

**XII CONGRESSO
NAZIONALE
FIMP 2018**

*Tutti i bambini...
un unico stivale!*



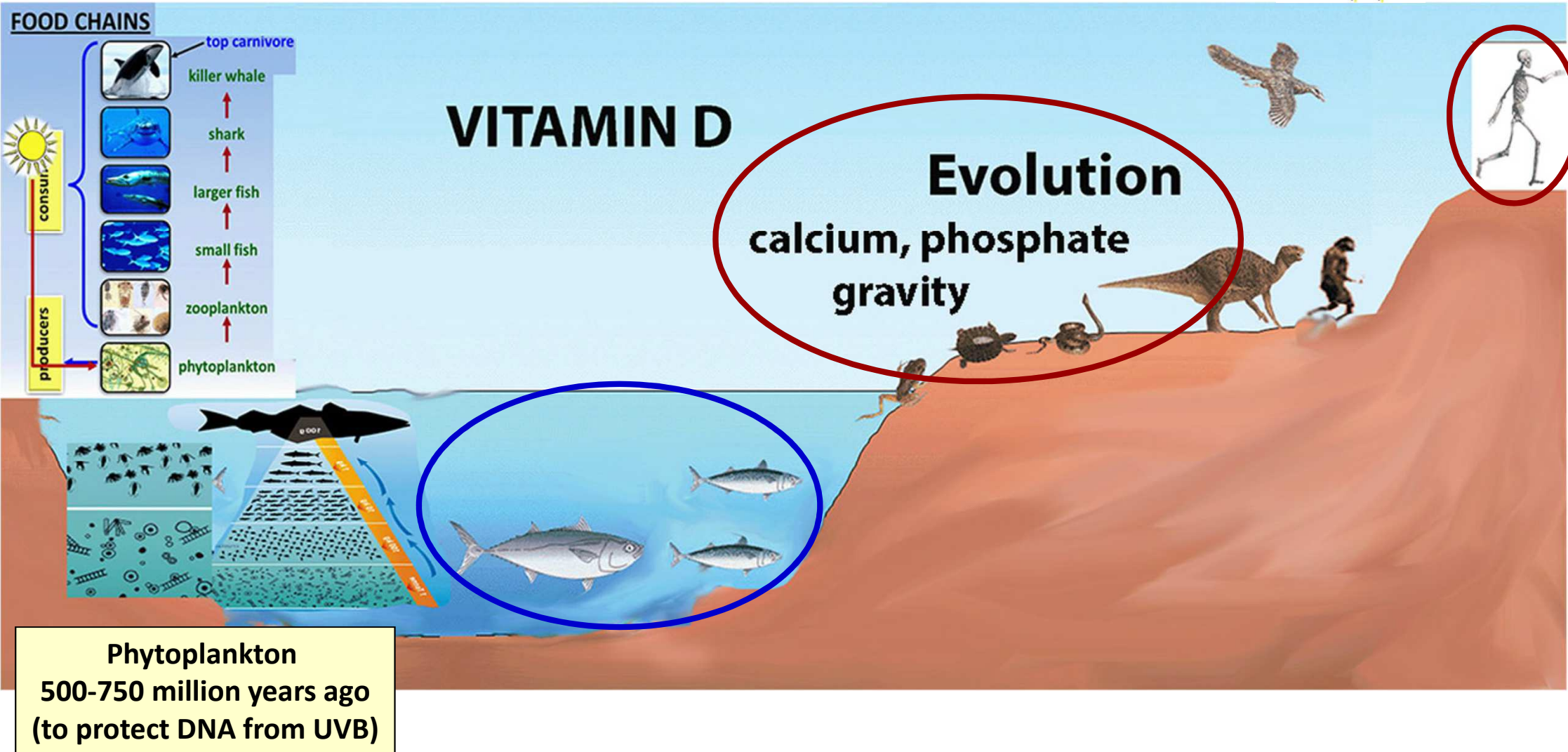
fimp Federazione
Italiana
Medici *Pediatr*

AIM
GROUP
INTERNATIONAL

Francesco Vierucci

LA VITAMINA D OLTRE IL PRIMO ANNO: IL RUOLO NELLA SECONDA E TERZA INFANZIA
Sistema Muscolo-scheletrico

The vitamin D story



(Hernigou P et al. Int Orthop Mar 2018)

