IL RUOLO DELLA VITAMINA D E DEI PROBIOTICI NELLA IMMUNO-MODULAZIONE DELLA RISPOSTA ALLERGICA

Vitamina D: L'azione

Diego Peroni

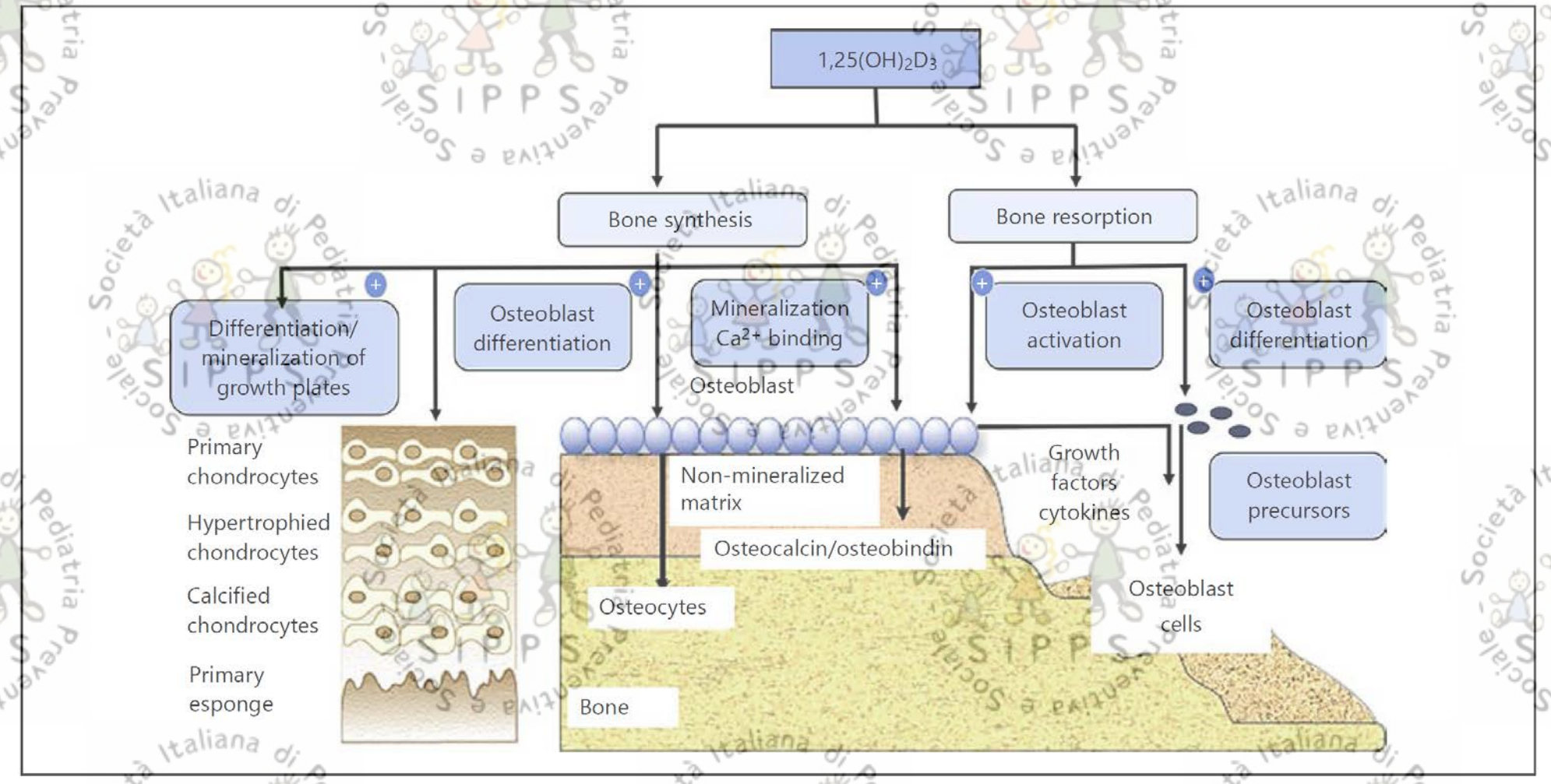
U.O. di Pediatria

Università di Pisa

- ✓ **Le basi immunologiche**
- ✓ L'associazione
- ✓ La supplementazione
- ✓ Le conclusioni

diego.peroni@unipi.it

Vitamin D: Classic and Novel Actions. A Gil, Ann Nutr Metab 2018;72:87



Vitamin D classic actions in the bone system

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

Uday S, Arch Dis Child 2018

Factors causing vitamin D deficiency in high-income countries such as the UK specifically include the following:

1. ***Latitude***: lack of UVB radiation for at least 6 months of the year due to its geographical location.

2. ***Ethnicity***: dark skin (Fitzpatrick skin type IV (light brown), V (dark brown) and VI (black)) massively reduces cutaneous synthesis of vitamin D.

3. ***Culture***: covered clothing, low dietary vitamin D and calcium intake.

4. ***Sunscreen***: excessive use of sunscreen due to fear of skin cancer

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

Uday S, Arch Dis Child 2018

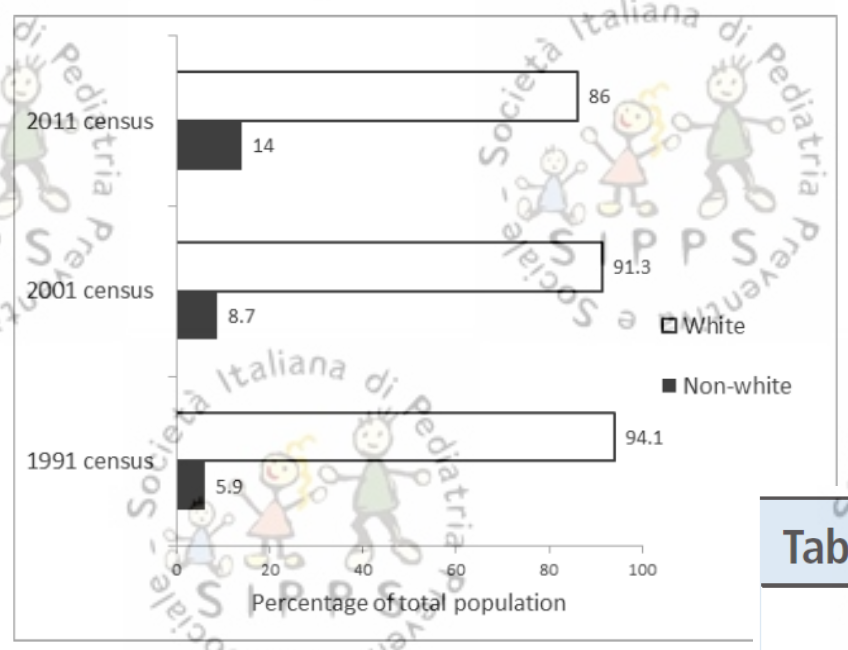


Table 1 Rickets overall is a rare disease in high-income countries.

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.

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

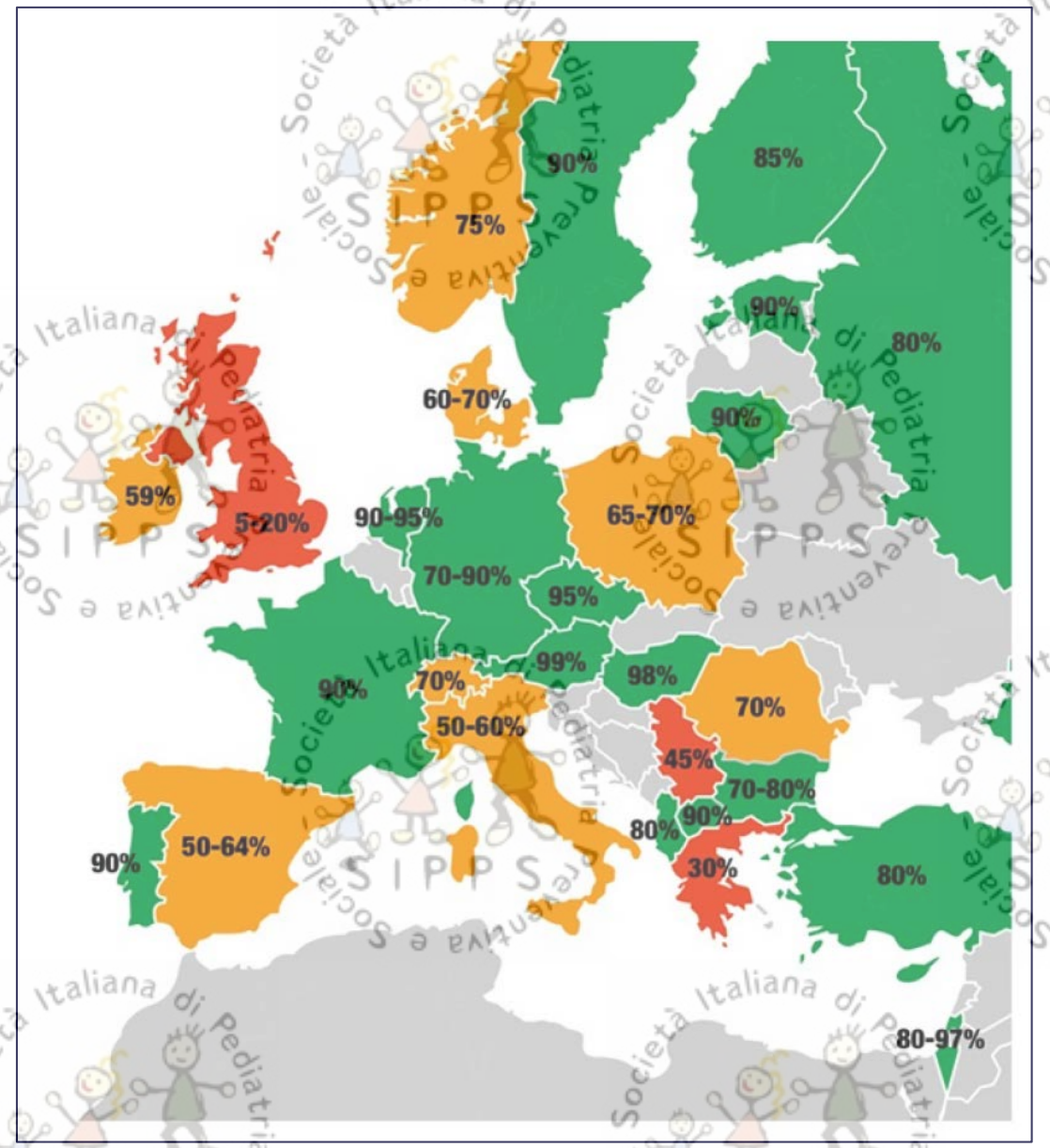
Uday S, Arch Dis Child 2018

Adherence rates for infant vitamin D supplementation in the first year of life in Europe, with UK reporting the lowest rates.

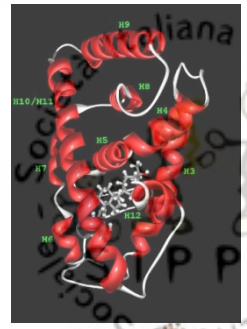
Good adherence (≥80% of infants supplemented) is indicated in green,

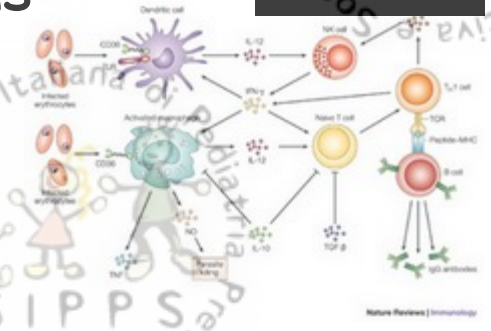
moderate adherence (79%–50%) in orange and

low adherence (<50%) in red.



