La Vitamina D ieri, oggi e domani

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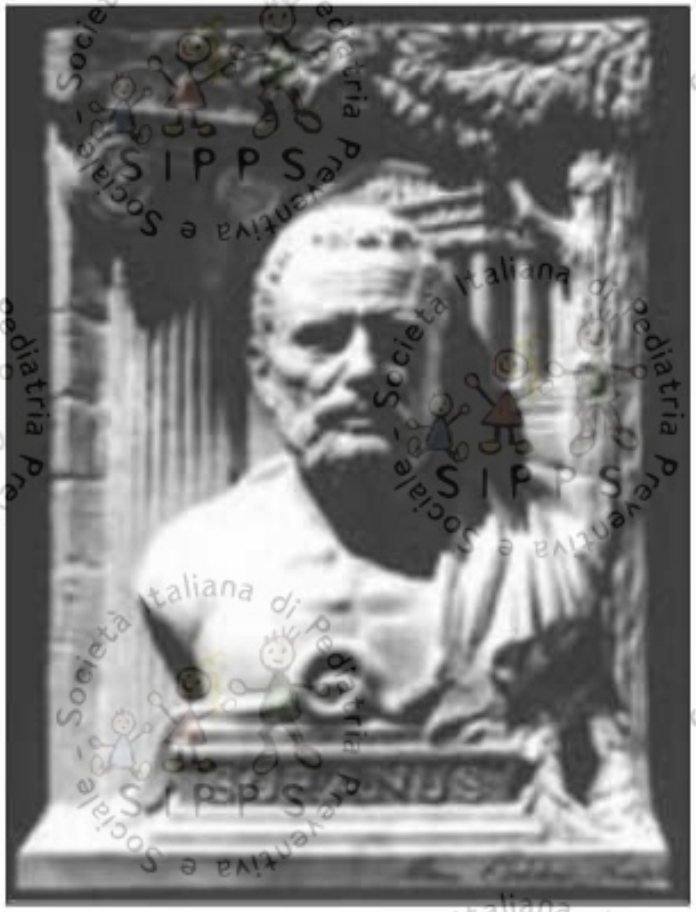
HISTORY OF RICKETS AND OF DISCOVERY OF VITAMIN D



Sorano di Efeso
(98-138 d.C.)

Galeno di Pergamon
(129-200 d.C.)

Children in ancient Rome had vitamin D deficiency, study says

More than 1 in 20 children had rickets

By: ASHLEY STRICKLAND, CNN

Posted: Aug 20, 2018 01:32 AM PDT Updated: Aug 20, 2018 01:32 AM PDT

CNN

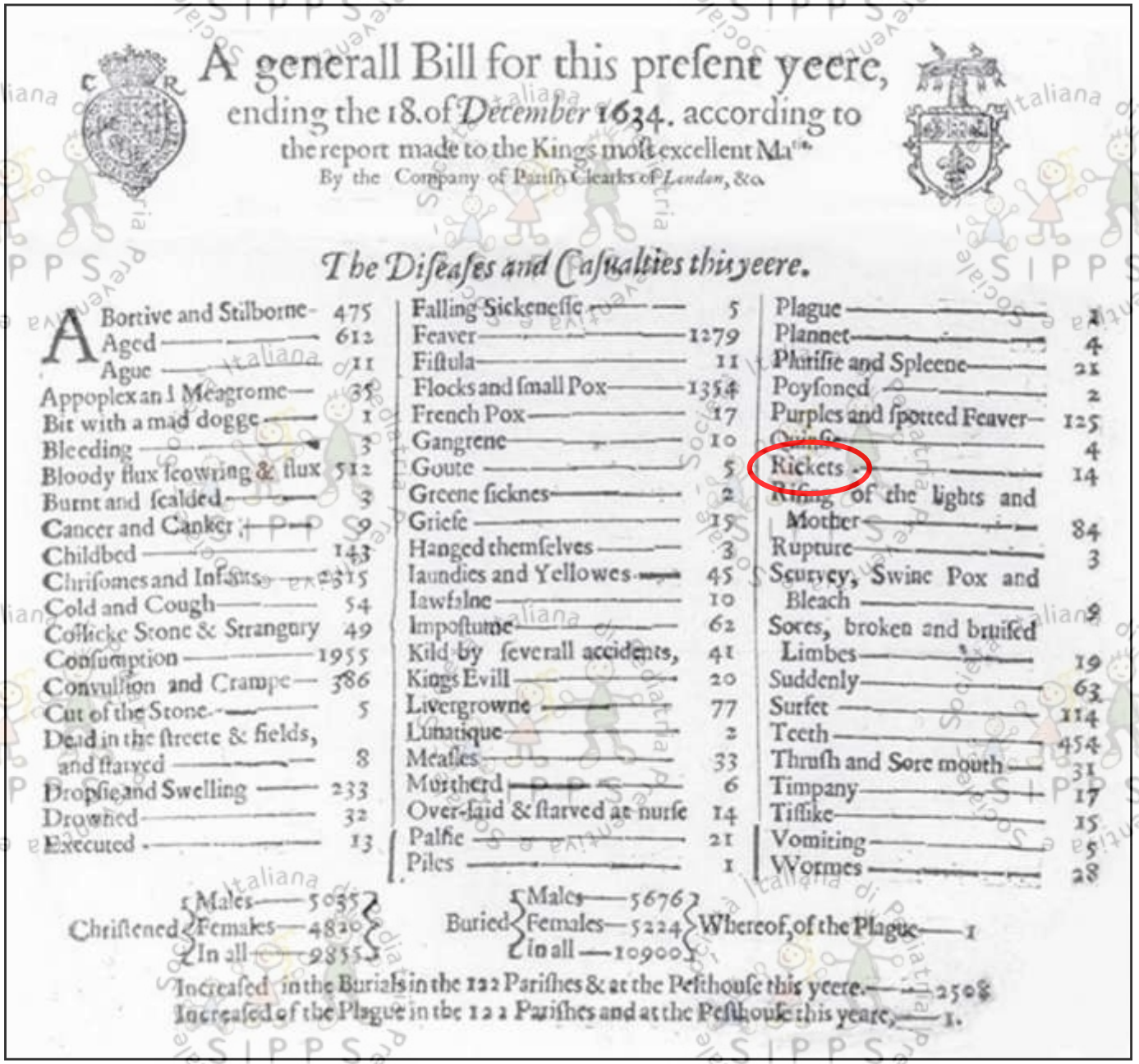
BREAKING NEWS AUG 2018

(CNN) - A new analysis of skeletons from ancient Roman cemeteries across Europe has revealed that vitamin D deficiency was a problem for children 2,000 years ago.

Researchers compared bones from ancient cemeteries spread from northern England to southern Spain, dating from the first to the sixth centuries, with those from Industrial Revolution-era cemeteries.

They expected to see rickets, a condition caused by vitamin D deficiency, in children living during and after the Industrial Revolution because of pollution and cramped living situations in urban areas. But when the researchers studied 2,787 skeletons of children and adults in 18 Roman Empire cemeteries, they realized that a lack of vitamin D is a longstanding issue for Europeans.

1634: compare per la prima volta il termine “rickets” nel registro dei decessi della città di Londra



A generall Bill for this present yeere,
ending the 18. of *December* 1634. according to
the report made to the Kings most excellent Ma^tie
By the Company of Parish Clearks of *London*, &c.

The Diseases and Casualties this yeere.