American Journal of Public Health
and THE NATION'S HEALTH

Volume 26

July, 1936

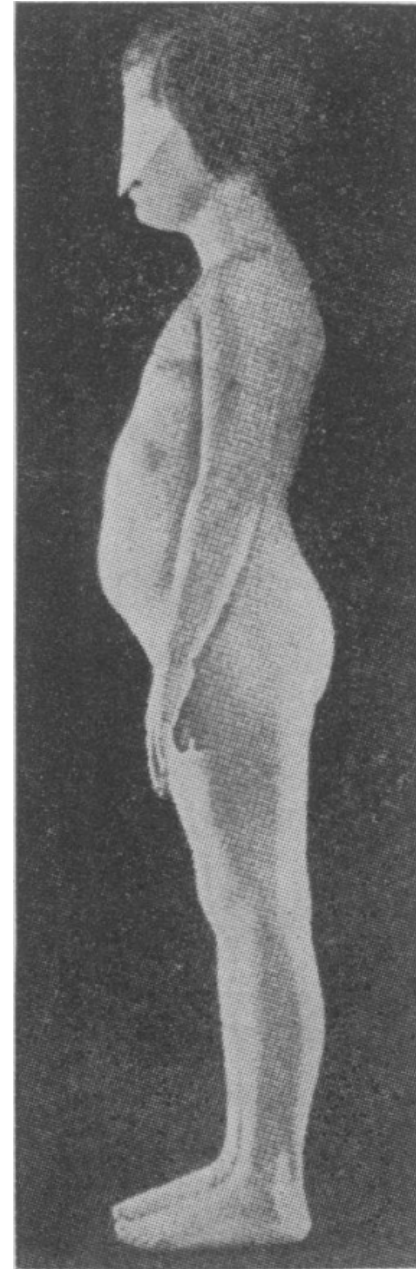
Number 7

Vitamin D in Child Health*

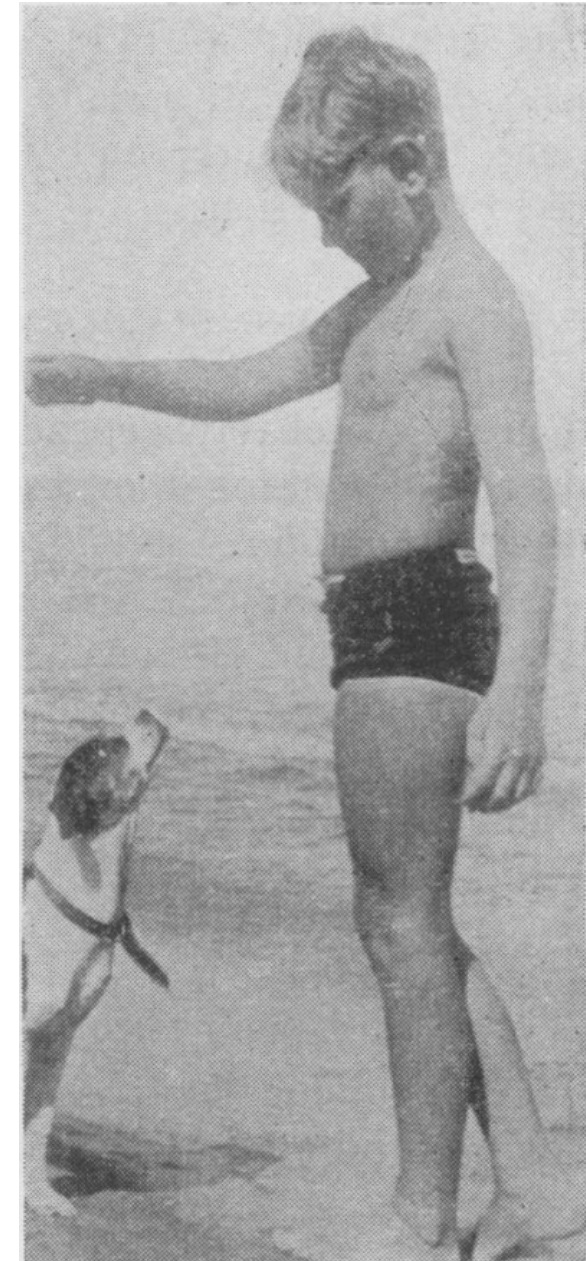
FRED O. TONNEY, M.D., F.A.P.H.A.

The influence of vitamin D upon the child's physical development is viewed from the standpoint of:

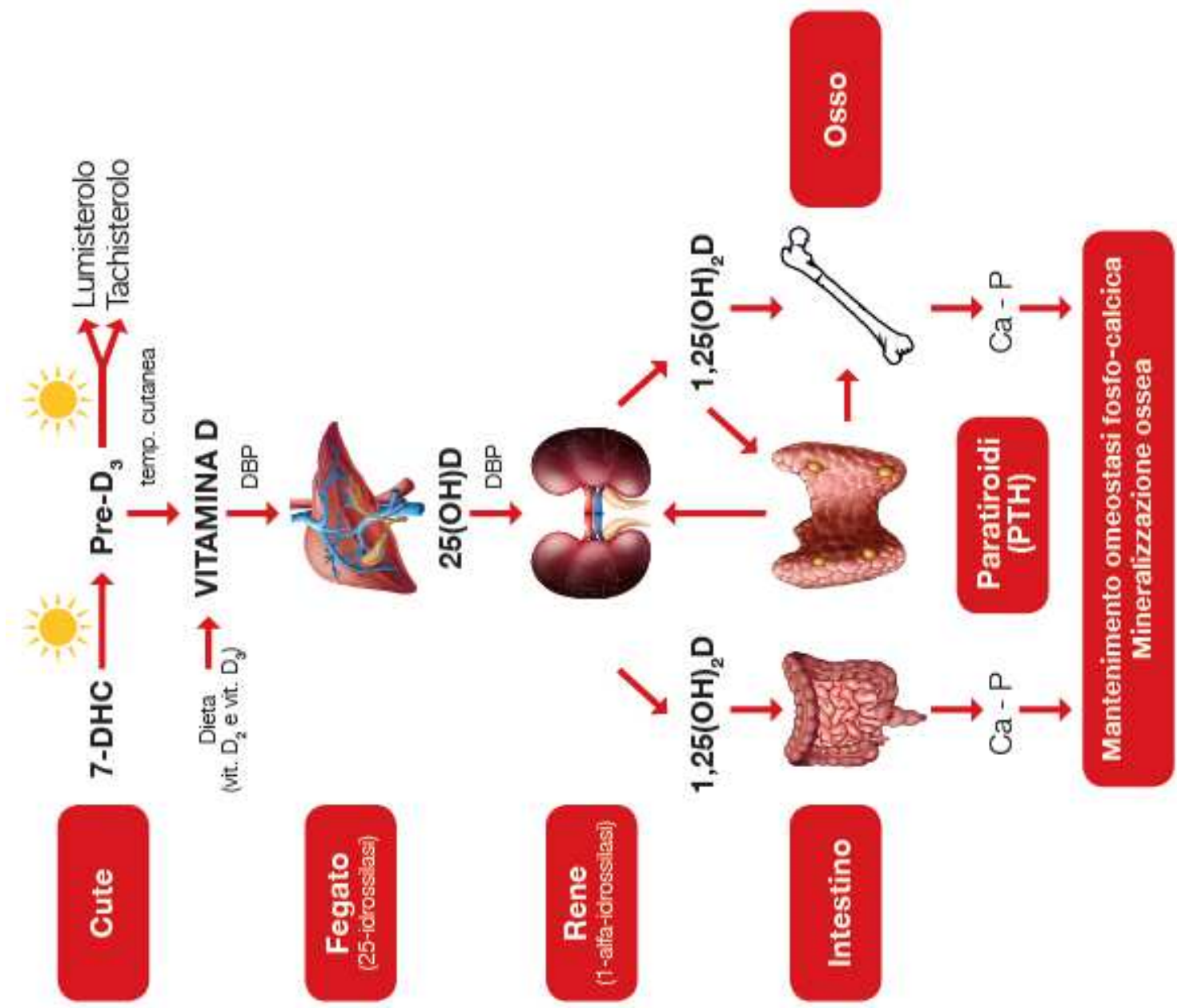
- growth,
- bone development,
- tooth development,
- posture,
- resistance to the infections.