Multiple Functions of Vitamin D



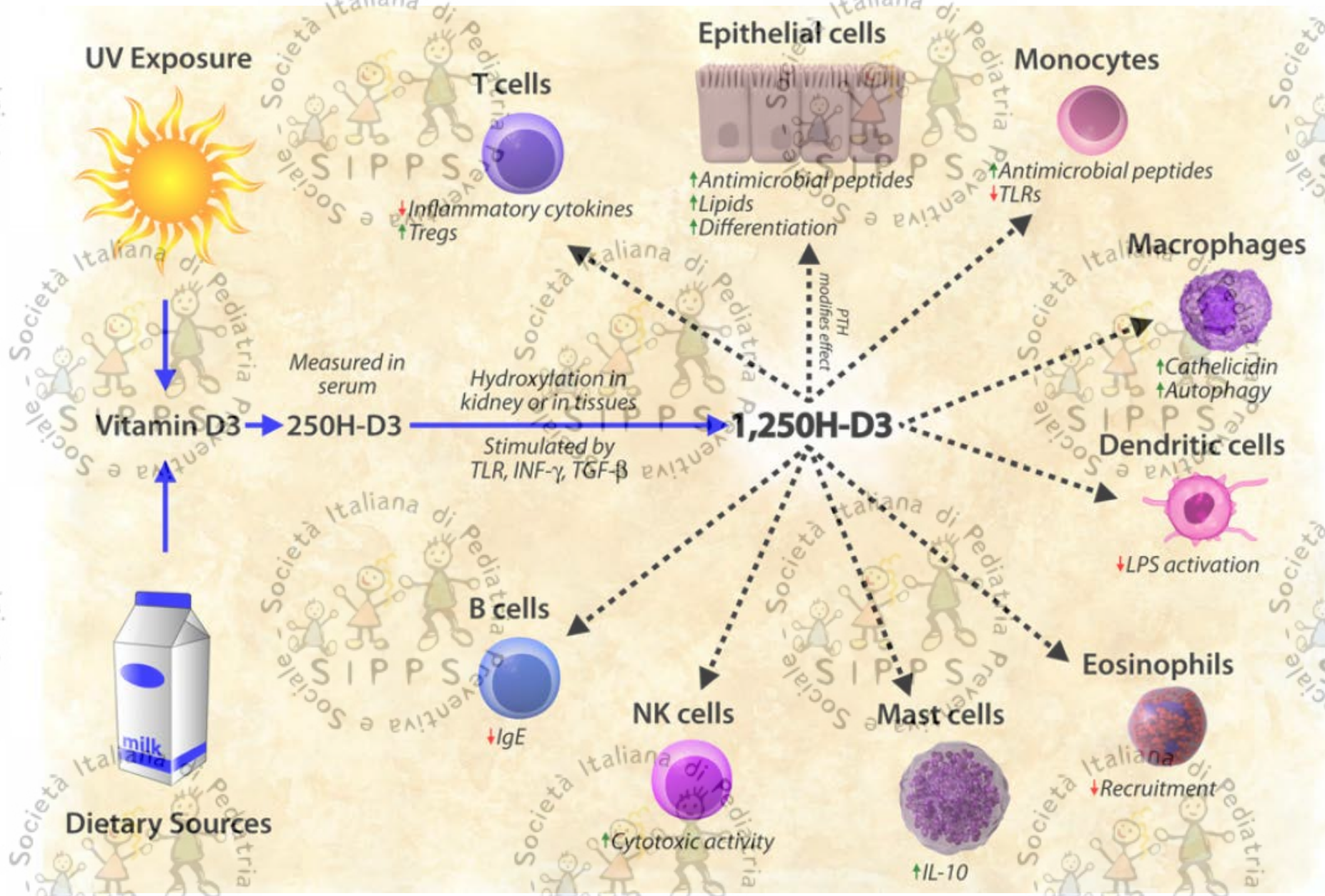


✓The **vitamin D receptor** (VDR), the nuclear hormone receptor that mediates most if not all of the functions of its preferred ligand 1,25 dihydroxyvitamin D [1,25(OH)2D] or calcitriol, **is found in most tissues of the body.**

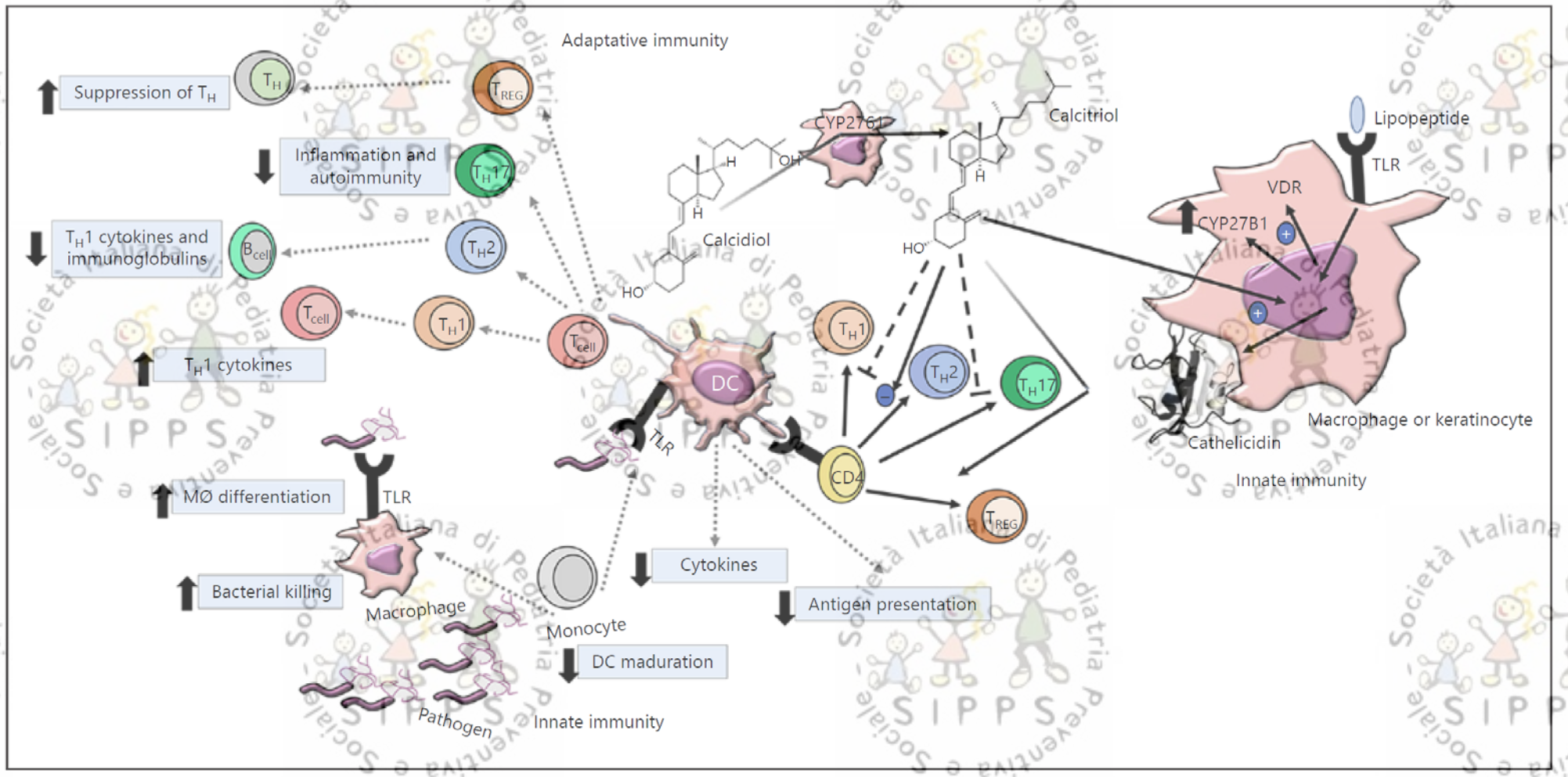
✓Indeed, many of these tissues also contain the **enzyme, CYP27B1,** which converts the major circulating metabolite of vitamin D, 25 hydroxyvitamin D (25OHD calcidiol), to 1,25(OH)2D (calcitriol).

✓Thus, it has been suspected for some time that **vitamin D exerts its actions not only on classic tissues regulating calcium homeostasis** such as **bone**, **gut** and **kidney** but also on **other tissues**.

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



Vitamin D: Classic and Novel Actions. A Gil, Ann Nutr Metab 2018;72:87

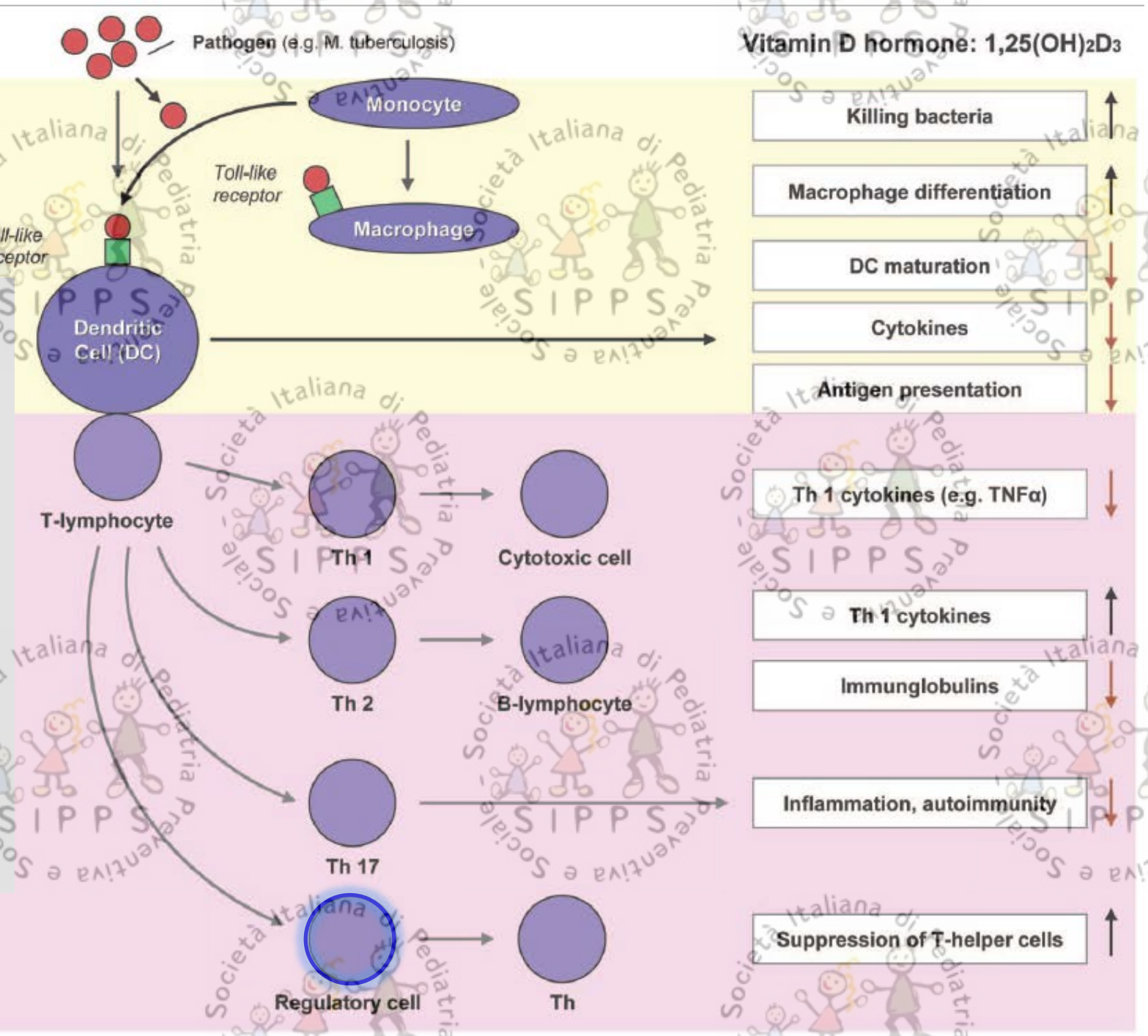


Vitamin D novel actions in the immune system

Vitamin D and immune system.

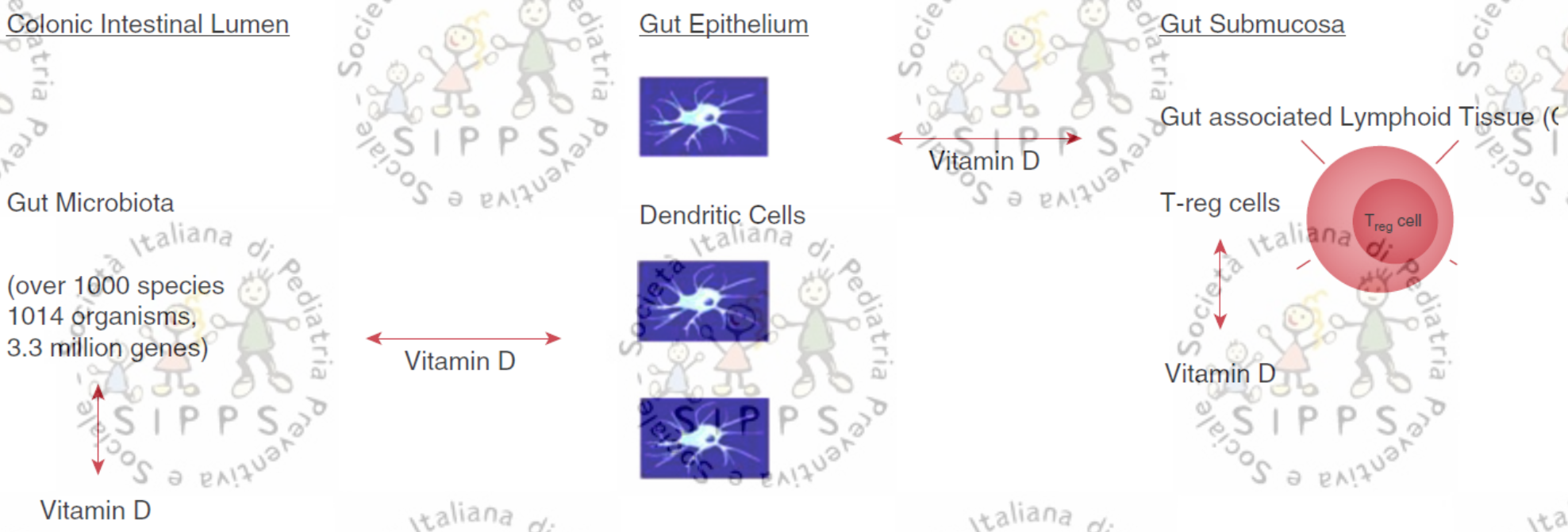
1α,25(OH)2D appears to influence susceptibility to and severity of infection via multiple mechanisms via the innate and adaptive immune system.

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



Vitamin D, the Gut Microbiome, and the Hygiene Hypothesis. How Does Asthma Begin?