Abortive and Stilborne	475	Falling Sickeneſſe	5	Plague	1
Aged	612	Feaver	1279	Plannet	4
Ague	11	Fiſtula	11	Phiſiſie and Spleene	21
Appoplex and Meagrome	35	Flocks and ſmall Pox	1354	Poyſoned	2
Bit with a mad dogge	1	French Pox	17	Purples and ſpotted Feaver	125
Bleeding	3	Gangrene	10	Quinſie	4
Bloody flux ſcowring & flux	512	Goute	5	Rickets	14
Burnt and ſcalded	3	Greene ſickneſs	2	Riſing of the lights and Mother	84
Cancer and Canker	9	Griefe	15	Rupture	3
Childbed	143	Hanged themſelves	3	Scurvey, Swine Pox and Bleach	9
Chriſomes and Infants	2315	Iaundies and Yellowes	45	Sores, broken and bruiſed Limbes	19
Cold and Cough	54	Iawfalne	10	Suddenly	63
Collicke Stone & Strangury	49	Impoſtume	62	Surfet	114
Conſumption	1955	Kild by ſeverall accidents	41	Teeth	454
Convulſion and Crampe	386	Kings Evill	20	Thruſh and Sore mouth	31
Cut of the Stone	5	Livergrowne	77	Timpany	17
Dead in the ſtreete & fields, and ſtarved	8	Lunatique	2	Tiſſike	15
Dropſie and Swelling	233	Meaſles	33	Vomiting	5
Drowned	32	Murthered	6	Wormes	28
Executed	13	Over-laid & ſtarved at nurſe	14		
		Palſie	21		
		Piles	1		

Chriſtened { Males 5035, Females 4820, In all 9855 }
Buried { Males 5676, Females 5224, In all 10900 }
Whereof, of the Plague 1

Increaſed in the Burials in the 122 Pariſhes & at the Peſthouſe this yeere 2508
Increaſed of the Plague in the 122 Pariſhes and at the Peſthouſe this yeare 1.

DISPUTATIO MEDICA
INAUGVRALIS,
DE
Morbo puerili Anglorum,
quem patrio idiômate indigenæ
vocant
The Rickets,
CVM
Deo fuppetias ferente,
Ex authoritate Nobiliſſimi Domini Rectoris Magnifici,
D. JOHANNIS POLYANDRI à KERCHOVEN
SS. Theologiæ Doctoris, ejuſdemque Facultatis in Illuſtriſſimâ Acad. Lugd. Bat. Profeſſoris primarii,
Decreto Illuſtriſſimæ Facultatis Medicæ, & Ampliſſimi Senatûs Academici conſenſu,
Pro Gradu Doctoratûs, ſummiſque in Medicinâ Privilegiis
conſequendis,
Diſcutiendam proponit
DANIEL WHISTLER, Anglo-
Saxonicus - Orientalis.
Ad diem 18. Octob. Horis & loco conſuetis.

LVGDVNI BATAVORUM,
Ex Officinâ
WILHEMI CHRISTIANI BOXII. 1645.

1645

DE
RACHITIDE
SIVE
MORBO PUERILI,
qui vulgò
The **Rickets** dicitur,
Tractatus;
1650
Operâ primò ac potiſſimùm
FRANCISCI GLISSONII
Doctoris & publici Profeſſoris Medicinæ in almâ *Cantabrigiæ* Academiâ,
& Socii Collegii Medicorum
Londinenſium, conſcriptus:
Adſcitis in operis ſocietatem
GEORGIO BATE,
&
AHASUERO REGEMORTERO
Medicinæ quoque Doctoribus, & periter Sociis Collegii Medicorum Londinenſium.

LONDINI,
Typis *Guil. Du-gardi*; Impenſis *Laurentii Sadler*, & *Roberti Beaumont*: apud quos venenunt in vico vulgò-vocato **Little Britain** 1650.

Francis Glisson (1597-1677)
Professor of Anatomy at the University of Cambridge.

Rickets in a High Social Class of Renaissance Italy: the Medici children

Exploration of the Medici Chapels in the Basilica of San Lorenzo in Florence

Burials of 9 juvenile members of the Medici family (16th–17th centuries).

Documentary sources &
^{13}C and ^{15}N bone collagen analysis

⇓

weaning around 2 years old

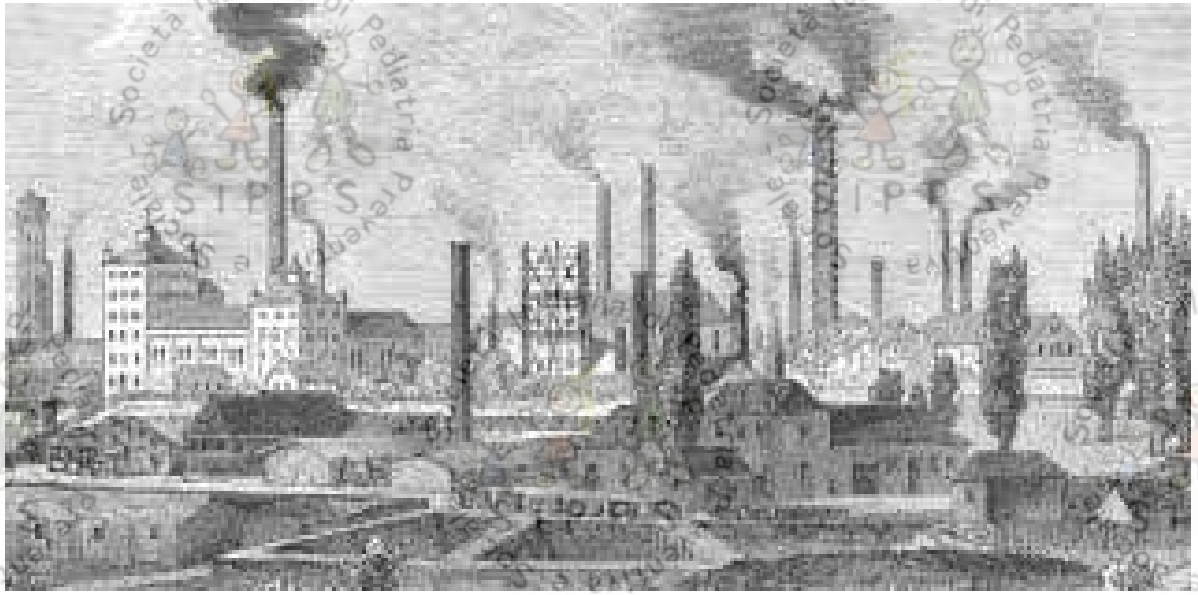
prolonged breastfeeding

Don Filippino, son of Joan of Austria: antero-posterior X-ray projection of the skull (increased biparietal diameter, high frontal bone and frontal bossing, wide coronal suture), deformed tibia and fibula

(Giuffra V. et al. Int. J. Osteoarcheol 2013)
(Watson T, Nature News 2013)

Industrial Revolution

The Industrial Revolution marked a period of development in the latter half of the 18° century that trasformed largely rural, agrarian societies in Europe and America into industrialized, urban ones.



In that period rickets increased drammatically: in some cities up to 90% of children was affected by rickets.