A **rachitic** child in typical lax posture

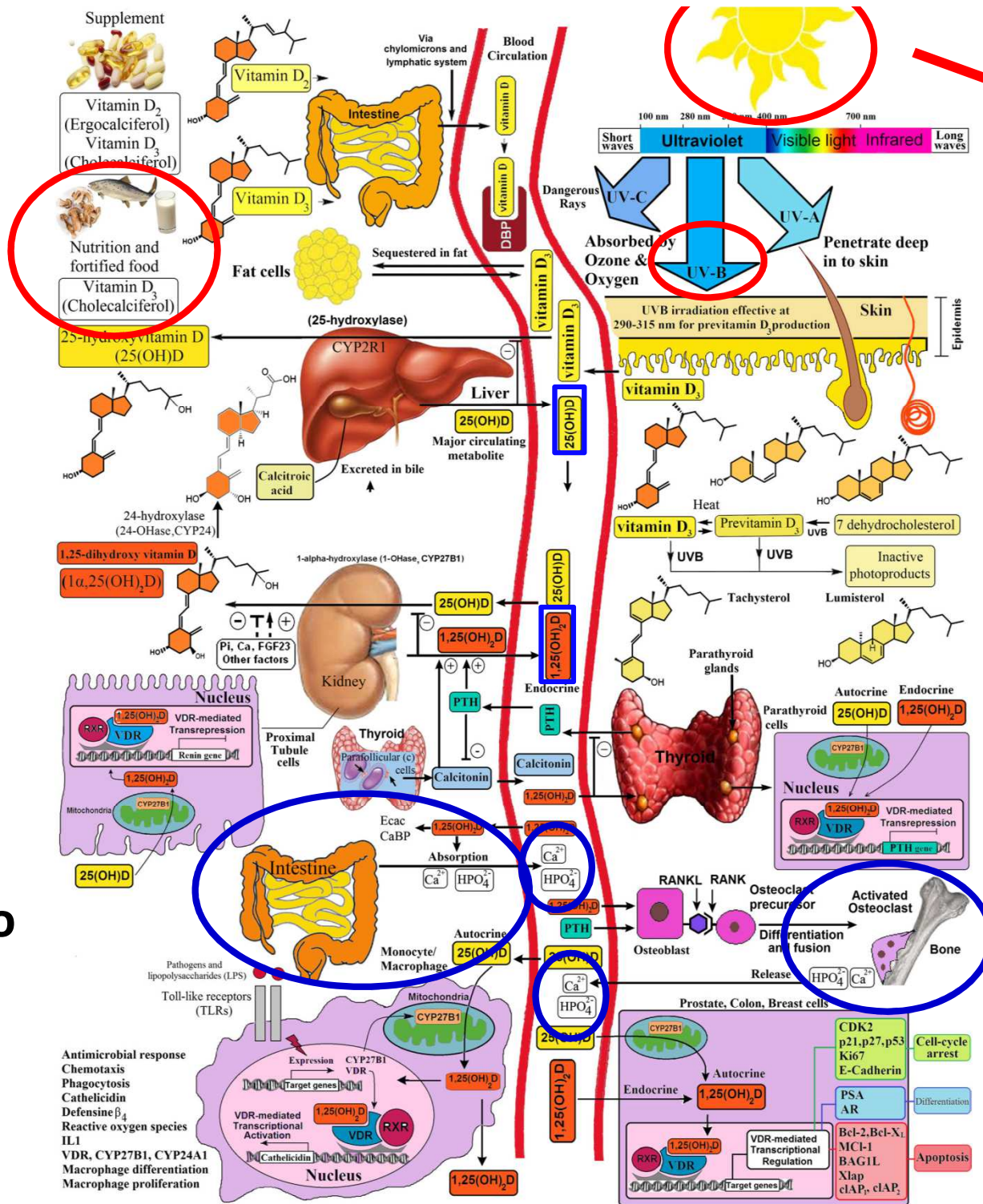


A normal child with good **muscle tonus**



10%

90%



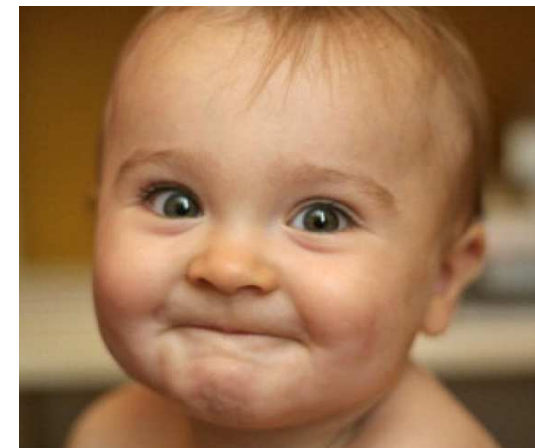
Calcio e fosforo

Calcio e fosforo

(Saggese G, Vierucci F, et al. Eur J Pediatr 2015)



Prima infanzia
(0-2 anni)



Seconda infanzia
(3-5 anni)



Terza infanzia
(6-11/12)



Adolescenza





Vitamin D in pediatric age: Consensus SIP, SIPPS & FIMP



- We recommend vitamin D supplementation in **all newborns independently of the type of feeding.**
- Vitamin D supplementation should be started within the **first days of life** and continued **throughout the first year.**

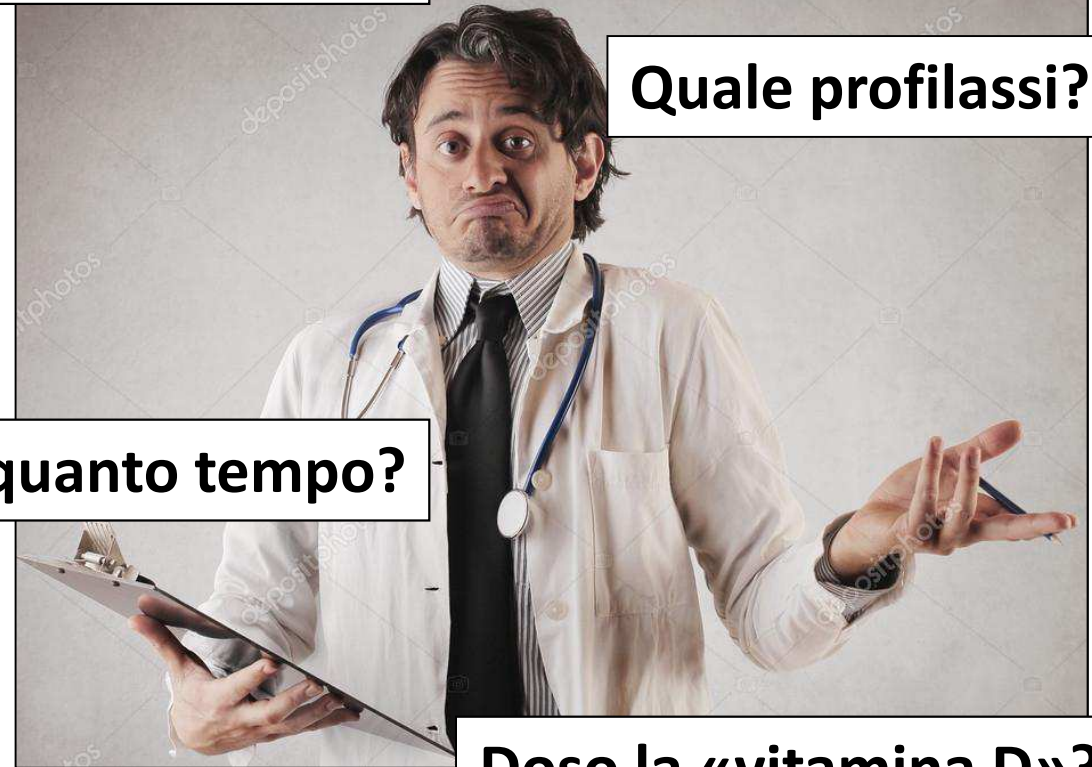
(Italian Journal of Pediatrics, May 2018)

E dopo il primo anno?