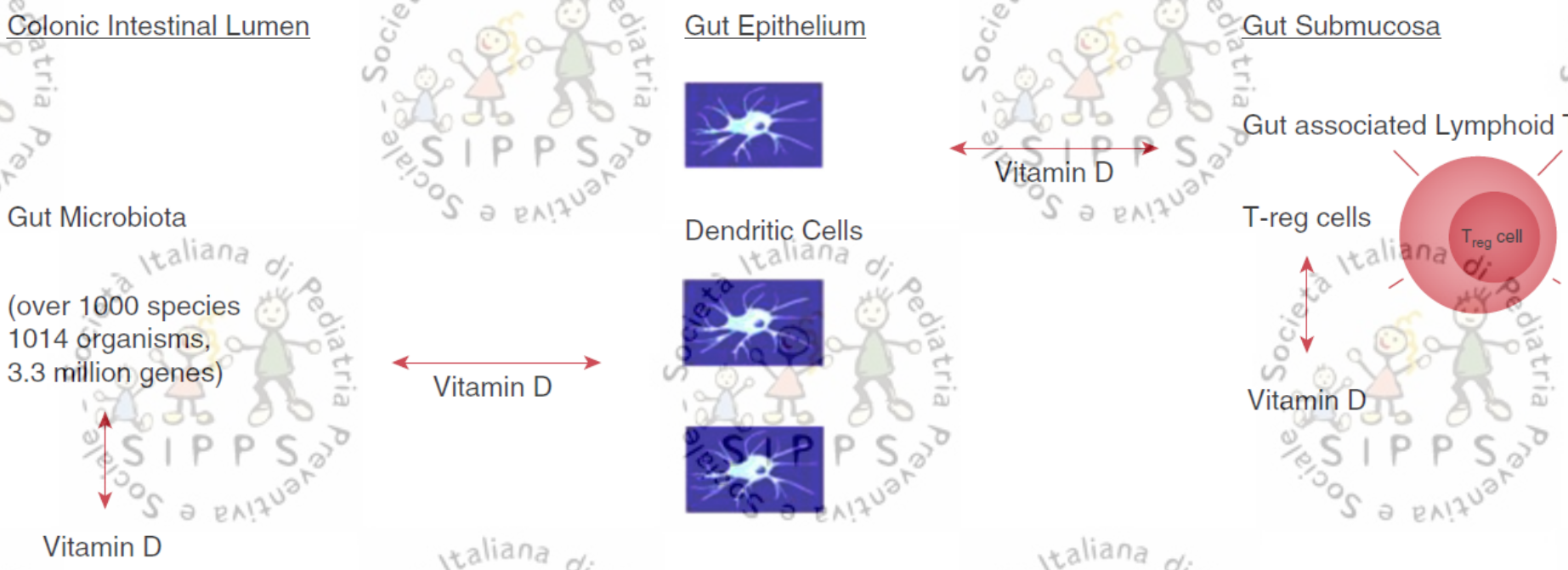
S Weiss, AJCCM, 2015; 191:492



Interactions of vitamin D with the gut microbiome and the fetal immune system. Vitamin D up-regulates **TGF-beta1 and IL-10**, which will **enhance Treg function and down-regulate CD4 T cells**, reducing both Th1 and Th2 CD41 cell inflammation.

Vitamin D, the Gut Microbiome, and the Hygiene Hypothesis. How Does Asthma Begin?

S Weiss, AJCCM, 2015; 191:492



Vitamin D also **enhances antigenic traffic between dendritic cells and Tregs**. **The gut microbiome** is the primary source of antigen for Treg cell processing and may also influence the development of immunity in the fetus. Vitamin D controls the development of GALT and dendritic cell trafficking from the gut dendritic cells in the gut epithelium to the Tregs.

Saggese et al. Italian Journal of Pediatrics (2018) 44:51
https://doi.org/10.1186/s13052-018-0488-7

Italian Journal of Pediatrics

REVIEW Open Access

Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians

Giuseppe Saggese[1†], Francesco Vierucci[2*†], Flavia Prodam[3], Fabio Cardinale[4], Irene Cetin[5], Elena Chiappini[6], Gian Luigi de' Angelis[7], Maddalena Massari[5], Emanuele Miraglia Del Giudice[8], Michele Miraglia Del Giudice[8], Diego Peroni[1], Luigi Terracciano[9], Rino Agostiniani[10], Domenico Careddu[11], Daniele Giovanni Ghiglioni[12], Gianni Bona[13], Giuseppe Di Mauro[14] and Giovanni Corsello[15]

Table 1 Vitamin D content in some foods

Food	Vitamin D average content (IU)
Milk and dairy products	
Cow's milk	5–40/l
Goat's milk	5–40/l
Butter	30/100 g
Yogurt	2.4/100 g
Cream	30/100 g
Other Foods	
Pork	40–50/100 g
Beef liver	40–50/100 g
Snapper (genus *Dentex dentex*), cod, gilthead (*Sparus auratus*), dogfish (*Mustelus mustelus*), sole, trout, salmon, herring	300–1500/100 g
Cod liver oil	400/5 ml
Egg yolk	20/100 g

Table 6 Risk factors for vitamin D deficiency in the first year of life

- Non-Caucasian ethnicity with dark skin pigmentation
- Inadequate diets (i.e. vegan diet)
- Chronic kidney disease
- Hepatic failure and/or cholestasis
- Malabsorption syndromes (i.e. cystic fibrosis, inflammatory bowel diseases, celiac disease at diagnosis, etc.)
- Chronic therapies: anticonvulsants, systemic glucocorticoids, antiretroviral therapy, systemic antifungals (i.e. ketoconazole)
- Infants born from mothers with multiple risk factors for vitamin D deficiency, particularly in absence of vitamin D supplementation during pregnancy

Table 7 Risk factors for vitamin D deficiency between 1 and 18 years of age

- Non-Caucasian ethnicity with dark skin pigmentation
- Reduced sunlight exposure (due to lifestyle factors, chronic illness or hospitalization, complex disability, institutionalization, covering clothing for religious or cultural reasons) and/or constant use of sunscreens
- International adoption
- Obesity
- Inadequate diets (i.e. vegan diet)
- Chronic kidney disease
- Hepatic failure and/or cholestasis
- Malabsorption syndromes (i.e. cystic fibrosis, inflammatory bowel diseases, celiac disease at diagnosis, etc.)
- Chronic therapies: anticonvulsants, systemic glucocorticoids, antiretroviral therapy, systemic antifungals (i.e. ketoconazole)

Table 2 Definition of vitamin D status according to several Societies and Organizations in the last 10 years

Society/Organization	Year	Severe deficiency	Deficiency	Insufficiency	Sufficiency/A
Canadian Pediatric Society [8]	2007	–	< 10 ng/ml	10–29 ng/ml	≥ 30 ng/ml
Lawson Wilkins Pediatric Endocrine Society [9]	2008	< 5 ng/ml	5–14 ng/ml	15–19 ng/ml	≥ 20 ng/ml
Institute of Medicine [10]	2011	–	< 12 ng/ml	12–20 ng/ml[a]	≥ 20 ng/ml
The Endocrine Society [11]	2011	–	< 20 ng/ml	21–29 ng/ml	≥ 30 ng/ml
British Paediatric and Adolescent Bone Group [12]	2012	–	< 10 ng/ml	10–19 ng/ml	≥ 20 ng/ml
French Society of Paediatrics [13]	2012	–	< 20 ng/ml	–	≥ 20 ng/ml
Asociación Espanola de Pediatría (Spain) [14]	2012	–	< 20 ng/ml	–	≥ 20 ng/ml
Federal Commission for Nutrition (Switzerland) [15]	2012	< 10 ng/ml	< 20 ng/ml	–	≥ 20 ng/ml
Nordic Nutrition Recommendations [16]	2012	–	< 12 ng/ml	12–20 ng/ml	≥ 20 ng/ml
German Nutrition Society [17]	2012	–	–	–	≥ 20 ng/ml
Health council of the Netherlands [18]	2012	–	–	–	≥ 12 ng/ml
European Society for Paediatric Gastroenterology Hepatology and Nutrition [19]	2013	< 10 ng/ml	< 20 ng/ml	–	≥ 20 ng/ml

IL RUOLO DELLA VITAMINA D E DEI PROBIOTICI NELLA IMMUNO-MODULAZIONE DELLA RISPOSTA ALLERGICA

Vitamina D: L'azione

Diego Peroni

U.O. di Pediatria

Università di Pisa

✓ L'associazione

diego.peroni@unipi.it

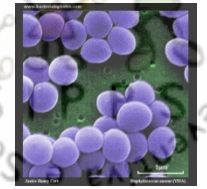
Studi che hanno valutato l'associazione tra dermatite atopica e vitamina D

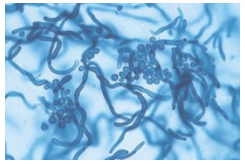
Studio	Conclusione
Dermatite atopica (AD) Camargo CA et al. 2007	Assunzione materna di vitamina D non correlata con insorgenza precoce di eczema infantile
Sidbury R et al. 2008	Beneficio non statisticamente significativo (nessuna differenza rilevante nel punteggio medio clinico di severità della DA, vitamina D vs placebo)
Oren E et al. 2008	Aumentata probabilità di DA nei pazienti obesi con deficienza di vitamina D rispetto a quelli con livelli di vitamina D normali
Gale CR et al. 2008	Aumentati livelli sierici di vitamina D nella madre hanno prodisposto lo sviluppo di DA nel bambino a 9 mesi
Back O et al. 2009	L'aumento di assunzione di vitamina D durante l'infanzia correlava con un aumentato rischio di DA a 6 anni
Myake Y et al. 2010	Ridotto rischio di DA infantile sopra un livello soglia di assunzione di vitamina D da parte della madre in gravidanza
Peroni DG et al. 2011	In una serie di 37 bambini italiani, riscontrata correlazione inversa tra concentrazione sierica di vitamina D e severità della DA
Javanbakht MH et al. 2011	La vitamina D, da sola o in associazione alla vitamina E, ha dimostrato un miglioramento significativo dell'indice SCORAD rispetto a placebo

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

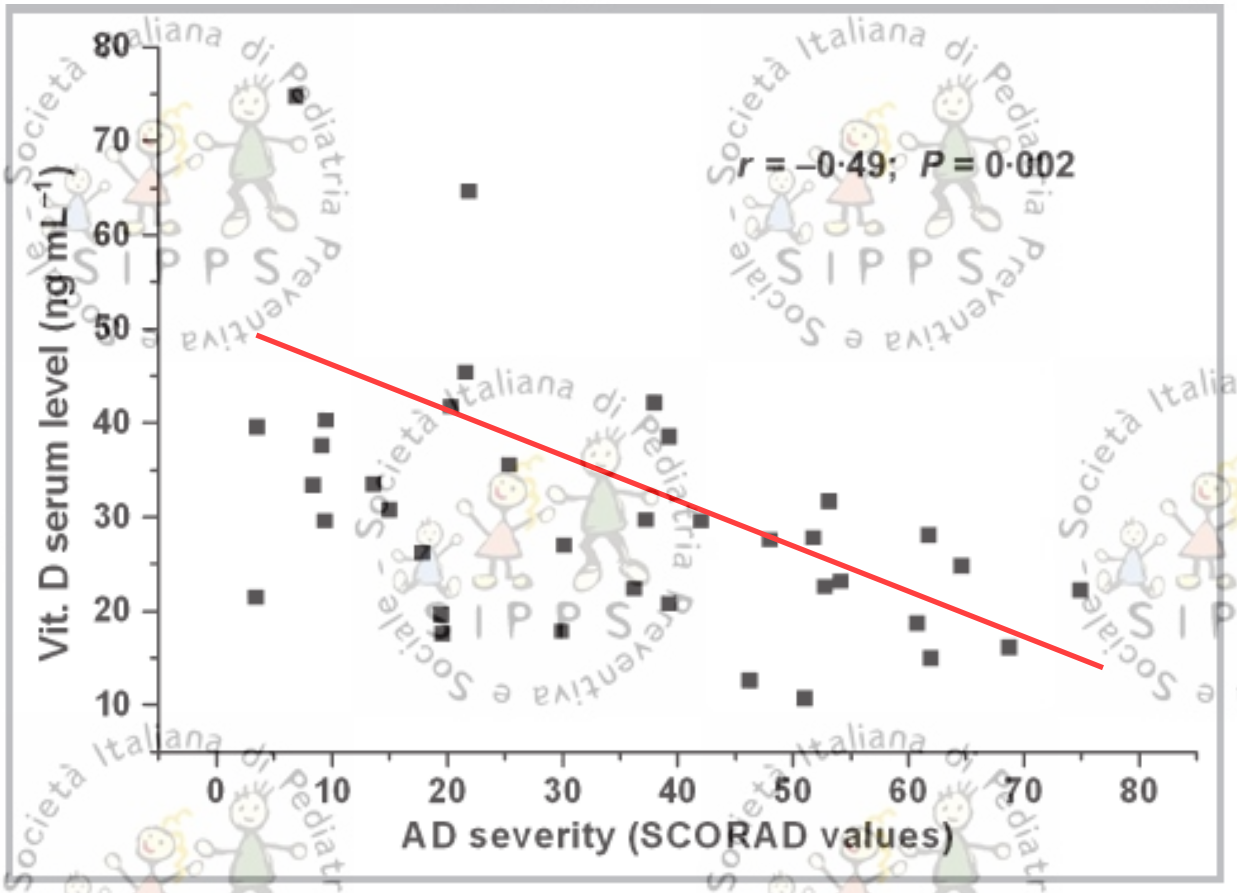
Peroni DG, Br J Dermatol. 2011;164:1078-82.