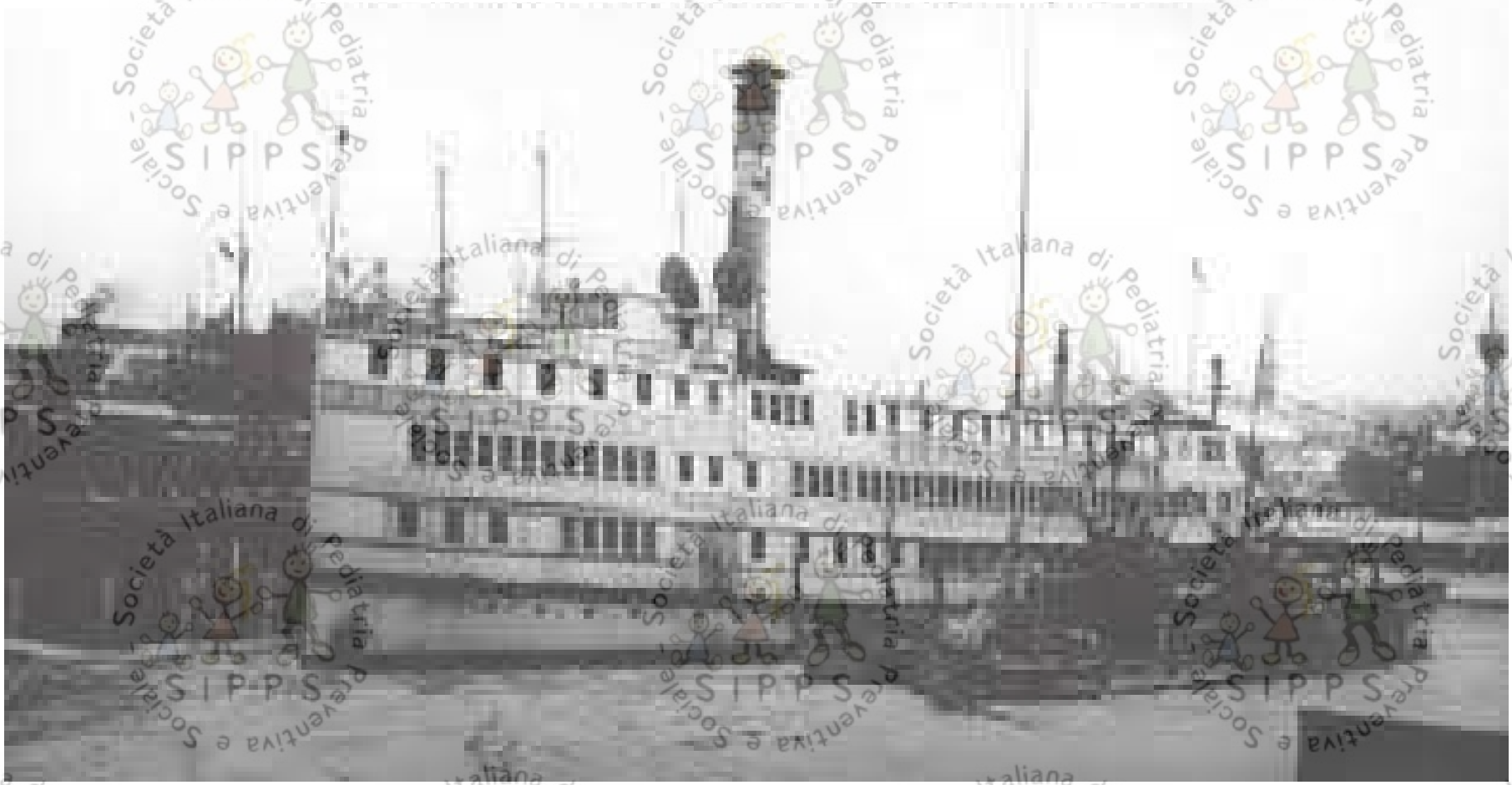
Nel 1919 Kurt Huldshinsky, pediatra tedesco, cura bambini con rachititismo con raggi ultravioletti prodotti artificialmente da una lampada a mercurio

prime decadi 1900

prevenzione/trattamento del rachitismo mediante irradiazione solare

Istituto di cure marine – Calambrone (Pisa)

USS Boston floating hospital, 1918



first decades of 20th century

Treatment of rickets – Meidling Hospital, Wien

(Rickets before the discovery of Vitamin D. O'Riordan JL et al, Sept 2014)

outdoor treatment in the shadow

outdoor treatment in the sun

first decades of 20th century
prevention & treatment of rickets

cod liver oil

La scoperta della Vitamina D

1919

Sir Edward Mellanby, medico e scienziato inglese, ipotizzò una carenza alimentare nell'eziopatogenesi del rachitismo. Con esperimenti sui cani, dimostrò per primo che alimenti "ricchi di vitamina A", come l'olio di fegato di merluzzo, contenevano un "fattore antirachitico".

1921

Elmer McCollum, biochimico dell' Università del Wisconsin, dopo distruzione della vitamina A, identificò questo fattore antirachitico come una nuova vitamina liposolubile, la quarta sino ad allora scoperta, per questo chiamata vitamina "D".

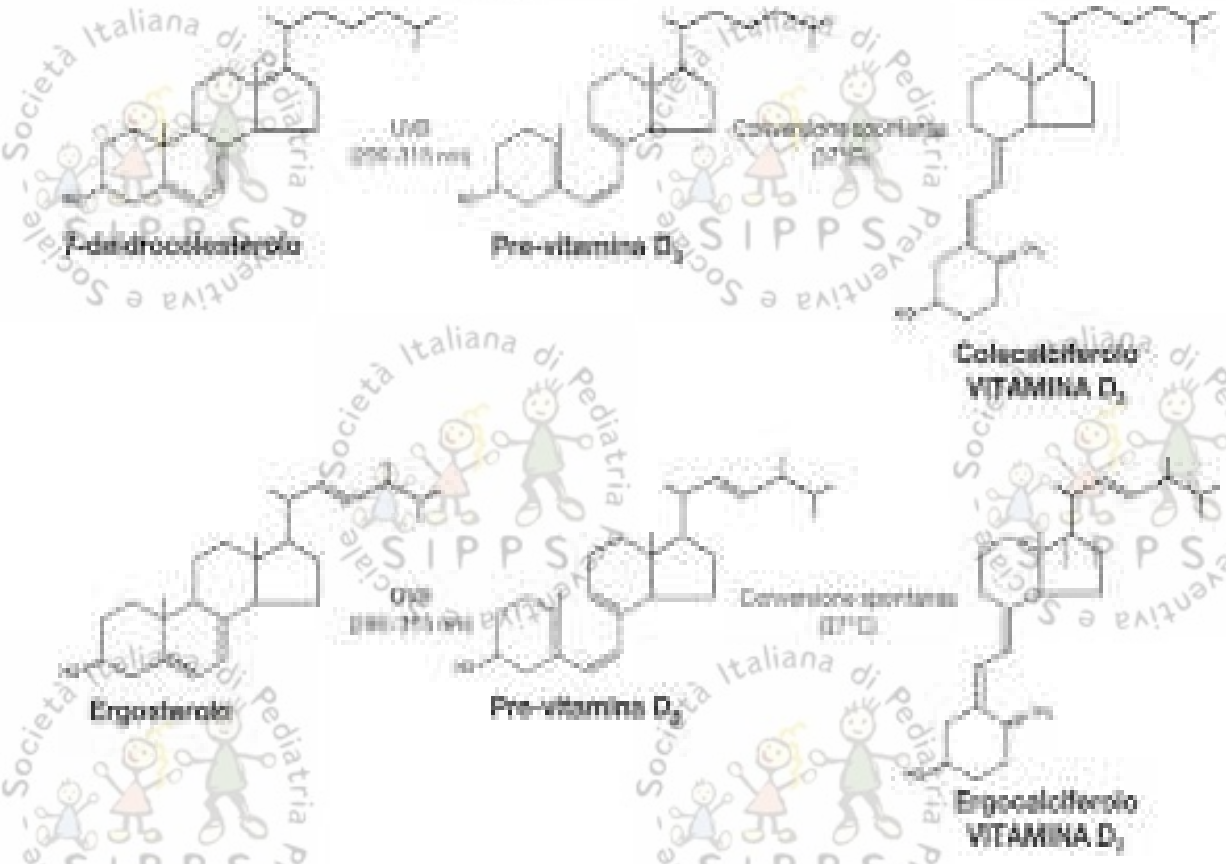
1924. Irradiation of animals or parts, substances and foods conferred antirachitic properties (Steenbock, Hess, Goldblatt)