Profilassi?



Quale profilassi?



Per quanto tempo?

Doso la «vitamina D»?

Lo stato vitaminico D durante la seconda e la terza infanzia in Italia

Studio	Periodo di arruolamento	N.	Età (range)	Città/ Regione (latitudine)	Deficit, % [25(OH)D < 20 ng/ml]	Insuff., % [25(OH)D: 20-29 ng/ml]	Ipovit. D, % [25(OH)D < 30 ng/ml]
Vierucci ⁸	ott 2010- set 2012	283	2-11 anni	Pisa (43°N)	40,3	35,0	75,3
Franchi ⁹	gen 2010- dic 2012	1.148 (caucasici)	0-16 anni	Verona (45°N)	44,2	30,6	74,8
Ciresi ¹⁰	gen 2011- dic 2012	80*	4-16 anni	Sicilia (37°N)	40,0	35,0	75,0
Stagi ¹¹	set 2010- dic 2013	679	2-18 anni	Firenze (44°N)	58,7	30,0	88,7
Prodam ¹²	lug 2009- dic 2013	575°	6-18 anni	Novara (45°N)	46,1	37,6	83,7

* Bambini affetti da deficit di ormone della crescita; ° Soggetti con sovrappeso/obesità.

«1 bambino su 2 ha un deficit di vitamina D»

(Vierucci F et al. Il Medico Pediatra 2018)

Chi è a rischio di deficit di vitamina D?

Elena, 4 anni



Fabio, 4 anni




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 Prodam³, Fabio Cardinale⁴, Irene Cetin⁵, Elena Chiappini⁶, Gian Luigi de' Angelis⁷, Maddalena Massari⁵, Emanuele Miraglia Del Giudice⁸, Michele Miraglia Del Giudice⁸, Diego Peroni¹, Luigi Terracciano⁹, Rino Agostiniani¹⁰, Domenico Careddu¹¹, Daniele Giovanni Ghiglioni¹², Gianni Bona¹³, Giuseppe Di Mauro¹⁴ and Giovanni Corsello¹⁵