- ✓37 children (8 months and 12 years) with AD,
- ✓SCORAD index,
- ✓Serum levels of 25-hydroxyvitamin D
- ✓sIgE to *S. aureus* and to *M. furfur*





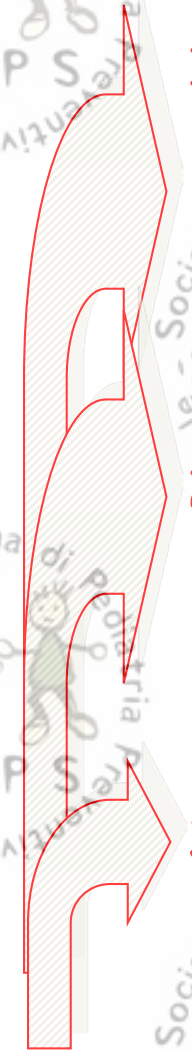
Correlation between serum vitamin D levels and individual SCORAD values.



Serum Vitamin D levels and Vitamin D supplementation do not correlate with the severity of chronic eczema in children. *Galli E, Eur Ann Allergy Clin Immunol. 2015;47(2):41-7.*

✓89 children with chronic eczema divided into two groups according to the state of sensitization (YES/NO).

✓a daily oral Vitamin D3 supplementation (2000 IUs) for 3 months or no supplementation.



1) Vitamin D concentrations in patients with moderate and severe eczema were not statistically different from Vitamin D concentration detected in the serum of patients with mild eczema.

2) No correlation was found between Vitamin D levels, total IgEs and SCORAD index, both in the Sensitized and in the Not-Sensitized group.

3) Vitamin D3 supplementation did not influence the SCORAD severity or the total IgEs concentration.

Altri studi che hanno valutato l'associazione tra dermatite atopica e vitamina D

Autore	Popolazione	Outcome	Risultati
Baiz 2014	293 neonati	ISAAC a 1-2-3-5 anni	Per ogni 5 ng/ml di incremento associazione negativa con la dermatite atopica. OR all'età di 1-3-5 anni: 0,84 (IC 95% 0,71-1,00), 0,82 (IC 95% 0,68-0,97) e 0,75 (IC 95% 0,63-0,88); OR per dermatite atopica precoce o tardiva (a 2 anni) 0,73 (IC 95% 0,62-0,90) e 0,75 (IC 95% 0,60-0,94).
Han 2015	39 adulti 33 bambini affetti (70 adulti e e 70 bambini gruppo di controllo)	Confronto livelli di 25(OH)D e correlazione con SCORAD	Livelli di 25(OH)D significativamente ridotti nei bambini con dermatite atopica (15,06 ± 4,64 ng/ml) in confronto con i bambini del gruppo di controllo (16, 25 ± 6,60 ng/ml) (p=0,036). Nessuna correlazione con lo SCORAD.
Wang 2014	498 bambini con dermatite atpica e 328 controlli no allergici	I soggetti sono stati classificati come deficienti (< 10 ng/ml), insufficienti (10-20 ng/ml) e sufficienti (≥ 20 ng/ml). La severità a lungo e a breve termine della dermatite atopica è stata valutata mediante SCORAD e NESS	I livelli di 25(OH)D (media ± DS) nei pazienti e nei controlli erano rispettivamente di 11,56 ± 6,12 ng/ml e 13,68 ± 5,8 ng/ml (p<0.001). La gravità della dermatite atopica valutata con SCORAD e NESS mostrava una associazione inversa con i livelli di 25(OH)D.
Baek 2014	226 bambini con dermatite atopica ed allergia alimentare	Livelli di 25(OH)D e severità della dermatite atopica	Il deficit di vitamina D aumenta il rischio di allergia alimentare (OR 5,0; IC 95% 1,8-14,1), specialmente a latte (OR 10,4; IC 95% 3,3-32,7) e grano (OR 4,2; IC 95% 1,1-15,8). Lo SCORAD è associato in maniera indipendente ai livelli di 25(OH)D dopo aver corretto per il livello di sensbilizzazione (p=0,031).
Chiu 2015	164 coppie madre bambino	Sensibilizzazione allergica, prevalenza di asma e dermatite atopica	Livelli materni di 25(OH)D < 20 ng/ml si associavano ad una maggiore prevalenza di sensibilzzazione allergica a 2 anni. Livelli elevati di 25(OH)D si associavano a minore rischio di eczema (OR 0,12; IC 95% 0,02-0,63; p=0,012) e asma (OR 0,22; IC 95% 0,06-0,92; p=0,038) all'età di 4 anni.

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

Baiz N, JACI; 2014; 133:147

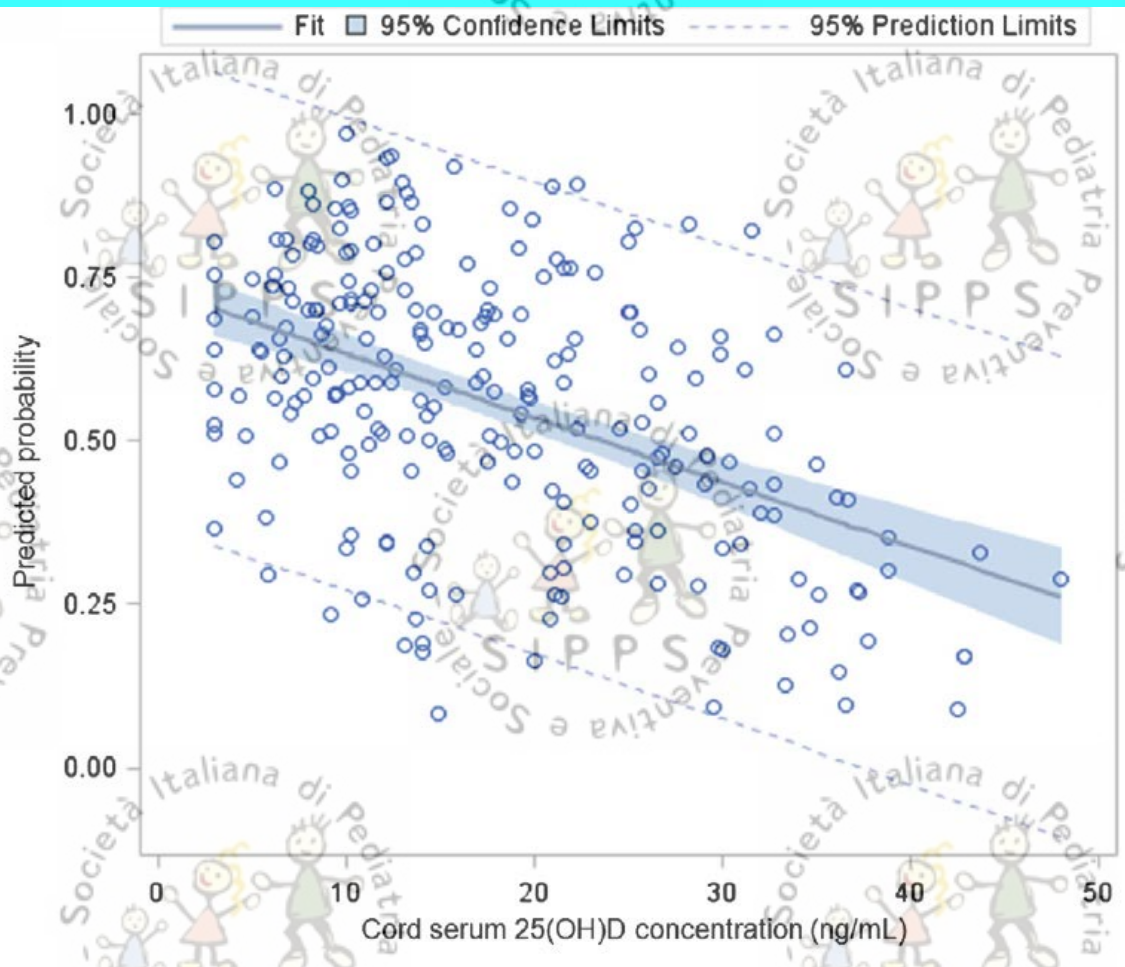
aim was to investigate in

239 newborns the

associations between cord serum 25(OH)D levels and

asthma,wheezing, allergic rhinitis, and atopic dermatitis in the offspring from birth to 5 years.

Adjusted associations between cord serum 25(OH)D levels and predicted probabilities of atopic dermatitis by age of 5 years



Low Retinol-Binding Protein and Vitamin D Levels Are Associated with Severe Outcomes in Children Hospitalized with Lower Respiratory Tract Infection and Respiratory Syncytial Virus or Human Metapneumovirus Detection. JL Hurwitz, J Pediatr 2017;187:323

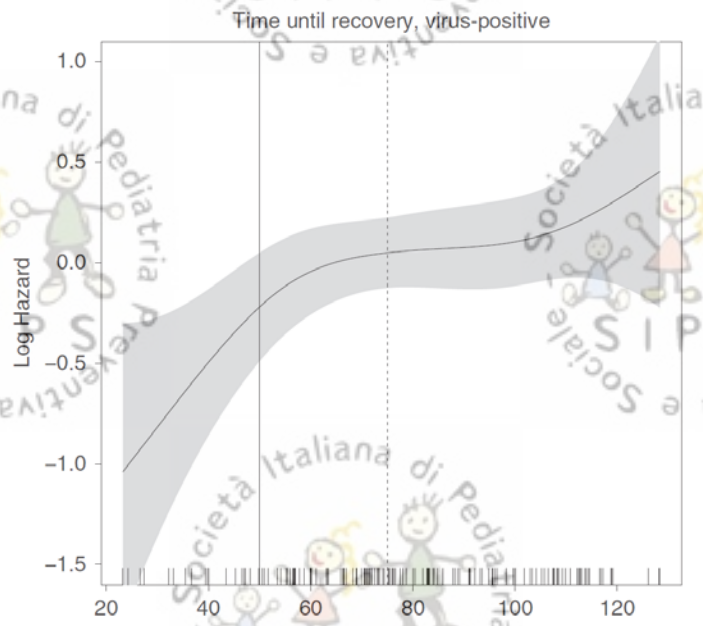
Table II. Bivariate comparison of clinical outcomes between vitamin deficiency groups

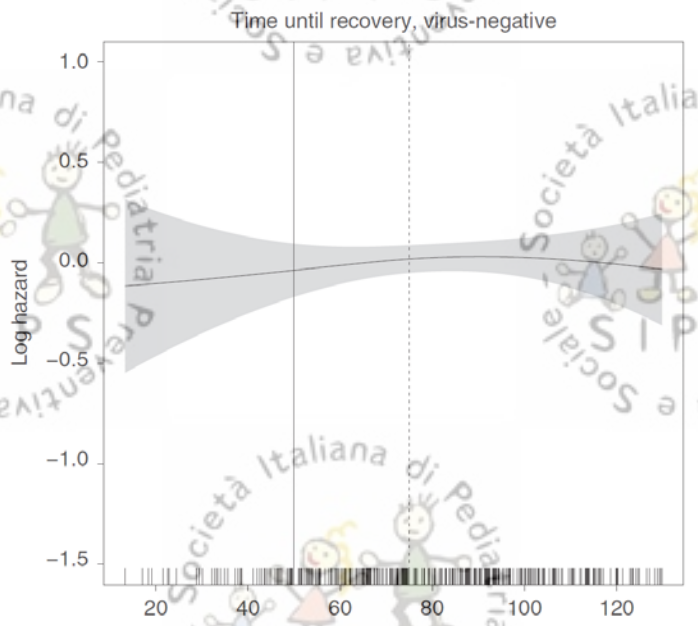
	Outcomes		
Deficiency groups	LOS >3 d	ICU admission	Mechanical ventilation
Vitamin A			
VAD (n = 41), n (%)	18 (44)	11 (27)	4 (10)
Non-VAD (n = 49), n (%)	22 (45)	4 (8)	2 (4)
P value, VAD vs non-VAD	1.00	.02	.41
OR (95% CI)	0.96 (0.42-2.21)	4.13 (1.20-14.17)	2.54 (0.44-14.64)
Vitamin D			
VDD (n = 11), n (%)	6 (55)	4 (36)	3 (27)
Non-VDD (n = 79), n (%)	34 (43)	11 (14)	3 (4)
P value (VDD vs non-VDD)	.53	.08	.02
OR (95% CI)	1.59 (0.45-5.64)	3.53 (0.89-14.1)	9.5 (1.64-55.13)
Vitamin A and vitamin D			
VAD+VDD (n = 7), n (%)	4 (57)	3 (43)	2 (29)
Neither deficiency (n = 45), n (%)	20 (44)	3 (7)	1 (2)
P value, VAD+VDD vs neither deficiency	.69	.03	.04
OR (95% CI)	1.67 (0.33-8.32)	10.5 (1.57-70.25)	17.6 (1.34-230.5)