America in the 30s and 40s

Near eradication of rickets in the United States

Adolf Windaus

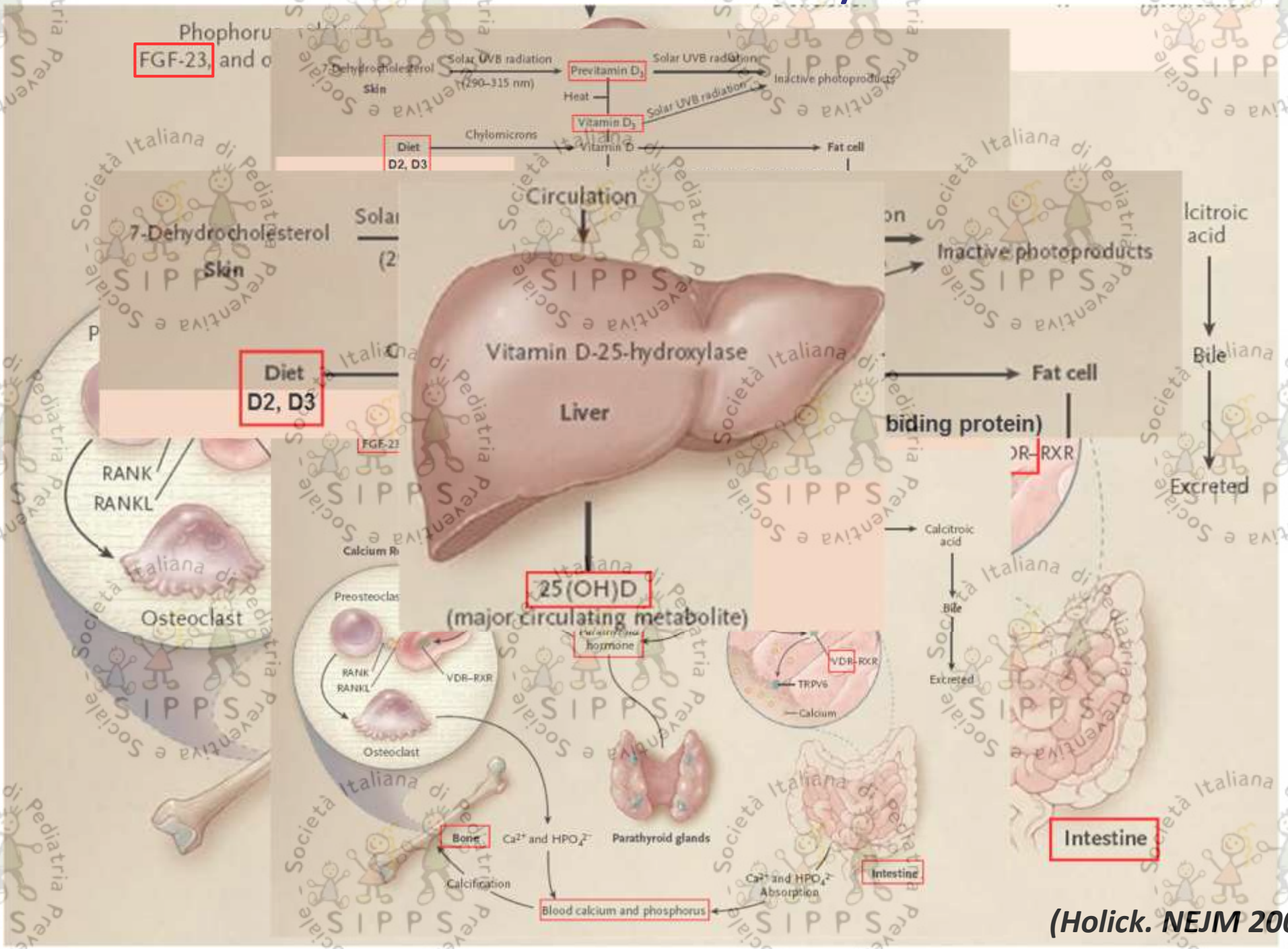
by the irradiation of a mixture of plant sterols isolated a substance with antirachitic properties (tachisterol=Vitamin D2) and by the irradiation of vertebrates skin isolated 7-dehydrocholesterol whose irradiation gave Vitamin D3.



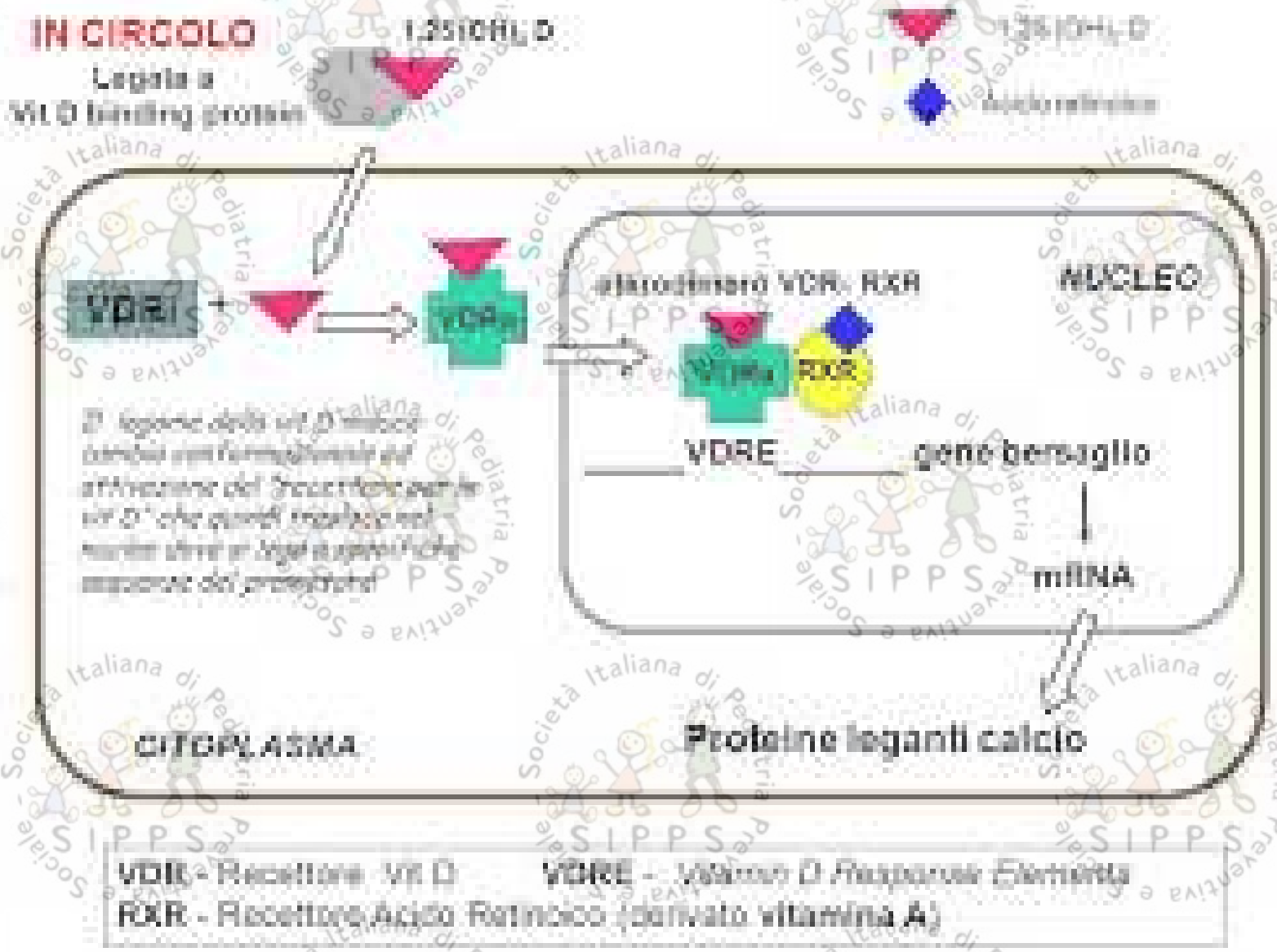
..verso la scoperta dell'ormone - Vitamina D

- **anni 30-60: disponibili forme sintetiche di vitamina D;**
- **anni 50: disponibili derivati radioattivi di vitamia D per studiarne il metabolismo;**
- **1968: isolato e sintetizzato il 25-OH-D (*calcidiolo*)**
- **1971: isolato e sintetizzato (Holick e De Luca) l'1,25-OH2-D (*calcitriolo*), l'ormone della vitamina D**

Vitamin D endocrine system



(Holick. NEJM 2007)



(Haussler MR., J Bone Miner Res , 1998)