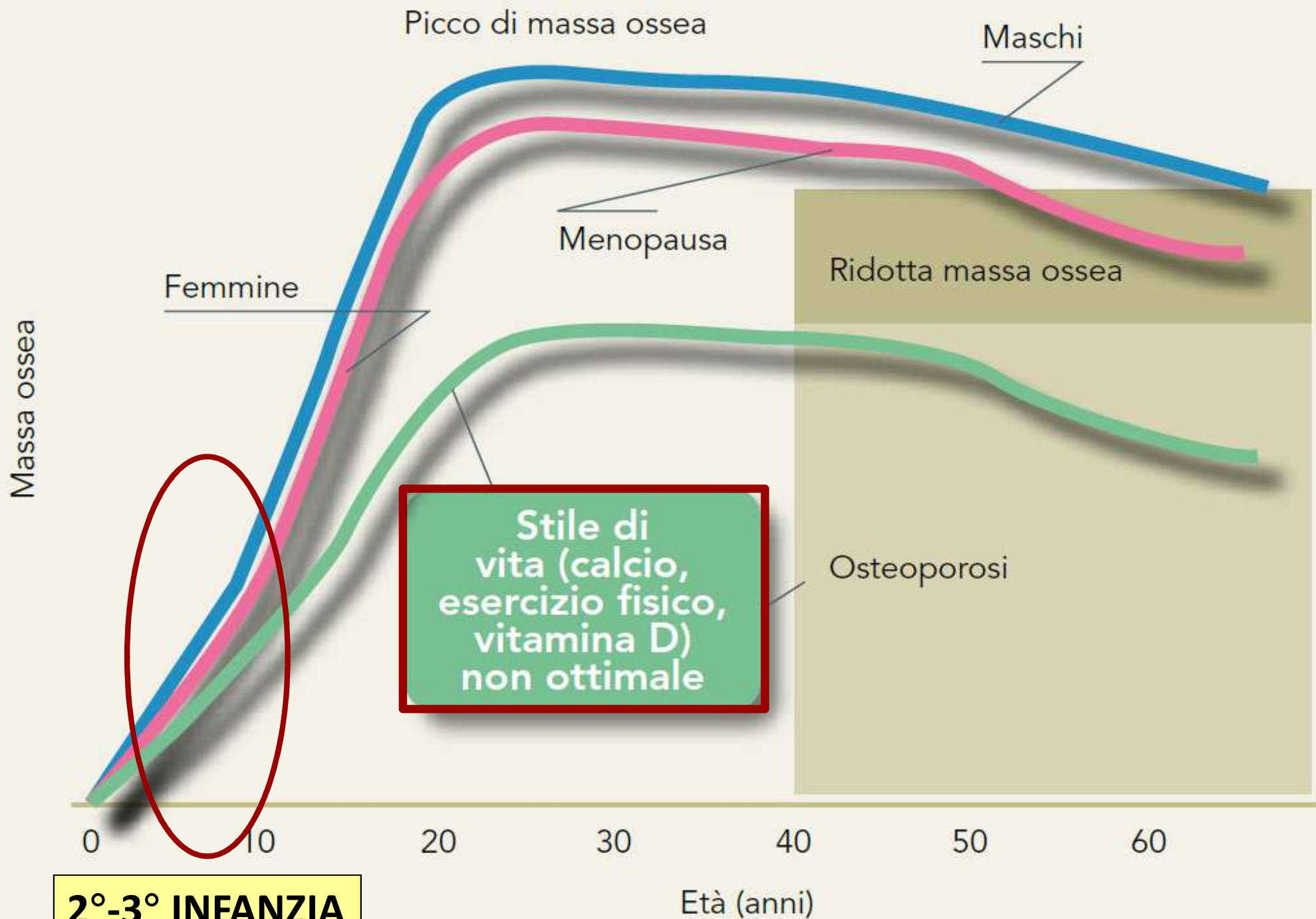
Caratteri sessuali

Peso

Statura

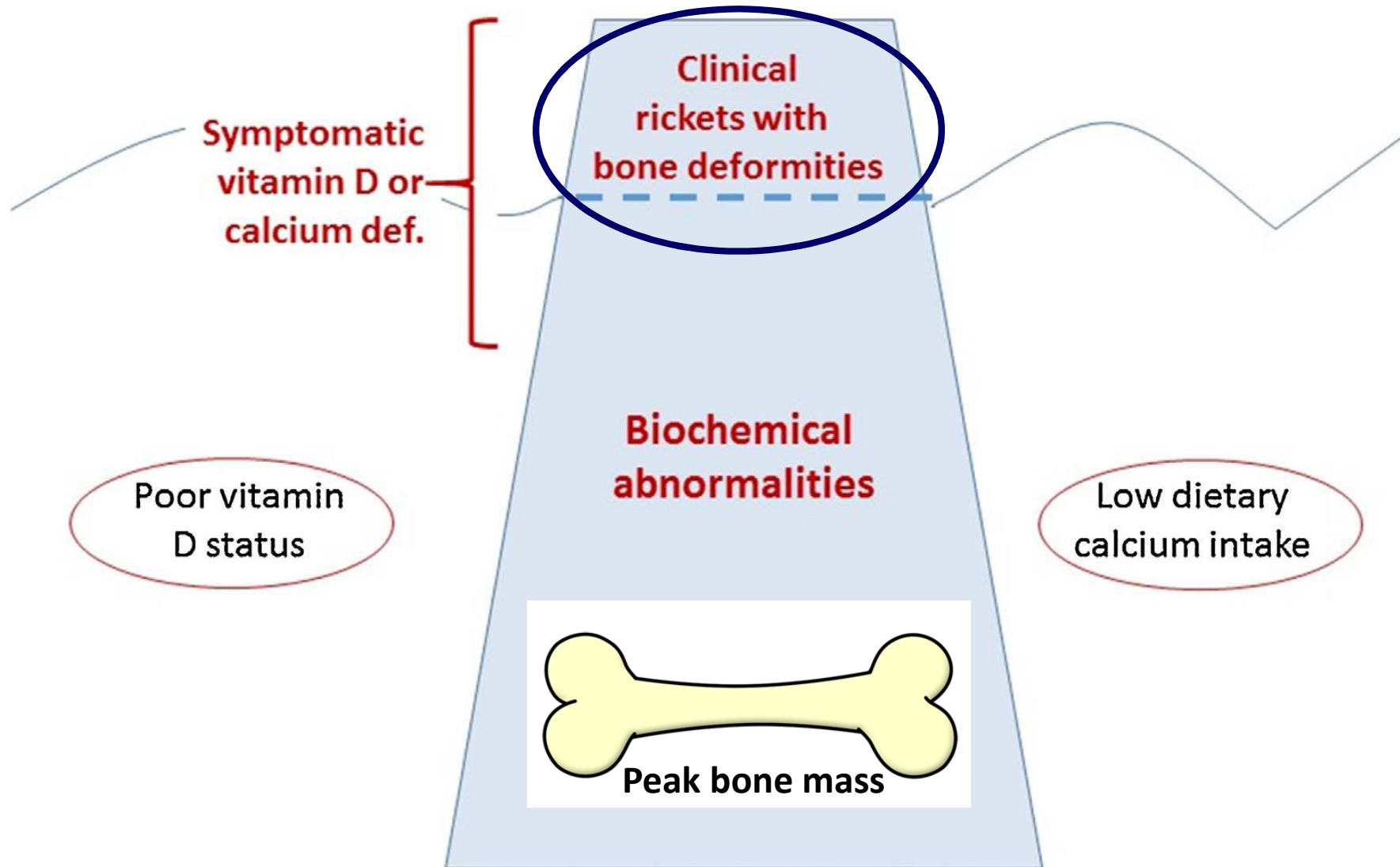


Massa ossea



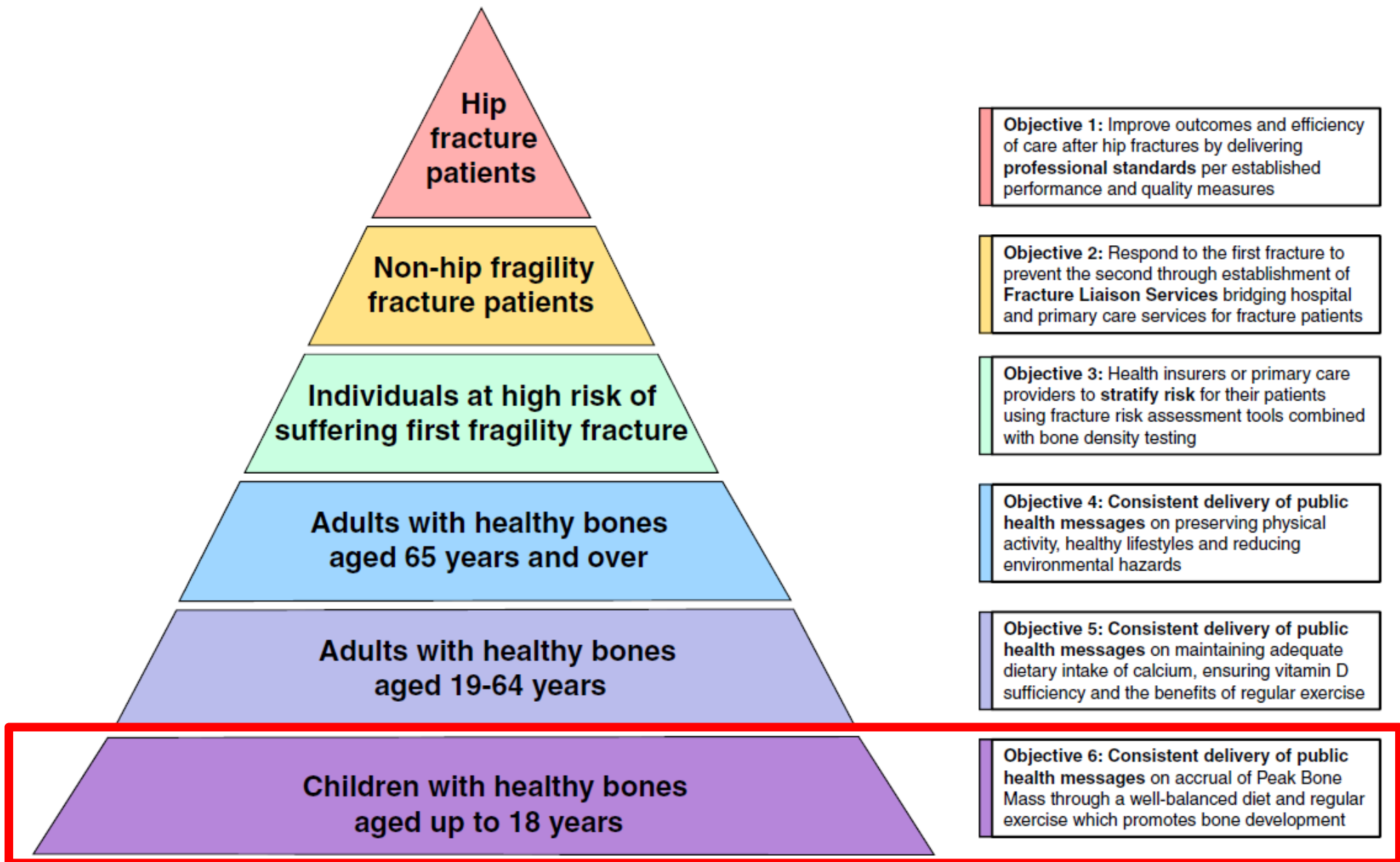
2°-3° INFANZIA

The tip of the iceberg



(Pettifor. J Steroid Biochem Mol Biol 2015)