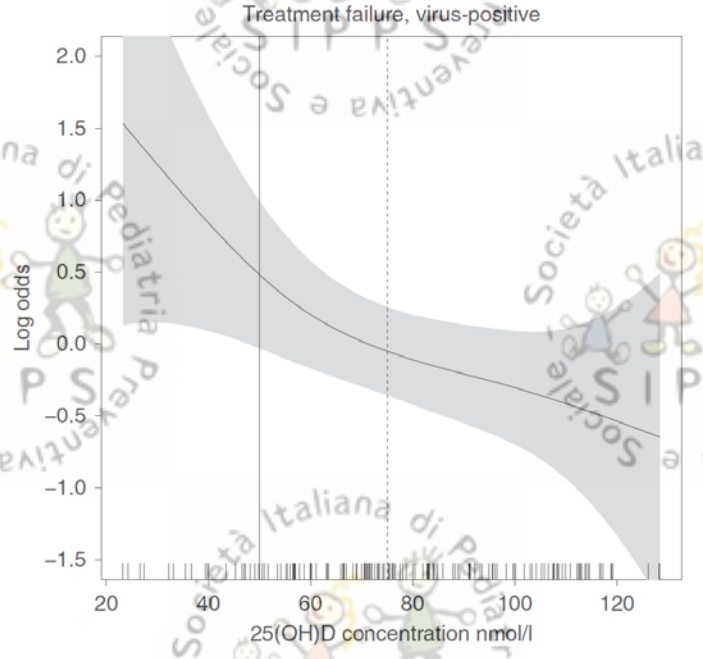
VAD and VDD were commonly detected among children aged <5 years in Memphis hospitalized with LRTI and RSV and/or hMPV detection.
Low vitamin levels were correlated with severe disease, supporting the continued evaluation of both vitamin A and D levels in US children

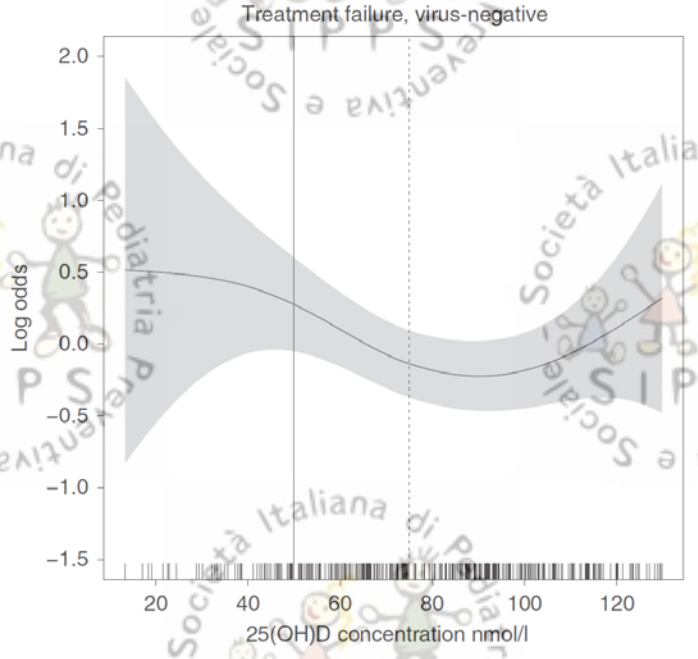
Vitamin D status is associated with treatment failure and duration of illness in Nepalese children with severe pneumonia.
Haugen J, Ped Res 2017

Our findings indicate that low vitamin D status (25(OH)Do50 nmol/l) is an independent risk factor for treatment failure and delayed recovery from severe lower respiratory infections in children









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

Shen-Hao Lai. 2017, PLoS ONE 12(3):e0173268

122 mother-infant pairs were enrolled

Maternal and cord blood were collected for determining the 25(OH)D level.

Questionnaires were recorded at birth and 6 months of age.

Infant lung function, including tidal breathing analysis, respiratory mechanics, and forced tidal expiration, was tested at 6 months of age

Table 3. Multiple linear regression analysis of lung function outcome (Z score of Rrs).

	Beta (s.e.)[#]	t	p value
High cord 25(OH)D	0.252 (0.088)	2.736	**0.005**
AR, father	-0.232 (0.103)	-2.416	**0.018**
Maternal smoke in pregnancy	-0.396 (0.196)	-2.024	**0.032**
NP colonization	-0.121 (0.90)	-1.353	0.182
Male	-0.109 (0.087)	-1.255	0.215
Asthma, mother	-0.144 (0.152)	-0.946	0.348
(Constant)	0.110 (0.102)	1.082	0.284
$R^2 = 0.293$			

AR, allergic rhinitis; NP, nasopharyngeal cavity.

[#] Beta (s.e.), regression coefficient (standard error)

Infants with low cord serum 25(OH)D levels have poorer lung function at 6 months of age compared with those with high levels. They also have a higher risk of a respiratory tract infection before this age.

Serum Vitamin D Levels and Markers of Severity of Childhood Asthma in Costa Rica

Brehm Am J Respir Crit Care Med 2009;179:765

- ✓ 25-hydroxyvitamin D levels
- ✓ 616 asthmatic children
- ✓ Vitamin D levels deficient (<20 ng/ml), insufficient (≥20 and <30 ng/ml), and sufficient (≥30 ng/ml)

Vitamin D levels were significantly and inversely associated with:

1) **total IgE and eosinophil count**

2) any **hospitalization** in the previous year (p=0.03),

3) any **use of anti-inflammatory medications** in the previous year (p=0.01),

4) **increased airway responsiveness** (p = 0.05).

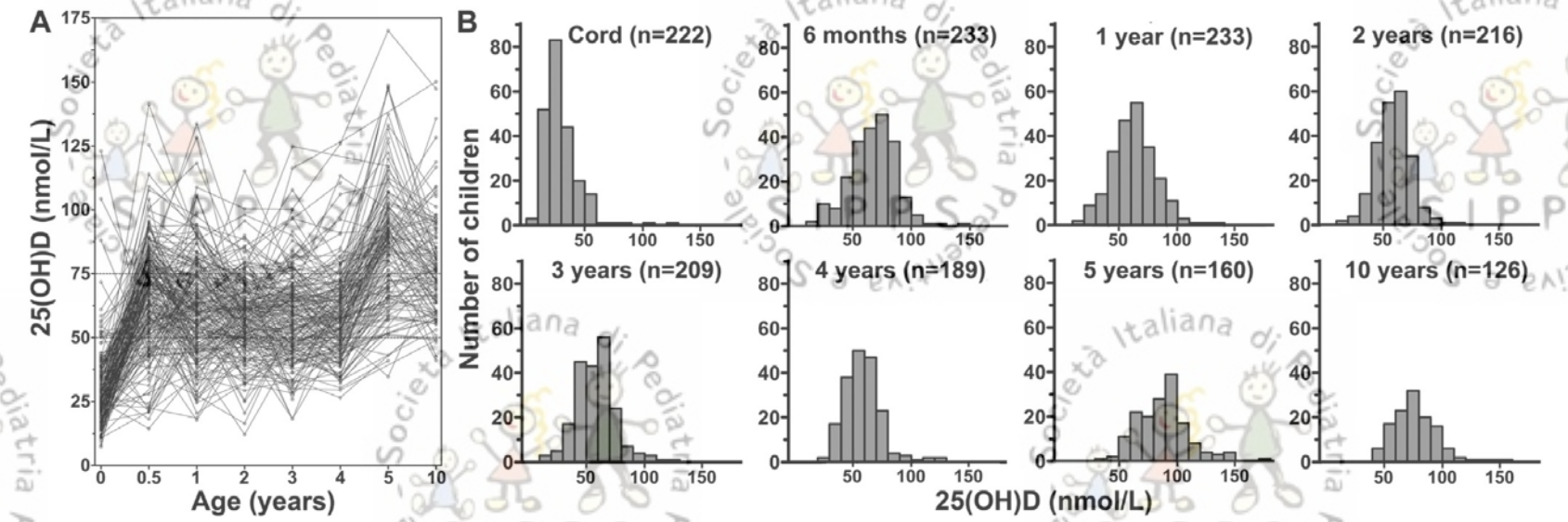
Vitamin D over the first decade and susceptibility to childhood allergy and asthma.

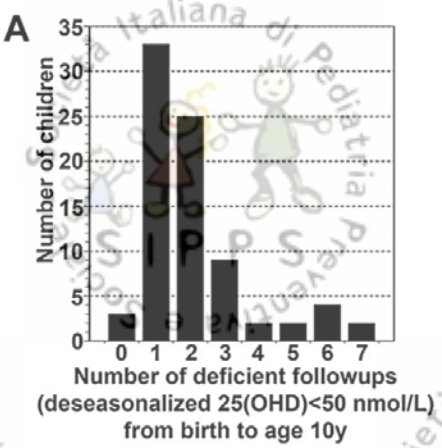
Hollams, JACI; 2017;139:472

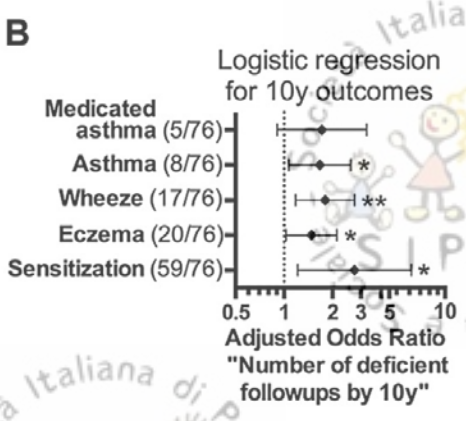
Asthma-, allergy-, and respiratory tract infection–associated phenotypes (including pathogen identification) were characterized in a high-risk birth cohort.

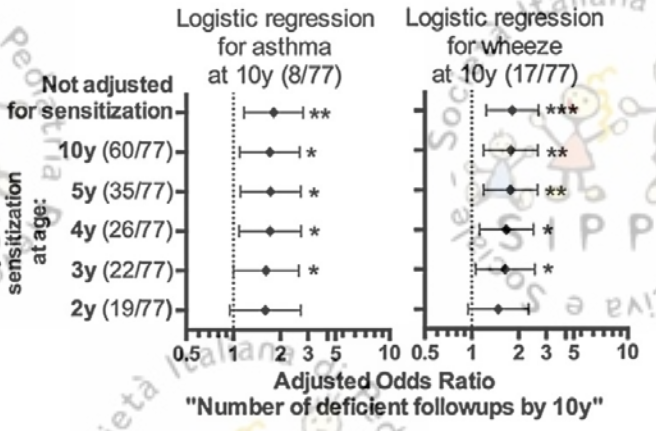
Plasma 25(OH)D concentrations were quantified at birth and at clinical follow-ups at the ages of 0.5, 1, 2, 3, 4, 5, and 10 years.

Relationships with clinical outcomes









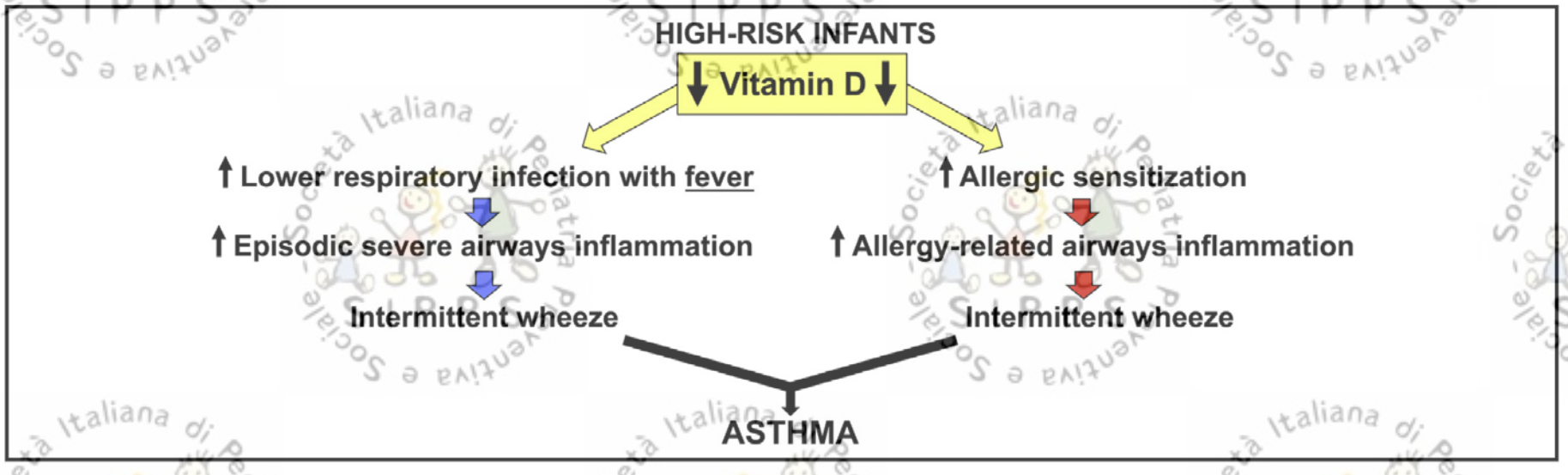
Vitamin D over the first decade and susceptibility to childhood allergy and asthma.

Hollams, JACI; 2017;139:472

Asthma-, allergy-, and respiratory tract infection–associated phenotypes (including pathogen identification) were characterized in a high-risk birth cohort.

Plasma 25(OH)D concentrations were quantified at birth and at clinical follow-ups at the ages of 0.5, 1, 2, 3, 4, 5, and 10 years.

