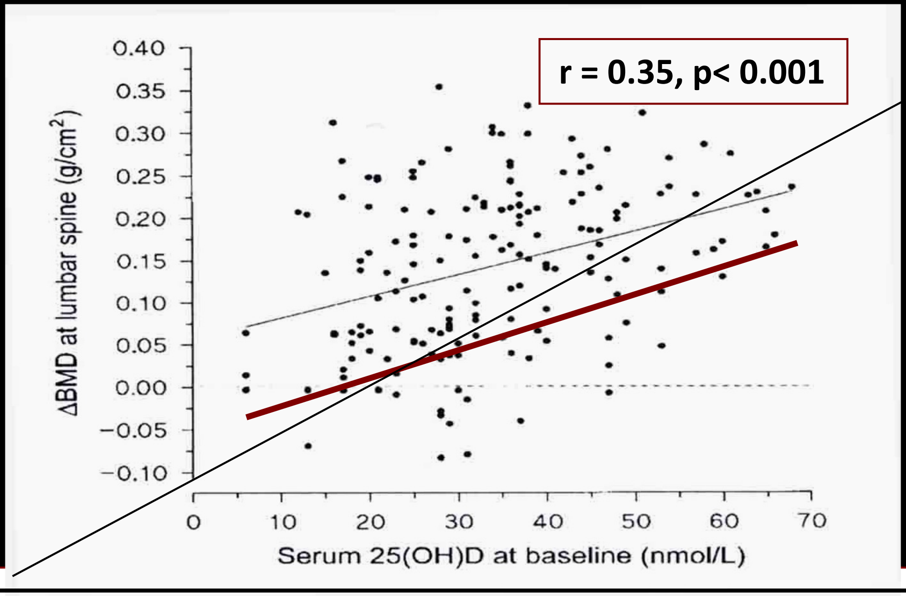
7%
,062)

3%
(N = 234)

a cross-sectional study on prevalence and
association with vitamin D receptor gene variants

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).



r = 0.35, p< 0.001

Relationship between peak bone mass and 25-OH-D levels in young Finnish men

(n = 220, age 18.3 - 20.6 y)

The relation between 25-hydroxyvitamin-D with peak bone mineral density in healthy young adults (n = 464, age 17-31 yrs

25-OH-D levels were related to the achievement of peak bone mass.

(Boot AM et al. J Pediatr Endocr Met 2011)

Calcium intake

along with Vitamin D
is essential for bone health
in children and adolescents