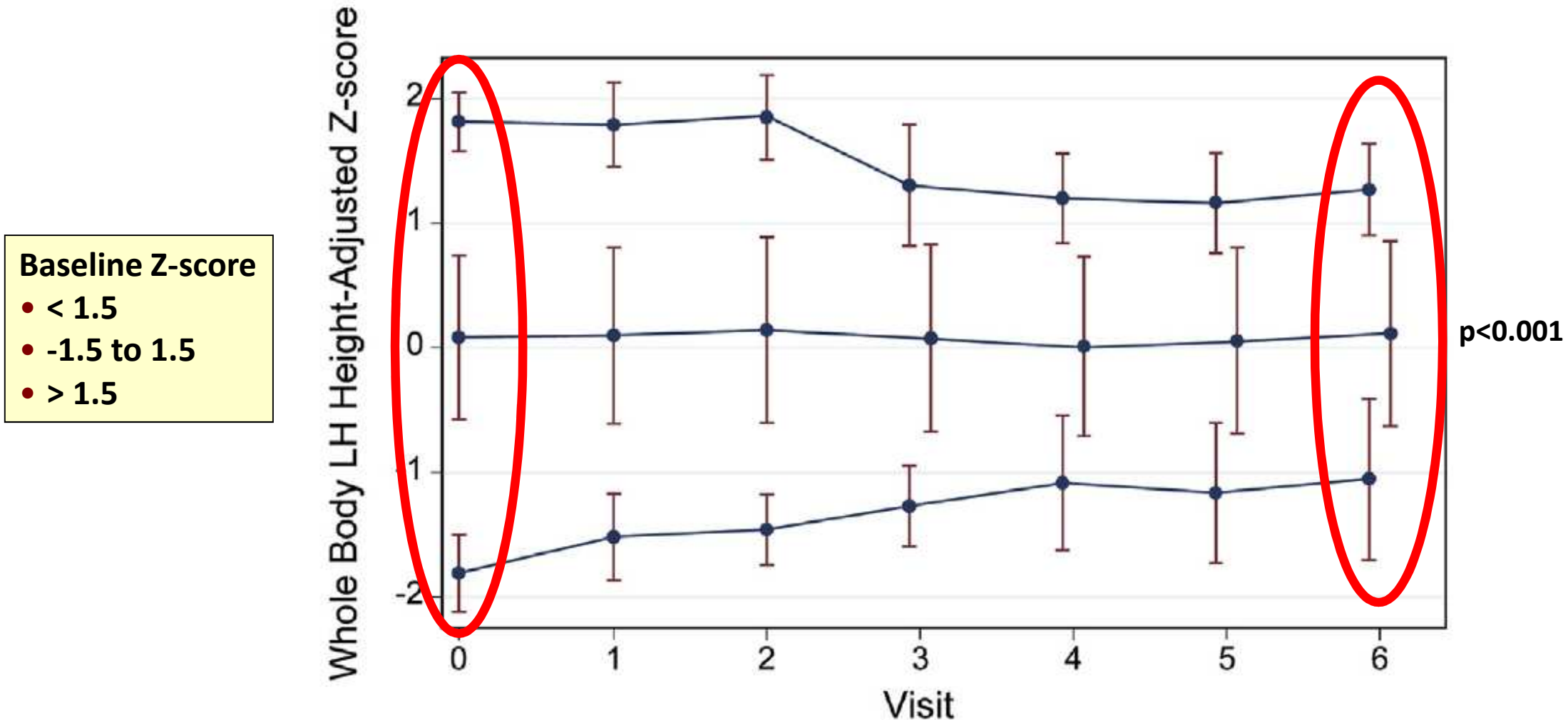
National Osteoporosis Foundation systematic approach to fragility fracture care and prevention for the USA



(Mitchell et al. Osteoporos Int Dec 2015)

Longitudinal tracking of DXA bone measures over 6 years in children and adolescents: persistence of low bone mass to maturity

(240 male and 293 female, age 6-17 years, yearly DXA evaluations for 6 years)



Bone status during childhood is a strong predictor of bone status in young adulthood, when peak bone mass is achieved.

The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations

Lifestyle Factor	Grade
<i>Macronutrients</i>	
Fat	D
Protein	C
<i>Micronutrients</i>	
Calcium	A
Vitamin D	B
Micronutrients other than calcium and vitamin D	D
<i>Food Patterns</i>	
Dairy	B
Fiber	C
Fruits and vegetables	C
Detriment of cola and caffeinated beverages	C
<i>Infant Nutrition</i>	
Duration of breastfeeding	D
Breastfeeding versus formula feeding	D
Enriched formula feeding	D
<i>Adolescent Special Issues</i>	
Detriment of oral contraceptives	D
Detriment of DMPA injections	B
Detriment of alcohol	D
Detriment of smoking	C
<i>Physical Activity and Exercise</i>	
Effect on bone mass and density	A
Effect on bone structural outcomes	B

Level of evidence:

A: strong

B: moderate

C: limited

D: inadequate

- 9 publications from 8 RCTs (tutti citati nella Consensus), 1 prospective study, and 3 cross sectional studies published since 2000, encompassing 2.962 individuals.
- 4 of the 8 RCTs provide evidence for a beneficial effect of vitamin D supplementation on bone accrual.
- Several unanswered questions remain (male sex, critical times during which supplementation may be most effective).

(Weaver et al. Osteoporos Int 2016; 27:1281-1386)



Full Length Article

Serum 25-hydroxyvitamin D and bone mineral density among children and adolescents in a Northwest Chinese city

S-25OHD is Associated with Hand Grip Strength and Myopathy at Five Years in Girls: An Odense Child Cohort Study

Rada Faris Al-Jwadi, Eva Jespersen, Christine Dalgård, Niels Bilenberg, Henrik Thybo Christesen

The Journal of Clinical Endocrinology & Metabolism
Endocrine Society

Submitted: February 08, 2018

JAMA Pediatrics | Original Investigation

Effect of Higher vs Standard Dosage of Vitamin D₃ Supplementation on Bone Strength and Infection in Healthy Infants
A Randomized Clinical Trial

Journal of Pediatric Gastroenterology and Nutrition, Publish Ahead of Print

DOI: 10.1097/MPG.0000000000002031

VITAMIN D INTERVENTION AND BONE – A RANDOMISED CLINICAL TRIAL IN FAIR AND DARK SKINNED CHILDREN AT NORTHERN LATITUDES

Serum 25-hydroxyvitamin D and intact parathyroid hormone influences muscle outcomes in children and adolescents[†]

Abbreviated Title: Vitamin D and muscle outcomes in early adolescents

Journal of Bone and Mineral Research

Calcified Tissue International

<https://doi.org/10.1007/s00223-018-0466-5>

ORIGINAL RESEARCH



Bone Mass Development in Childhood and Its Association with Physical Activity and Vitamin D Levels. The CHAMPS-Study DK