Vitamina D

azioni scheletriche

London, children with rickets

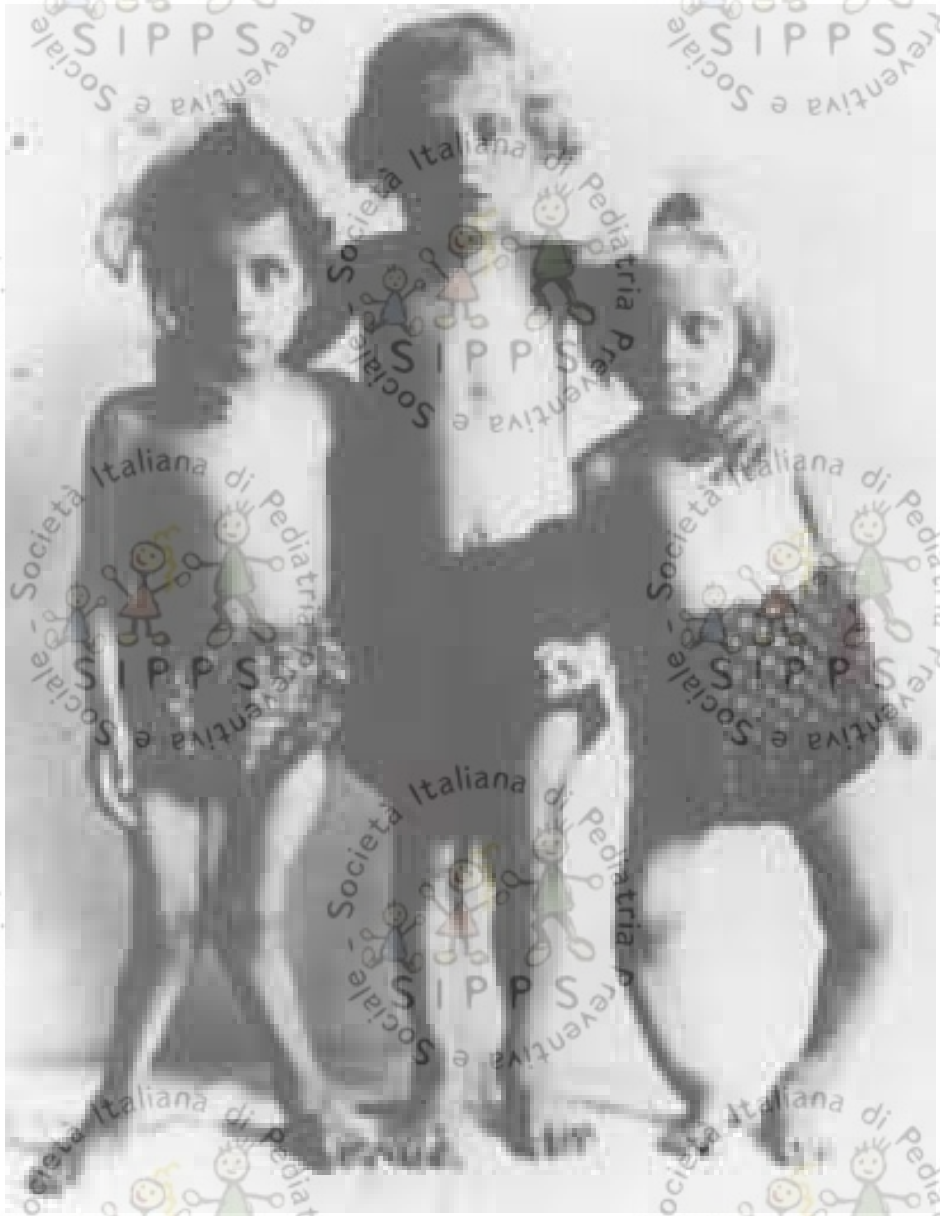


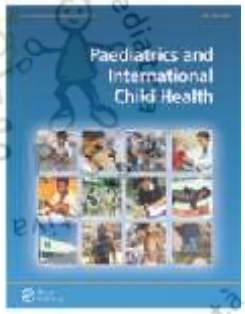
photo from the end of the 1800s

Vitamin D testing and treatment: a narrative review of current evidence

Pilz S.et al 2019

Endocrine Connections

Importantly, rickets is still a worldwide public health problem causing morbidity and mortality and is even increasing in Europe with immigrants from Middle East, Africa and Asia being at particularly high risk



Nutritional rickets around the world: an update

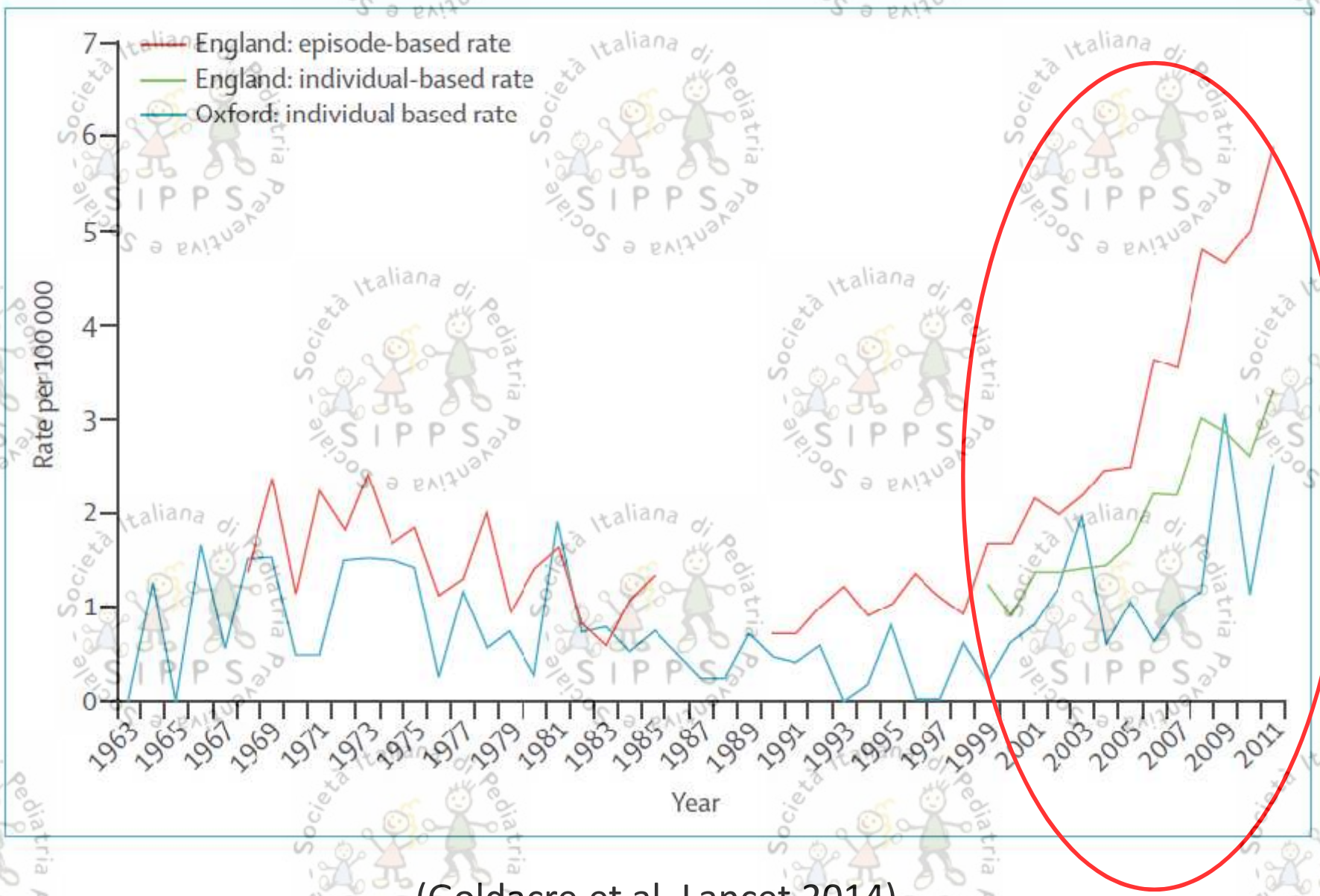
Mayo Clinic, Rochester, MN, USA 2017

Ana L. Creo, Tom D. Thacher, John M. Pettifor, Mark A. Strand & Philip R. Fischer

"Nutitional rickets continues to be an important health problem.

The prevalence is greatest in the Middle East, Asia and Africa. Immigration from these region probably account for the increased prevalence in Europe, North America and Australasia".

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

2018

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

Suma Uday,[1,2] Wolfgang Högler[1,2]

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.