Relationships with clinical outcomes



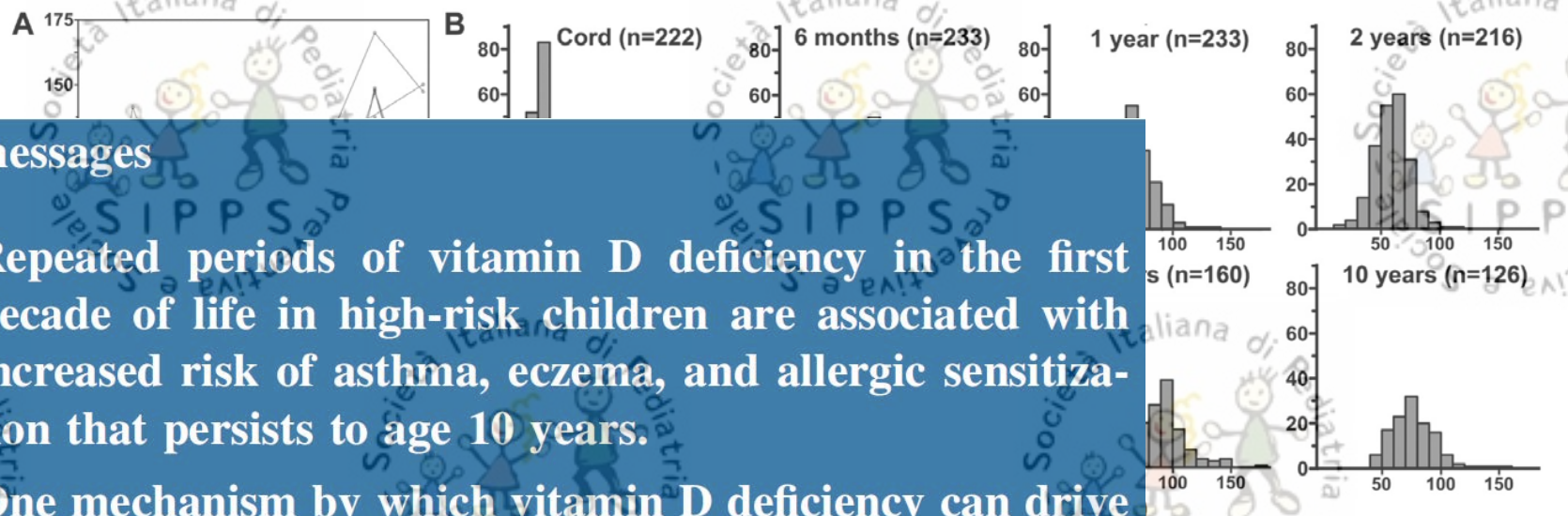
Vitamin D over the first decade and susceptibility to childhood allergy and asthma.

Hollams, JACI; 2017;139:472

Asthma-, allergy
respiratory trac
infection-associ
phenotypes (incl
pathogen
identification) w
characterized in
high-risk birth c

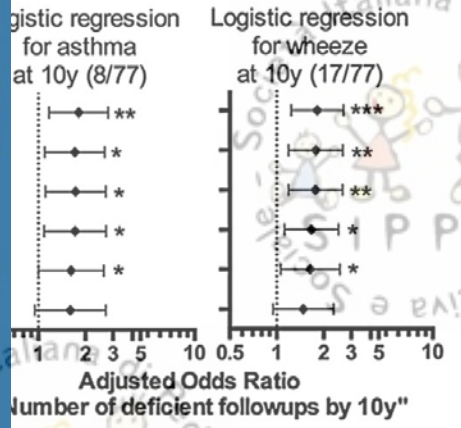
Plasma 25(OH)D
concentrations w
quantified at bir
at clinical follow
the ages of 0.5,
4, 5, and 10 year

Relationships wit
clinical outcomes



Key messages

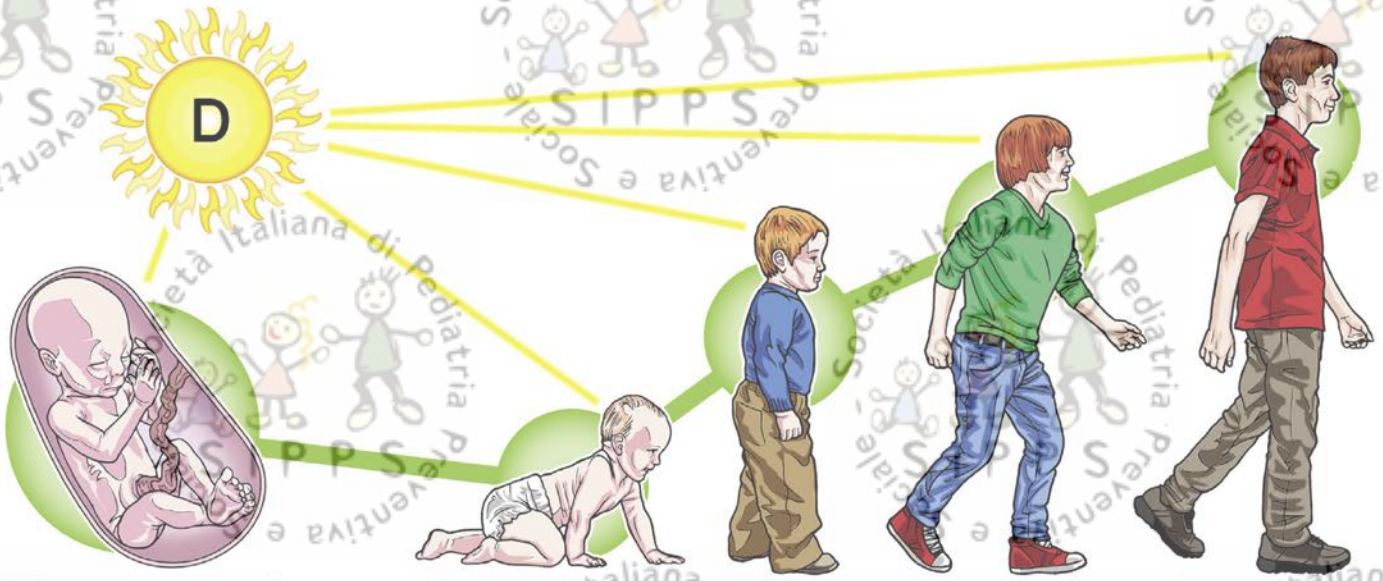
- Repeated periods of vitamin D deficiency in the first decade of life in high-risk children are associated with increased risk of asthma, eczema, and allergic sensitization that persists to age 10 years.
- One mechanism by which vitamin D deficiency can drive asthma development is by promoting early allergic sensitization, a known proasthmatic factor in high-risk children. We have observed an inverse relationship between 25(OH)D concentration and concurrent sensitization across the first decade of life, which was most pronounced during infancy.
- Vitamin D deficiency is also associated with early postnatal colonization of the airways by pathogenic bacteria, which has been recently identified as a risk factor for subsequent asthma development.



Vitamin D status through the first 10 years of life: A vital piece of the puzzle in asthma inception.

Litonjua A, J Allergy Clin Immunol 2017;139:459

Adequate vitamin D status prenatally and throughout childhood in the prevention of asthma and allergies. FVC, Forced vital capacity.



In utero

- Placental development
- Fetal programming
  - Gene expression
  - Epigenetic programming
- Lung development
  - Maturation
  - Sufactant production
- Immune development

Childhood

- Protection against allergies
- Establishment of a favorable microbiome (airway, intestinal)
  - Improved handling of respiratory infections
  - Decreased post-infection inflammation
- Normal lung growth
  - Normal FEV1 and FVC
  - Prevention of smooth muscle hypertropy and decreased inflammation
  - No airway hyperresponsiveness
- Immune regulation
  - Balanced Th1/Th2 response
  - Modulation of Th17 response
  - Potentiates tolerogenic potential of dendritic cells
- Genomic effects
  - Gene expression and regulation

IL RUOLO DELLA VITAMINA D E DEI PROBIOTICI NELLA IMMUNO-MODULAZIONE DELLA RISPOSTA ALLERGICA

Vitamina D: L'azione

Diego Peroni

U.O. di Pediatria

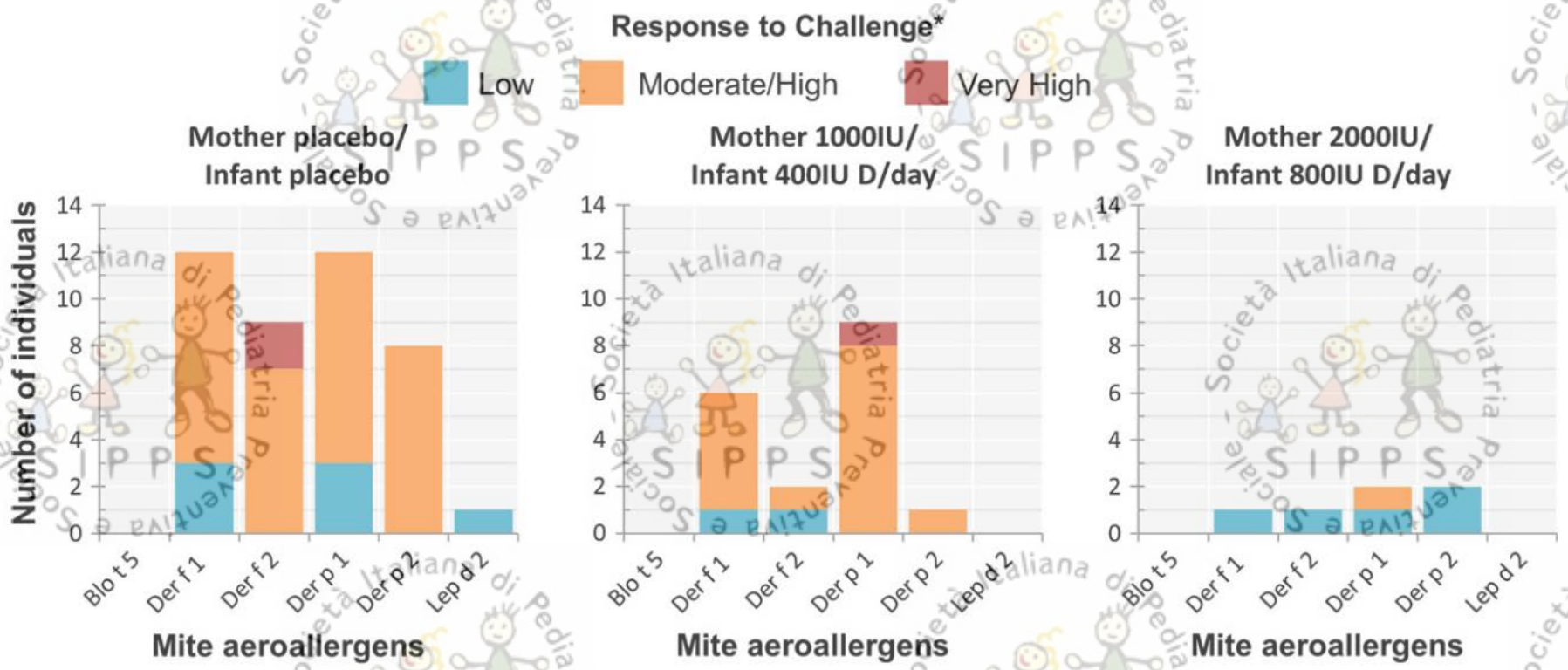
Università di Pisa

✓ **La supplementazione**

diego.peroni@unipi.it

Vitamin D supplementation during pregnancy and infancy reduces aeroallergen sensitization: a randomized controlled trial.

Grant, Allergy 2016



Woman/infant pairs were randomized to: placebo/placebo, 1000 IU/400 IU or 2000 IU/800 IU. When the children were 18 months old, we measured sIgE and identified acute primary care visits

Effect of Vitamin D3 Supplementation During Pregnancy on Risk of Persistent Wheeze in the Offspring. Chawes, JAMA. 2016;315(4):353.

COPSAC study cohort.

Vitamin D3 (2400 IU/d; n=315) or matching placebo tablets (n=308) from pregnancy week 24 to 1 week postpartum.

All women received 400 IU/d of vitamin D3 as part of usual pregnancy care.

Age at onset of persistent wheeze in the first 3 years of life

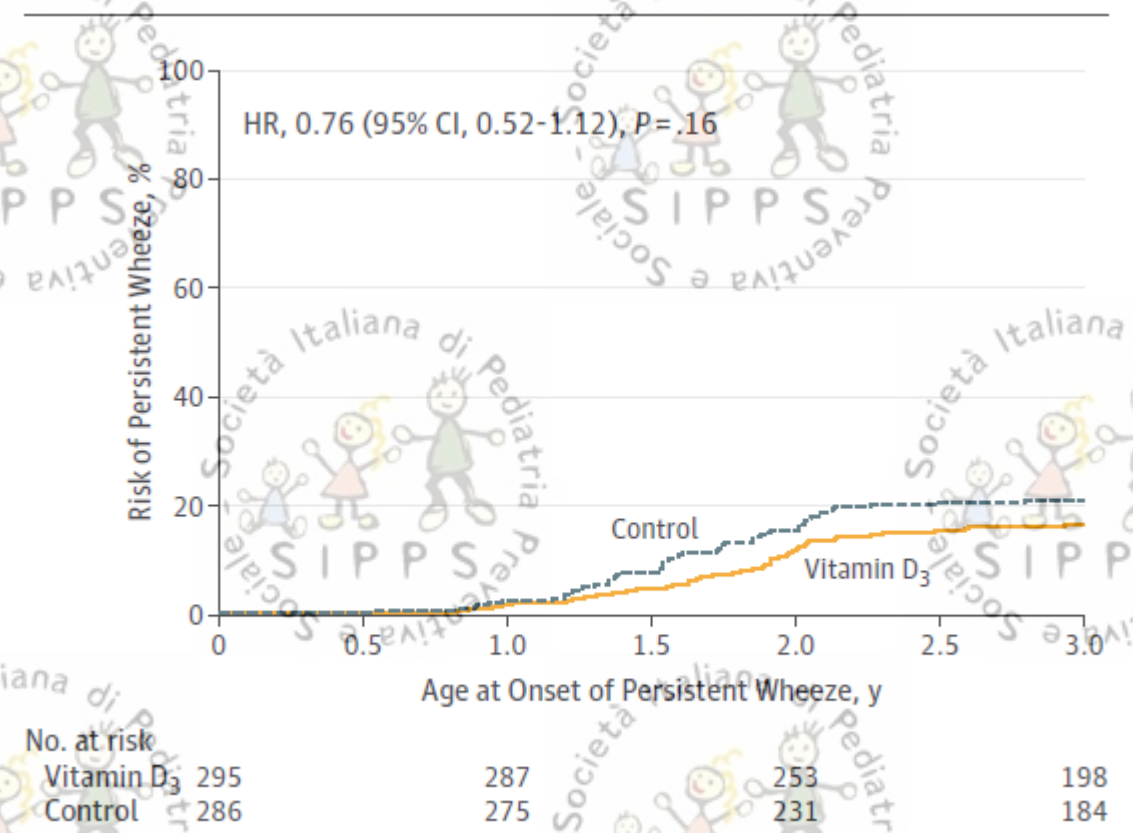
End Point	Vitamin D_3	Control	Estimate (95% CI)	*P* Value
Persistent wheeze, No. (%)	47 (16)	57 (20)	Hazard ratio (HR), 0.76 (0.52-1.12)	.16
Episodes of troublesome lung symptoms, mean (95% CI)	5.9 (5.2-6.6)	7.2 (6.4-8.1)	Incidence risk ratio (IRR), 0.83 (0.71-0.97)	.02
Asthma at 3 y, No. (%)	32 (12)	47 (14)	Odds ratio, 0.82 (0.50-1.36)	.45
Respiratory tract infections				
Upper, annual mean (95% CI)	5.2 (4.8-5.5)	5.3 (4.9-5.6)	IRR, 0.99 (0.90-1.09)	.84
Lower, No. (%)	94 (32)	95 (33)	HR, 0.96 (0.72-1.27)	.76

Effect of Vitamin D3 Supplementation During Pregnancy on Risk of Persistent Wheeze in the Offspring. Chawes, JAMA. 2016;315(4):353.