BMJ Open Does vitamin D supplementation improve bone density in vitamin D-deficient children? Protocol for an individual patient data meta-analysis

Tania Winzenberg,^{1,2} Christel Lamberg-Allardt,³ Ghada El-Hajj Fuleihan,⁴
Christian Mølgaard,⁵ Kun Zhu,^{6,7} Feitong Wu,¹ Richard D Riley⁸

[BMJ Open 2018 Jan 23;8:e019584]

Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis

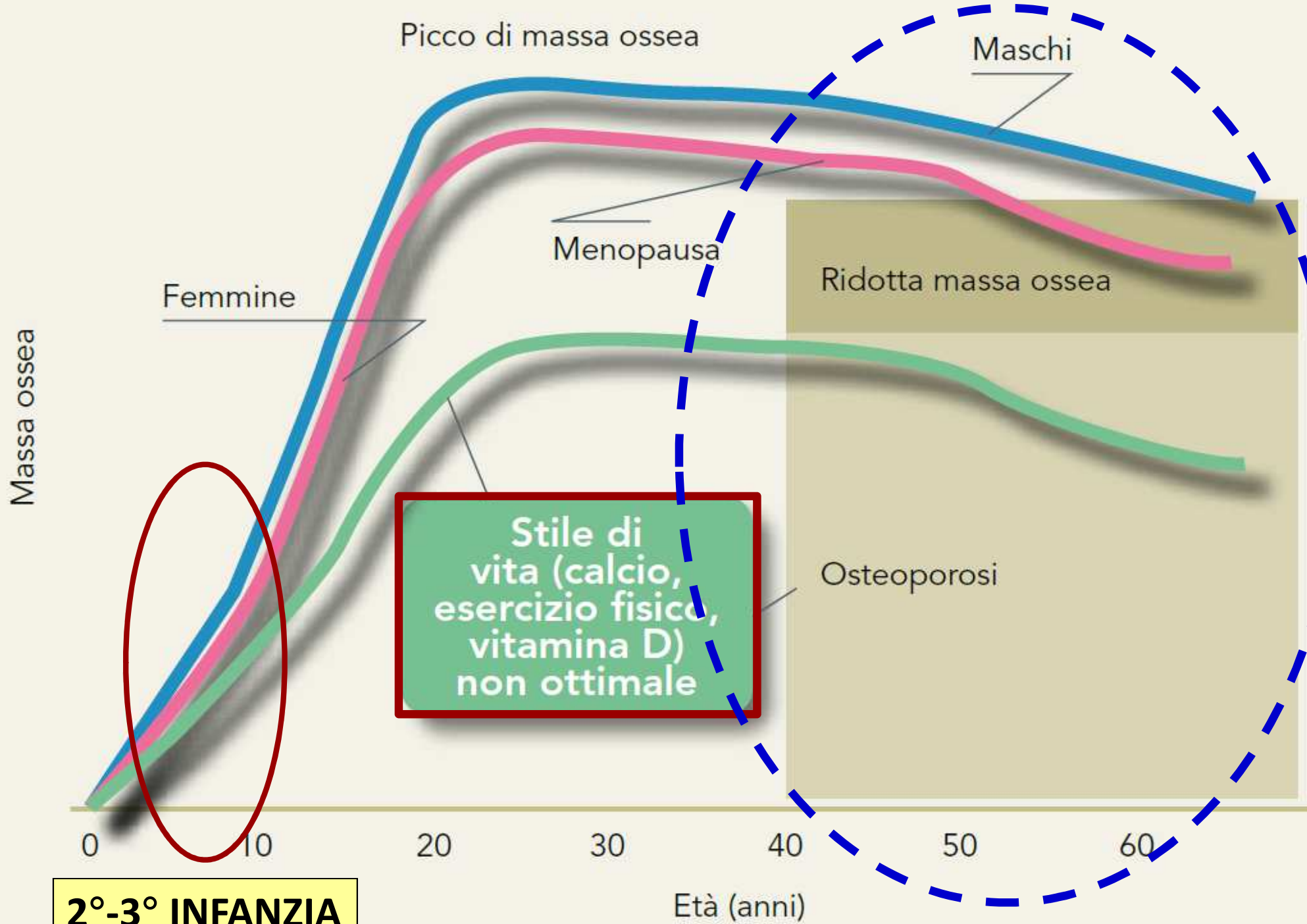
Mark J Bolland, Andrew Grey, Alison Avenell

We assessed RCTs of adults (>18 years) that compared vitamin D with untreated controls, placebo, or lower-dose vitamin D supplements.

Findings We identified 81 randomised controlled trials (n=53 537 participants) that reported fracture (n=42), falls (n=37), or bone mineral density (n=41). In pooled analyses, vitamin D had no effect on total fracture (36 trials; n=44 790, relative risk 1.00, 95% CI 0.93–1.07), hip fracture (20 trials; n=36 655, 1.11, 0.97–1.26), or falls (37 trials; n=34 144, 0.97, 0.93–1.02). Results were similar in randomised controlled trials of high-dose versus low-dose vitamin D and in subgroup analyses of randomised controlled trials using doses greater than 800 IU per day. In pooled

Interpretation Our findings suggest that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. There were no differences between the effects of higher and lower doses of vitamin D. There is little justification to use vitamin D supplements to maintain or improve musculoskeletal health. This conclusion should be reflected in clinical guidelines.

(Lancet Diabetes Endocrinol 2018 Oct 4)



Vitamin D and bone density, fractures, and falls: the end of the story?

There are few studies of severe vitamin D deficiency



Clinical Trial

25-Hydroxyvitamin D Threshold for the Effects of Vitamin D Supplements on Bone Density: Secondary Analysis of a Randomized Controlled Trial

Helen M Macdonald, Ian R Reid , Gregory D Gamble, William D Fraser, Jonathan C Tang, Adrian D Wood