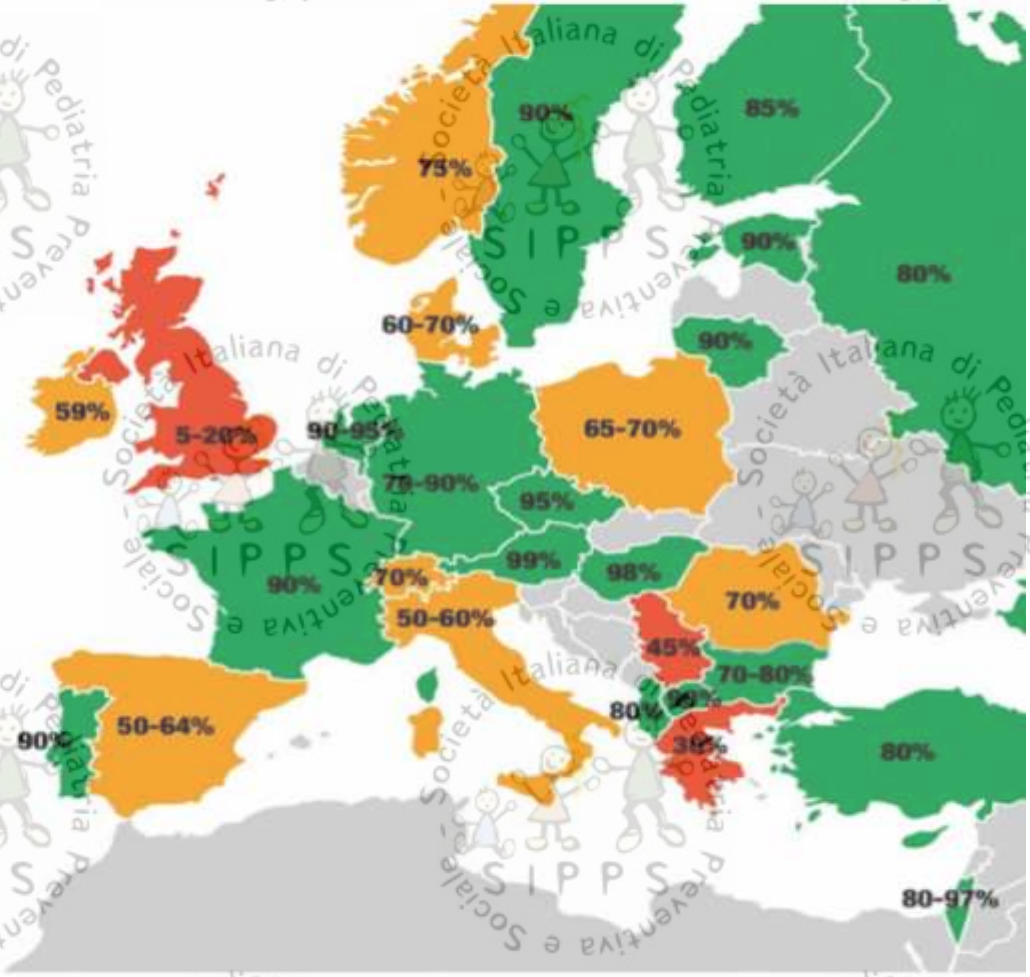
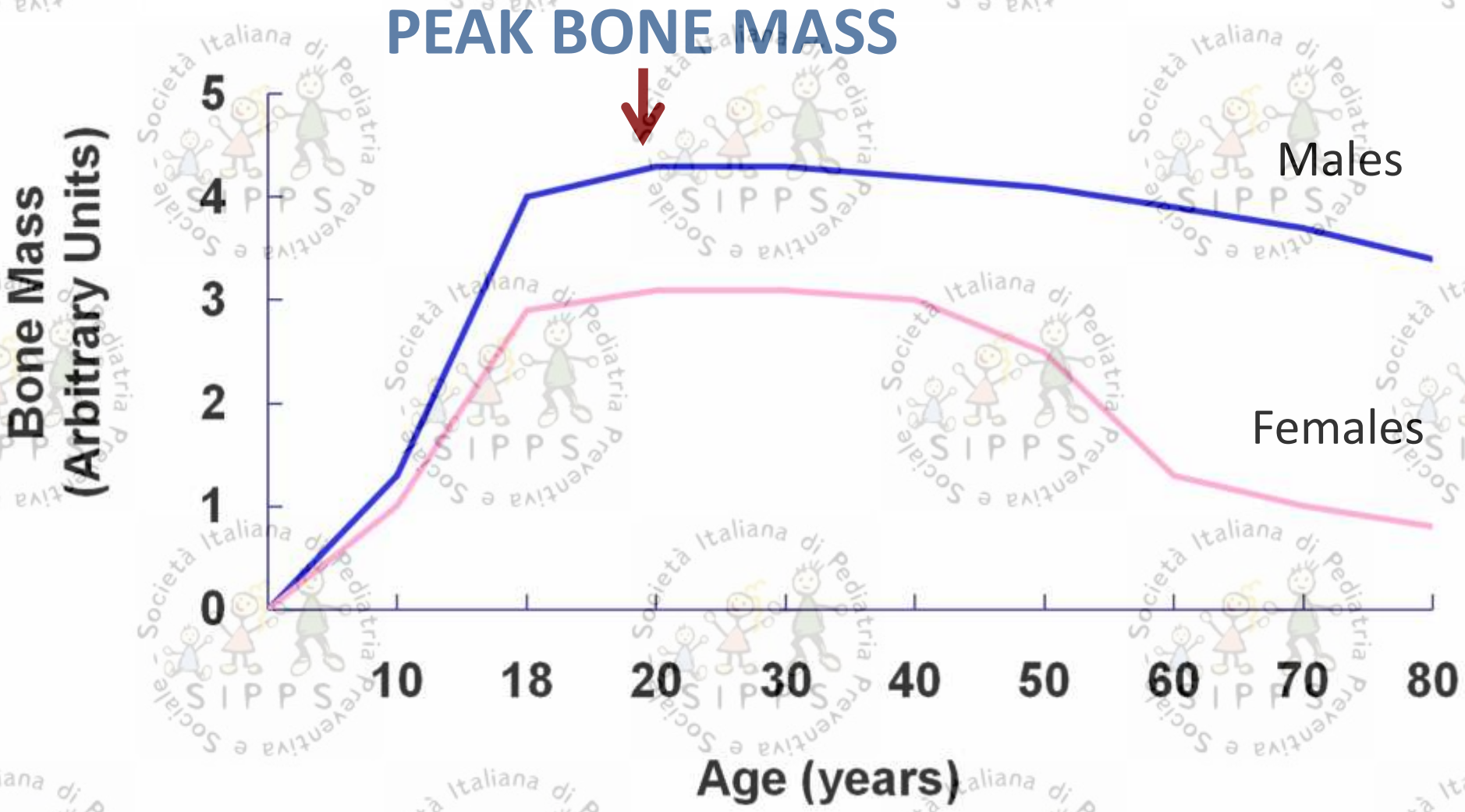


Figure 3 Adherence rates for infant vitamin D supplementation in the first year of life in Europe, with UK reporting the lowest rates.[13] Good adherence (≥80% of infants supplemented) is indicated in green, moderate adherence (79%–50%) in orange and low adherence (<50%) in red.

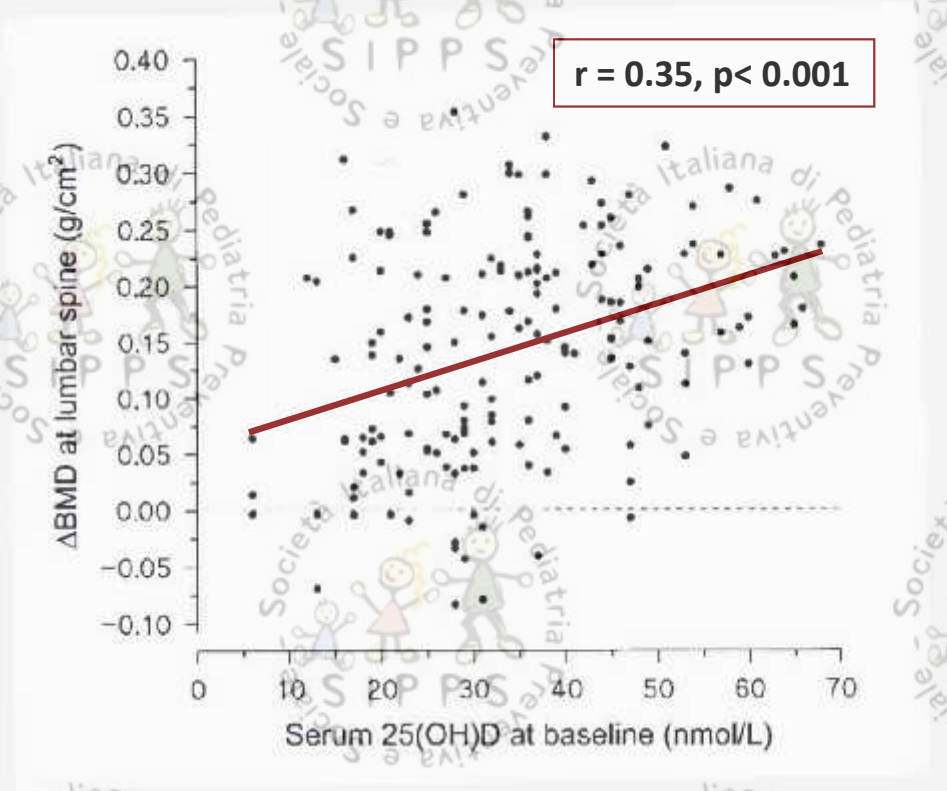
Changes in bone mass with age



(Cooper C. 1990)