The use of 2800 IU/d of vitamin D3 during the third trimester of pregnancy compared with 400 IU/d did not result in a statistically significant reduced risk of persistent wheeze in the offspring through age 3 years.

However, interpretation of the study is limited by a wide CI that includes a clinically important protective effect.

Effect of Vitamin D3 Supplementation on Risk of Persistent Wheeze in Children in the COPSAC



Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years.

Litonjua, JAMA. 2016;315(4):362

The Vitamin D Antenatal Asthma Reduction Trial 440 women were randomized to receive daily 4000 IU vitamin D plus 400 IU, and 436 women were randomized to receive a placebo plus a prenatal vitamin containing 400 IU vitamin D.

Coprimary outcomes of (1) parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age and (2) third trimester maternal 25-hydroxyvitamin D levels.

Table 3. Treatment Comparisons for Primary and Secondary Outcomes in the Vitamin D Antenatal Asthma Reduction Trial

	Vitamin D, IU/d			
	4400	400	Difference (95% CI)	*P* Value[a]
No. of offspring	405	401		
Coprimary End Points[b]				
Asthma or recurrent wheeze in first 3 y of life[c]				
Positive, No. (%)	98 (24.3)	120 (30.4)	−6.1 (−30 to 18)	.051
HR (95% CI)	0.8 (0.6 to 1.0)	1 [Reference]		
25 Hydroxyvitamin D ≥30 ng/mL[d]				
Women positive, No. (%)	289 (74.9)	133 (34.0)	40.9 (34.2 to 47.5)	<.001

Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years.

Litonjua, JAMA. 2016;315(4):362

The Vitamin D Antenatal Asthm… Tr…ized to receive daily 400… in… ed to receive a pla…

Coprimary… recurrent… hydrox…

Tab…

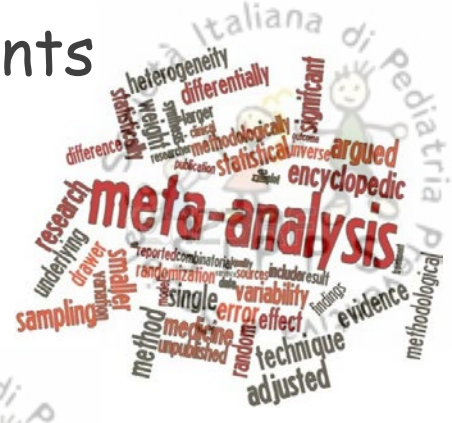
No. of of…	
Coprim…	
Asthm…	
Posi…	.051
HR (95…	
25 Hydroxyvitamin D…	
Women positive, No. (%)	…2 to 47.5) <.001

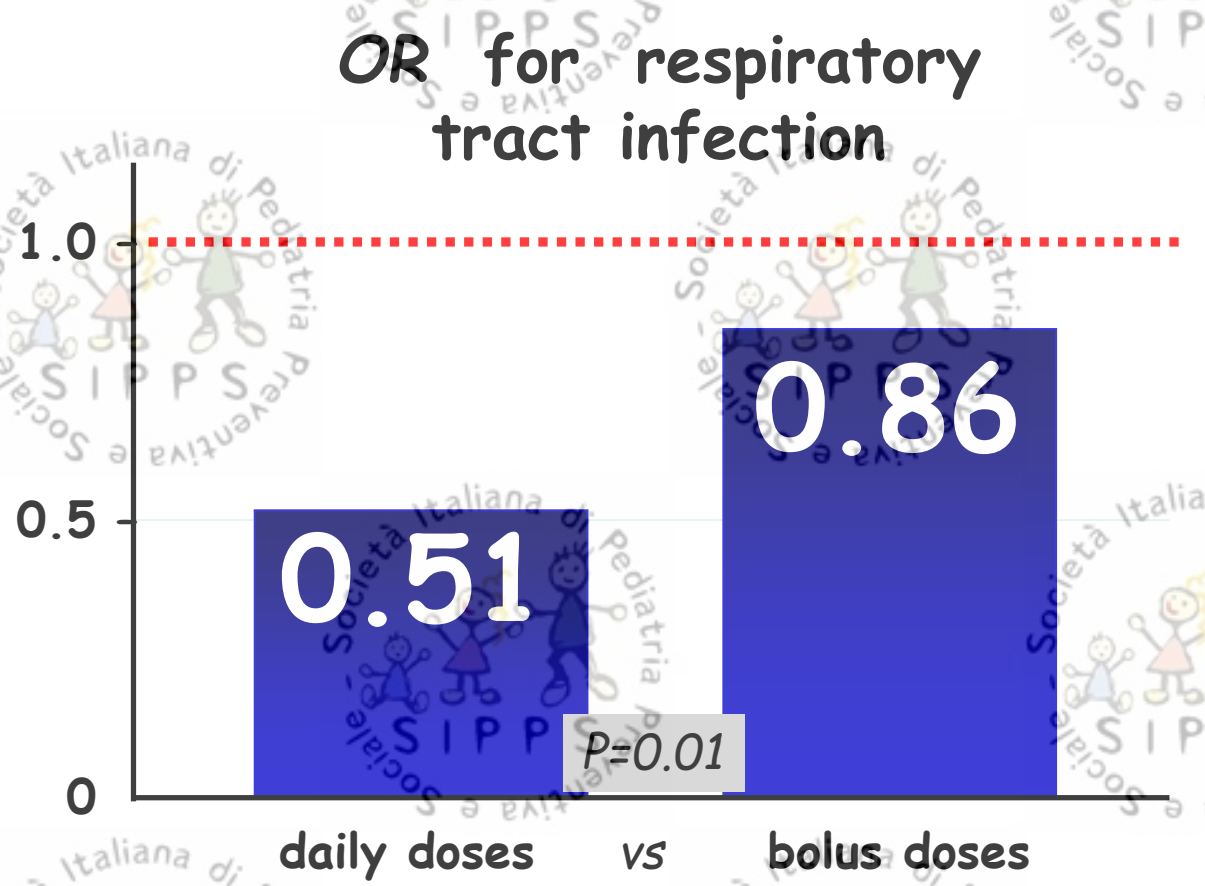
In pregnant women at risk of having a child with asthma, supplementation with 4400 IU/d of vitamin D compared with 400 IU/d significantly increased vitamin D levels in the women. The incidence of asthma and recurrent wheezing in their children at age 3 years was lower by 6.1%, but this did not meet statistical significance

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

Bergman P, PLoS One 2013; 8:e65835

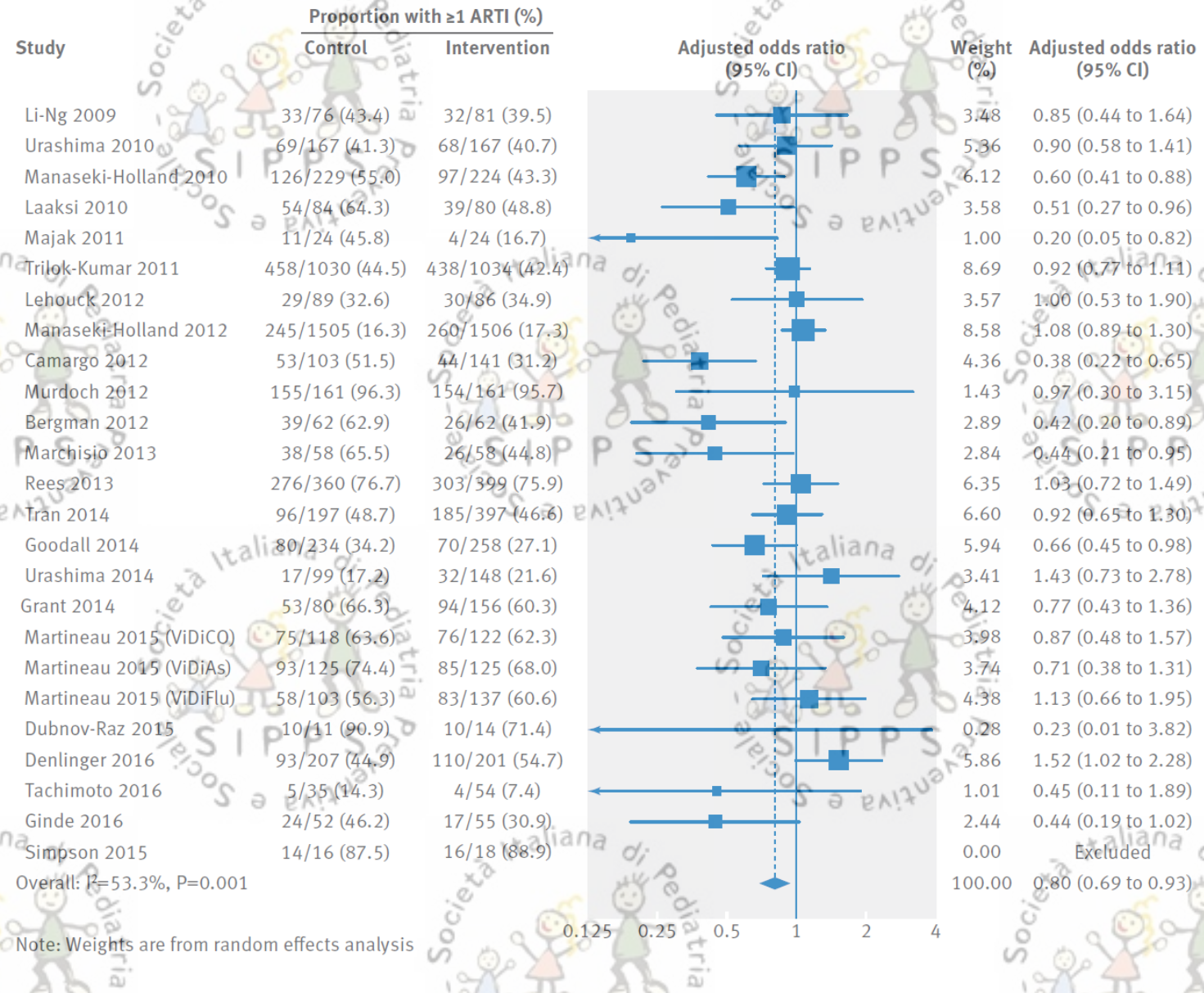
- ✓meta-analysis of 11 placebo-controlled studies
- ✓5660 patients included





Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data.

Martineau AR, BMJ 2017;356:i6583



Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data.

Martineau AR, BMJ 2017;356:i6583

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised controlled trials of vitamin D supplementation for the prevention of acute respiratory tract infection have yielded conflicting results

Individual participant data (IPD) meta-analysis has the potential to identify factors that may explain this heterogeneity, but this has not previously been performed

WHAT THIS STUDY ADDS

Meta-analysis of IPD from 10 933 participants in 25 randomised controlled trials showed an overall protective effect of vitamin D supplementation against acute respiratory tract infection (number needed to treat (NNT)=33)

Benefit was greater in those receiving daily or weekly vitamin D without additional bolus doses (NNT=20), and the protective effects against acute respiratory tract infection in this group were strongest in those with profound vitamin D deficiency at baseline (NNT=4)

These findings support the introduction of public health measures such as food fortification to improve vitamin D status, particularly in settings where profound vitamin D deficiency is common

Do vitamin D supplements help prevent respiratory tract infections?

A clinically useful effect remains uncertain despite hints in a new analysis

Mark J Bolland *associate professor*[1], Alison Avenell *professor*[2]

[1]Department of Medicine, University of Auckland, Auckland, New Zealand; [2]Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

We think that they should be **viewed as hypothesis generating only**, requiring confirmation in well designed adequately powered randomised controlled trials.