Vitamin D status as a determinant of peak bone mass

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



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

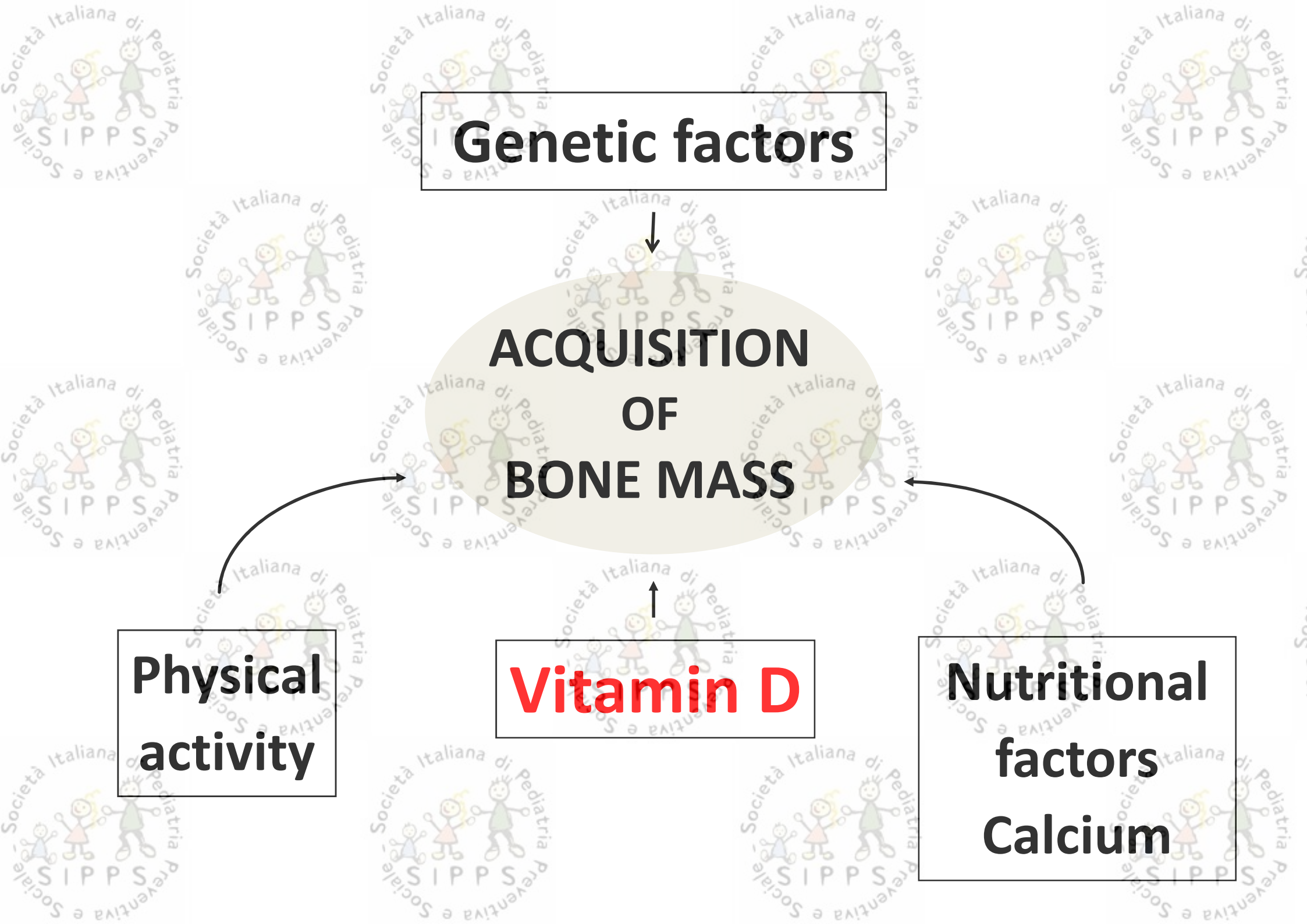
(Lehtonen-Veromaa et al. Am J Clin Nutr 2002)

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

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

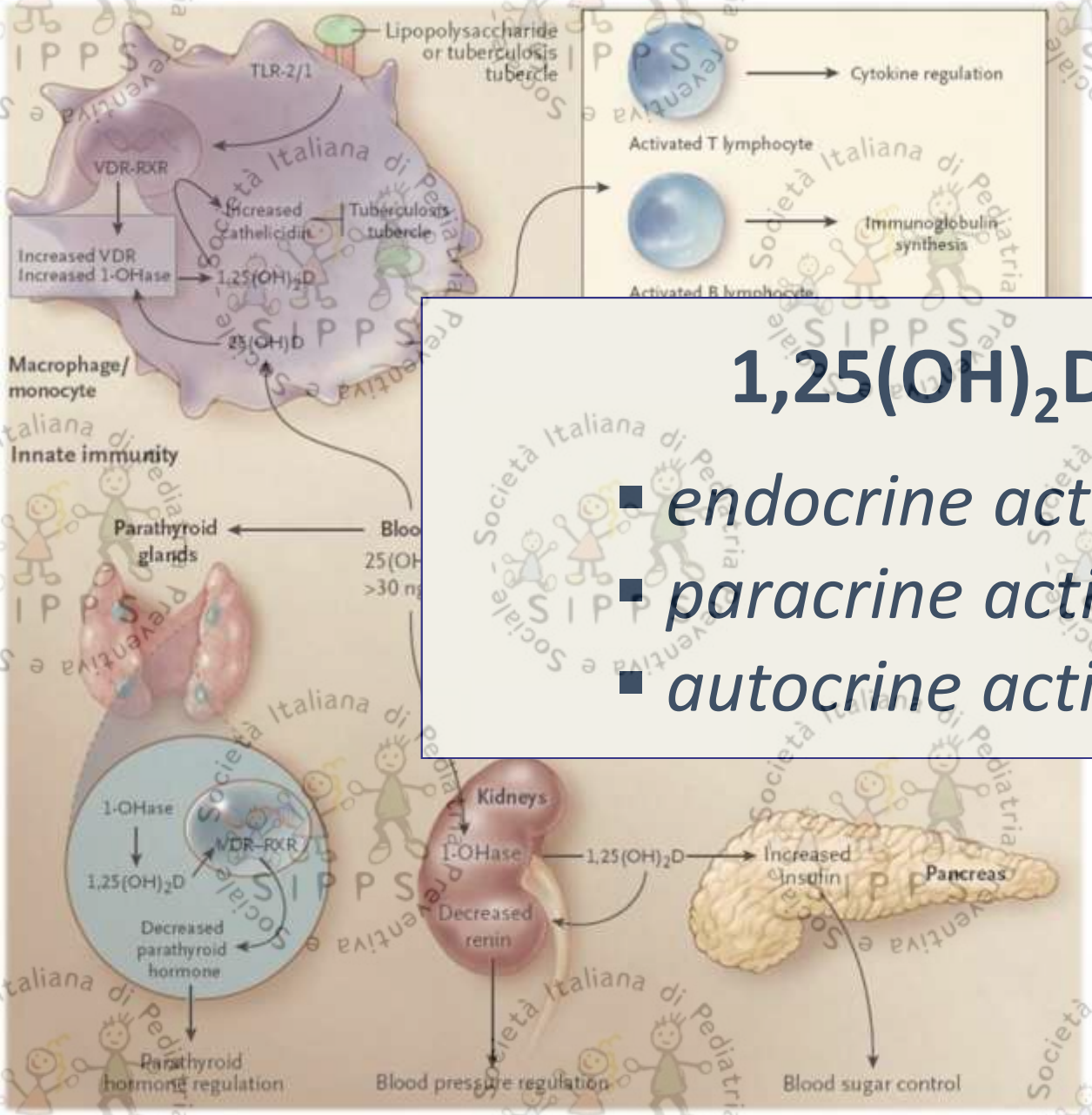
(Valimaki et al. JCEM 2004)