Several very large such randomised **controlled trials of vitamin D supplements will report on the effects on respiratory** infections **within the next few years**.

These trials have **not targeted individuals with very low serum concentrations of vitamin D**, and there is still **a need for trials** in these population groups.

Do vitamin D supplements help prevent respiratory tract infections?

A clinically useful effect remains uncertain despite hints in a new analysis

Mark J Bolland *associate professor*[1], Alison Avenell *professor*[2]

[1]Department of Medicine, University of Auckland, Auckland, New Zealand; [2]Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

We think th **erating only**, requi **wered** randomise

Sever **amin D supp** infecti

These tr **ry low serum concentration need for trials** in these population groups.

Should these results change clinical practice? Probably not. The results are heterogeneous and not sufficiently applicable to the general population.

But..

DERMATO-ENDOCRINOLOGY
2016, VOL. 0, NO. 0, e1248324 (16 pages)
http://dx.doi.org/10.1080/19381980.2016.1248324

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS

Estimated economic benefit of increasing 25-hydroxyvitamin D concentrations of Canadians to or above 100 nmol/L

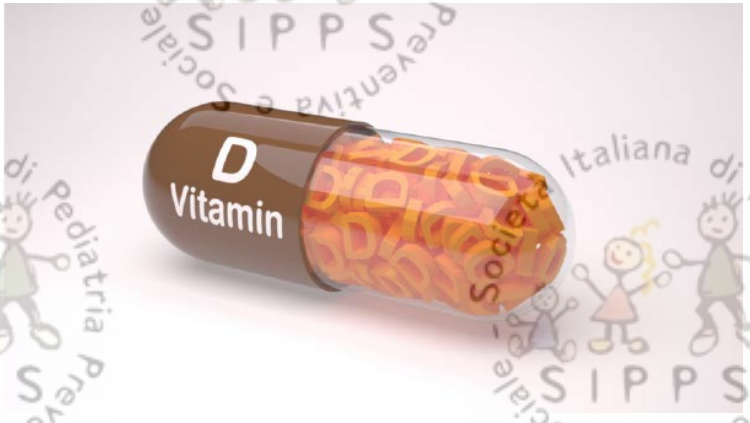
William B. Grant [a], Susan J. Whiting [b], Gerry K. Schwalfenberg [c], Stephen J. Genuis [d], and Samantha M. Kimball [e]

Respiratory infections

Influenza and pneumonia accounted for 5,694 deaths of Canadians in 2012.[54] The total economic impact for respiratory infections was $5.4 billion in 2008.[55] The estimated economic burden in 2016 is

$$\$5.4 \text{ billion} \times (1.033)^2 \times (0.994)^6 \times (36.3 \text{ million}/33.3 \text{ million}) = \$6.1 \text{ billion}$$

Clinical trials support the role of vitamin D in reducing risk of influenza.



thebmj

BMJ 2017;356:j847 doi: 10.1136/bmj.j847 (Published 2017 February 16)

RESEARCH NEWS

Check for updates

Vitamin D supplementation does cut respiratory infections, new study suggests

Gareth Iacobucci

Martineau added, "Influenza vaccination programmes are motivated by the principle that, **when a disease is common, even minor reductions in incidence can have significant public health benefits**; vitamin D fortification programmes might well be motivated by the same principle, particularly given that ARI is a major cause of industrial absenteeism, health service use, and antibiotic prescribing.

"We acknowledge that the general population may not be motivated to take supplements—this is why we highlight the importance of food fortification as an effective way to boost vitamin D status at a population level."

IL RUOLO DELLA VITAMINA D E DEI PROBIOTICI NELLA IMMUNO-MODULAZIONE DELLA RISPOSTA ALLERGICA

Vitamina D: L'azione

Diego Peroni

U.O. di Pediatria

Università di Pisa

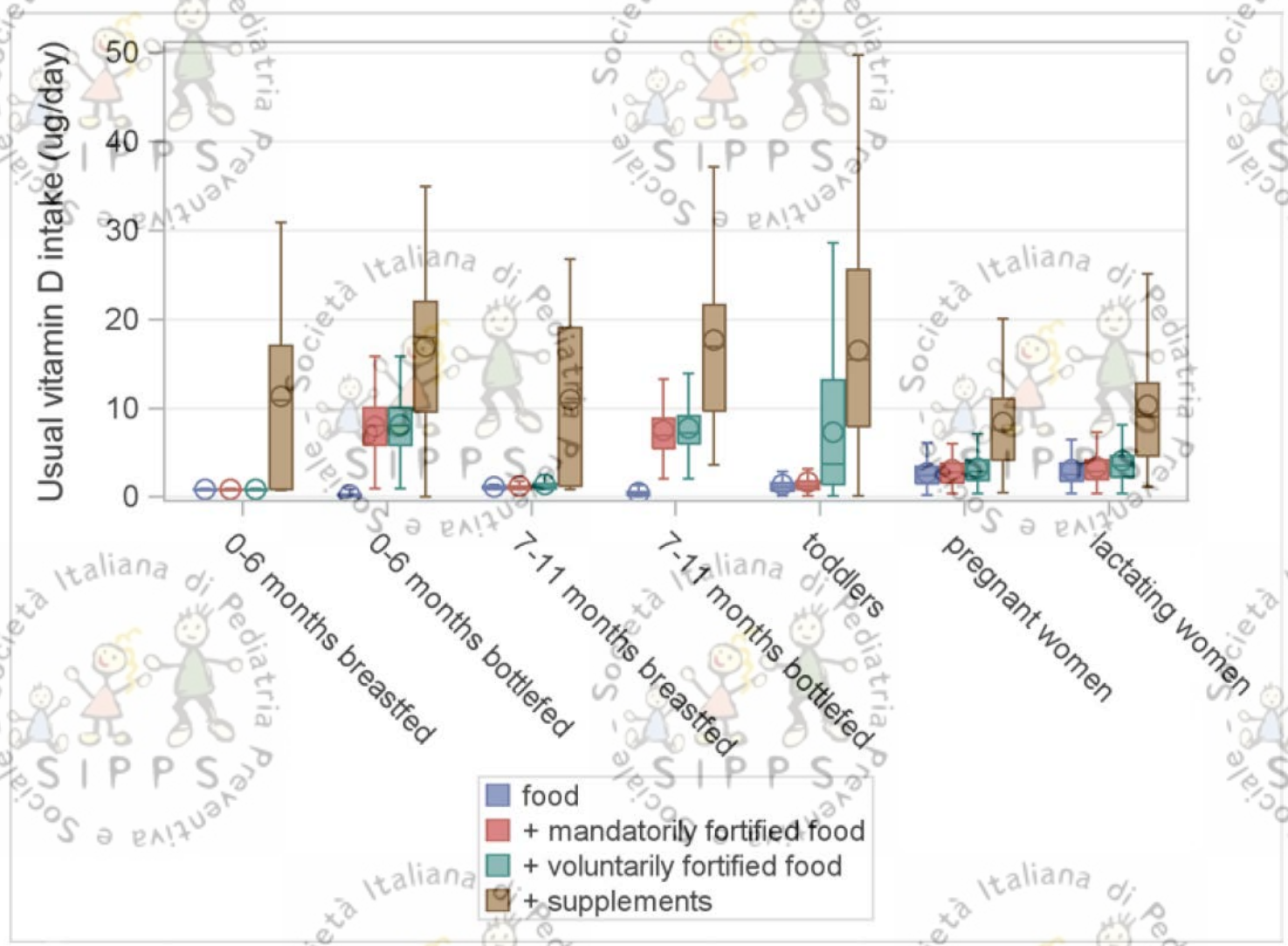
✓ **Le conclusioni**

diego.peroni@unipi.it

Do Current Fortification and Supplementation Programs Assure Adequate Intake of Fat-Soluble Vitamins in Belgian Infants, Toddlers, Pregnant Women, and Lactating Women?

Moyersoen, Nutrients 2018, 10, 223

By means of an online self-administered frequency questionnaire, this study aimed to evaluate the intake of vitamins A, D, E, and K in Belgian infants (n = 455), toddlers (n = 265), pregnant women (n = 161), and lactating women (n = 165).



How should we give vitamin D supplementation? evaluation of the pediatricians' knowledge in Turkey.

Kara Elitok et al. Italian Journal of Pediatrics (2017) 43:95

Table 2 Distribution of the participants' opinion on recommending vitamin D supplement

			Pediatric Resident n(%)	Pediatrician	p
To which infants and children do you recommend vitamin D supplement?	Feeding	With breast milk only	16 (14.5)	13 (12.1)	
		Regardless of feeding	92 (83.6)	93 (86.9)	0.761
		With formula only	2 (1.8)	1 (0.9)	
	To the infants and children with inadequate exposure to the sunlight		26 (23.6)	25 (23.4)	0.127
	With disease likely to impair vitamin D metabolism		22 (20.0)	22 (20.6)	0.133
	Those that experience frequent respiratory tract infection		7 (6.4)	7 (6.5)	0.216
	Those with weakness and muscle pain		7 (6.4)	8 (7.5)	0.200
Why do you recommend vitamin D supplement to the infants and children?	To prevent rickets and vitamin D deficiency		97 (88.2)	104 (97.2)	0.008
	For fontanelle closure		17 (15.5)	4 (3.7)	0.002
	To prevent infections		14 (12.7)	26 (24.3)	0.013
	Other		2 (1.8)	9 (8.4)	

How should we give vitamin D supplementation? evaluation of the pediatricians' knowledge in Turkey. Kara Elitok et al. Italian Journal of Pediatrics (2017) 43:95

Table 3 Distribution of the participants' opinions on the time, duration, method and seasonal differences of recommending vitamin D supplement

		Pediatric resident n (%)	Pediatrician	p
When do you recommend to start vitamin D supplement?	At birth	24 (21.8)	26 (24.3)	0.186
	On the 15th day after birth	75 (68.2)	77 (72.0)	
	In a month after birth	5 (4.5)	4 (3.7)	
	When the infant is 3-month-old	5 (4.5)	0 (0.0)	
	Other	1 (0.9)	0 (0.0)	
For how long do you recommend vitamin D supplement?	Until the closure of fontanelle	20 (18.2)	1 (0.9)	0.001
	Until the 6th month of life	2 (1.8)	1 (0.9)	
	Until the age of 1 year	45 (40.9)	52 (48.6)	
	Until the age of 2 years	36 (32.7)	44 (41.1)	
	Until the age of 3 years and longer	7 (6.4)	9 (8.4)	
At what dose do you recommend vitamin D supplement?	Daily 200 IU	2 (1.8)	0 (0.0)	0.336
	Daily 400 IU	99 (90)	95 (88.8)	
	Daily 600 IU	6 (5.5)	8 (7.5)	
	Breaking an ampoule and receiving orally	1 (0.9)	0 (0.0)	
	No comment	2 (1.8)	4 (3.7)	
Do you recommend different dose of vitamin D depending on the season (summer-winter)?	Only in winter	7 (6.4)	0 (0.0)	0.012
	Entire year, higher in winter	45 (40.9)	37 (34.6)	
	Entire year at the same dose	58 (52.7)	70 (65.4)	
Method of vitamin D supplement?	Drop	92 (83.6)	90 (84.1)	0.521
	Drop + multivitamin	10 (9.1)	12 (11.2)	
	Drop + ampoul	2 (1.8)	0 (0.0)	
	Multivitamin	6 (5.5)	5 (4.7)	

How should we give vitamin D supplementation? evaluation of the pediatricians' knowledge in Turkey. Kara Elitok et al. Italian Journal of Pediatrics (2017) 43:95

Table 3 Distribution of the participants' opinions on the time, duration, method and seasonal differences of recommending vitamin D supplement

		Pediatric resident n (%)	Pediatrician	p
When do you recommend to start vitamin D supplement?	At birth	24 (21.8)	26 (24.3)	0.186
	On the 15th day after birth	75 (68.2)	77 (72.0)	
	In a month after birth	5 (4.5)	4 (3.7)	
	When th[illegible] 3-month	[illegible] (4[illegible]	[illegible] (0.0)	
For how long do you recommend vita[illegible]	[illegible]	[illegible]	[illegible]	0.001
At what dose do you [illegible]	[illegible]	[illegible]	[illegible]	
Do you recommend diffe[illegible] on the season (summer-wi[illegible]	[illegible]	[illegible]	[illegible].0)	0.012
	[illegible]	[illegible]	[illegible] (34.6)	
	[illegible]	[illegible]	70 (65.4)	
Method of vitamin D supplement?	[illegible]	92 (83.6)	90 (84.1)	0.521
	Drop + multiv[illegible]	10 (9.1)	12 (11.2)	
	Drop + ampoul	2 (1.8)	0 (0.0)	
	Multivitamin	6 (5.5)	5 (4.7)	

The present study suggest that the knowledge of pediatricians about recommendation of vitamin D needs to be enhanced by education programs

Saggese et al. Italian Journal of Pediatrics (2018) 44:51
https://doi.org/10.1186/s13052-018-0488-7

Italian Journal of Pediatrics

REVIEW Open Access

Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians

Giuseppe Saggese[1†], Francesco Vierucci[2*†], Flavia Prodam[3], Fabio Cardinale[4], Irene Cetin[5], Elena Chiappini[6], Gian Luigi de' Angelis[7], Maddalena Massari[5], Emanuele Miraglia Del Giudice[8], Michele Miraglia Del Giudice[8], Diego Peroni[1], Luigi Terracciano[9], Rino Agostiniani[10], Domenico Careddu[11], Daniele Giovanni Ghiglioni[12], Gianni Bona[13], Giuseppe Di Mauro[14] and Giovanni Corsello[15]