Genetic factors
ACQUISITION
OF
BONE MASS
Physical activity
Vitamin D
Nutritional factors
Calcium

Vitamina D

azioni extrascheletriche

Extraskeletal actions of vitamin D



(Holick MF. NEJM 2007)

$1,25(OH)_2D$

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

$1,25(OH)_2D$:

- **controls directly or indirectly up to 1,250 genes;**
- **reduces cellular proliferation**
- **ces**
- **tion; induces**
- **and inhibits**
- **sis (reducing risk**
- **immunomodulatory action, reducing risk of autoimmune diseases;**
- **promotes innate immunity, reducing risk of recurrent infections.**

BMJ

Vitamin D: drug of the future

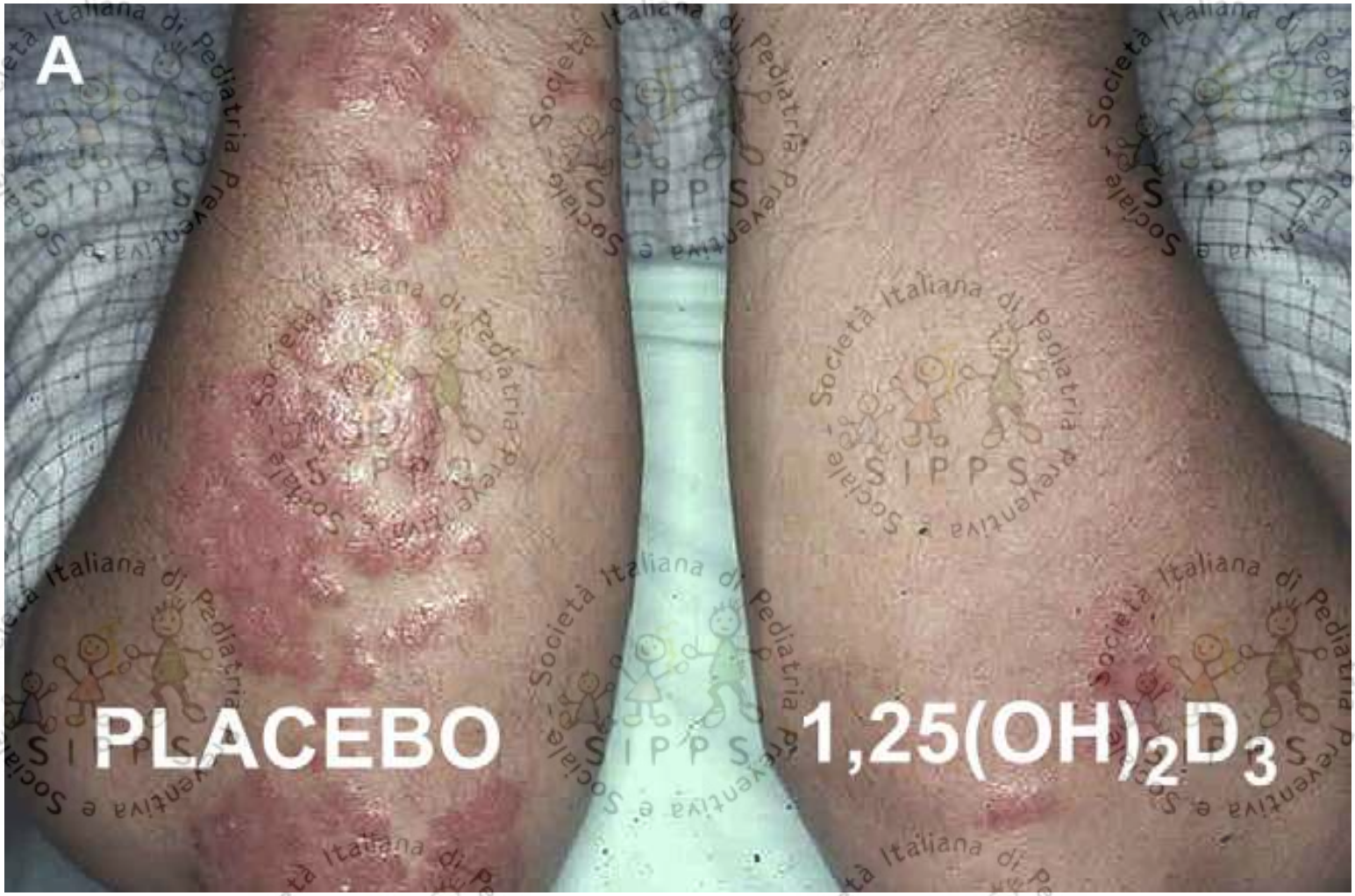
(Gueli N et al, 2016)

Heliotherapy for pulmonary tuberculosis

The Texas Building of the Relief Society, 1923

Psoriasis

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



(Courtesy dr. Holick MF. 1979)

European Journal of Pediatrics, 2017, E. Basatemur et al.

Costs of Vitamin D testing and prescribing among children in primary care

Source: records of 722,525 : electronic healthcare children and adolescents aged 0-17 years held in the England Health Network database.

- **Combined costs of Vitamin D tests and prescriptions:**
  - **in 2008: 1,647 pounds per 100,000 person-years**
  - **in 2014: 28,913 pounds per 100,000 person-years**

TOTAL COSTS AT NATIONAL LEVEL IN ENGLAND IN 2014: 4.31 MILLION POUNDS

Vitamin D testing and treatment: a narrative review of current evidence

Clinicians are confronted with an overwhelming testing for 25(OH)D concentrations and self-supplementation of vitamin D in the general population. It is therefore recommended that vitamin D testing should not be misused as a universal population-wide screening tool, but rather be applied only in selected individuals at high risk of vitamin D deficiency.

S. Pilz et al, 2019

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 in pediatric age:
Consensus of the Italian Society of Pediatrics
jointly with the Italian Society of Preventive Pediatrics
and the Italian Federation of Pediatricians

Saggese G et al. It J Ped, 44,51,2018

Vitamin D and respiratory tract infections (RTI)

- *Recent studies suggested an effect between Vitamin D deficiency or supplementation on the incidence of respiratory infections in children.*

- *However, because current rvidence is weak, we suggest against Vitamin D administration as a therapy for respiratory infections, beyond the correction of a documented Vitamin D deficiency.*

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Vitamin D in pediatric age:
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Saggese G et al. It J Ped, 44,51,2018

Vitamin D and asthma

-Low 25(OH)D levels may be associated with a worse asthma control and increased risk of exacerbations.

-Effect of vitamin D supplementation confirmed benefits on asthma exacerbations but effects on other asthma-related outcomes are mixed and inconclusive.

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

"Intervention studies for extraskeletal health effects are so far inconclusive, but the results of several ongoing randomized clinical trials may help to delineate these effects more clearly in the next future"

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

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

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

Ipovitaminosi D e conseguenze cliniche

livelli di 25-OH-D

< 20 ng/ml
deficienza

20-30 ng/ml
insufficienza

ñ 30 ng/ml
sufficienza

azioni scheletriche

azioni extra-scheletriche

Ipovitaminosi D: fattore modificabile di rischio!

Fattori che interferiscono sui livelli di 25-OH-D

- etnia
- indice di massa corporea (BMI)
- latitudine
- stagione
- radiazione UVB
- integrazione vitaminica
- fattori genetici (polimorfismi DBP)
- epimeri 25-OH-D
- metodi di dosaggio (CLIA, RIA, Tandem Mass)

Clin Chem Lab Med. 2017 .

Assessment of vitamin D status - a changing landscape.

Herrmann M, et al