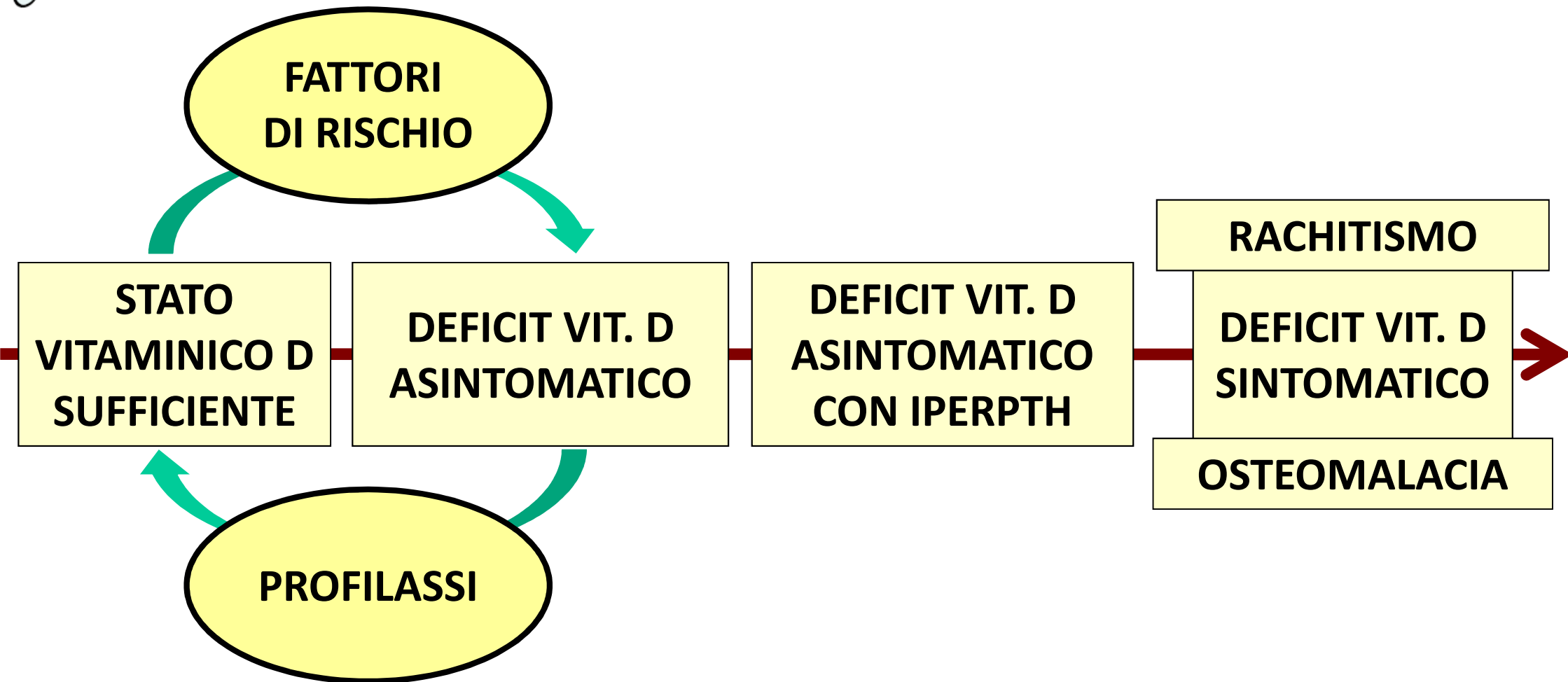
First published: 17 April 2018 | <https://doi-org.bibliosan.clas.cineca.it/10.1002/jbmr.3442> | Cite

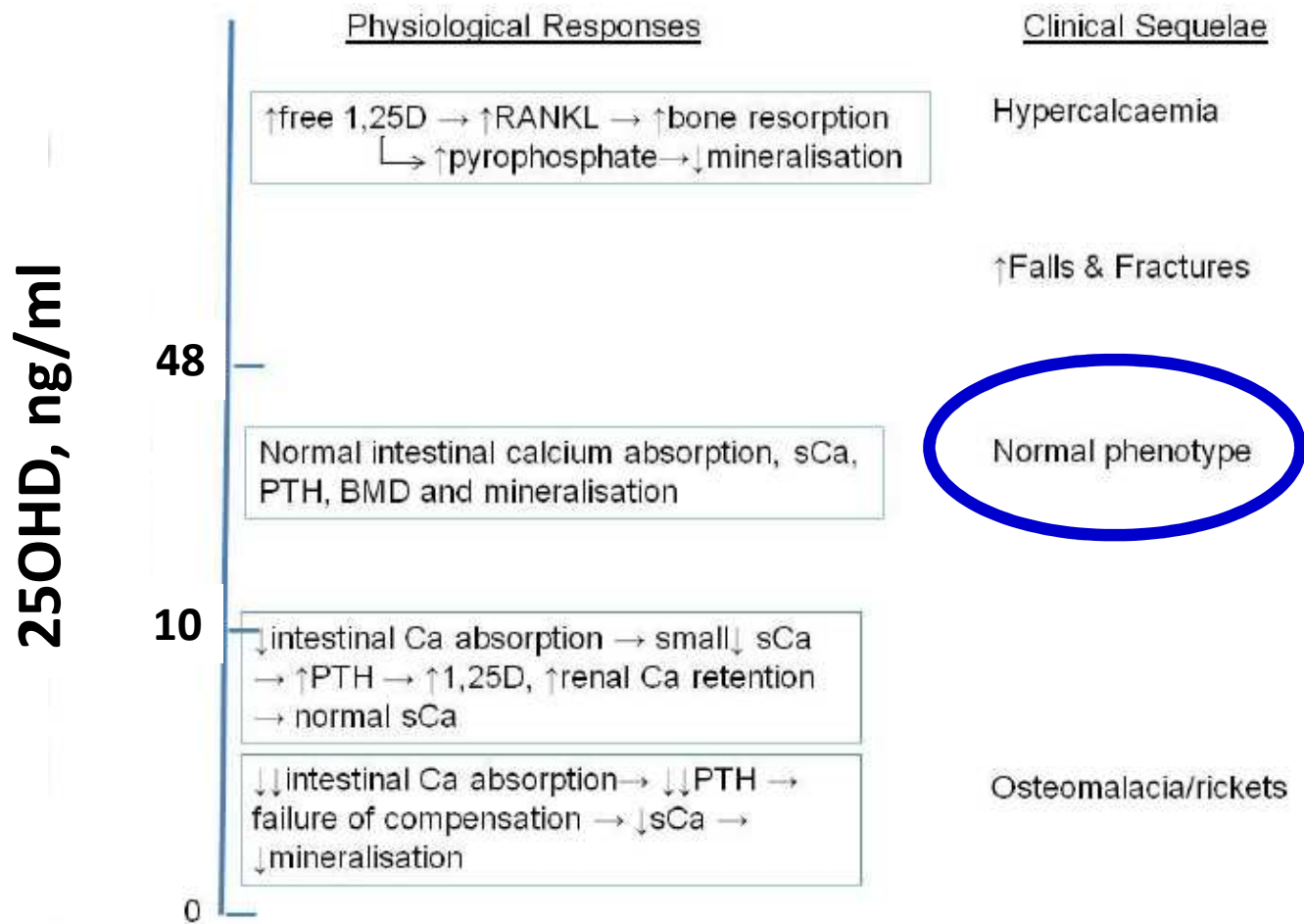
**The Aberdeen study (UK):
n = 305 postmenopausal
women in late winter**

In a study of 400 IU and 1000 IU daily versus placebo, in those with baseline serum **25OHD < 10 ng/ml** there was a significant increase in spine BMD with both 400 IU and 1000 IU daily and in hip BMD with 1000 IU, suggesting that **people with very low serum 25OHD could benefit from treatment.**



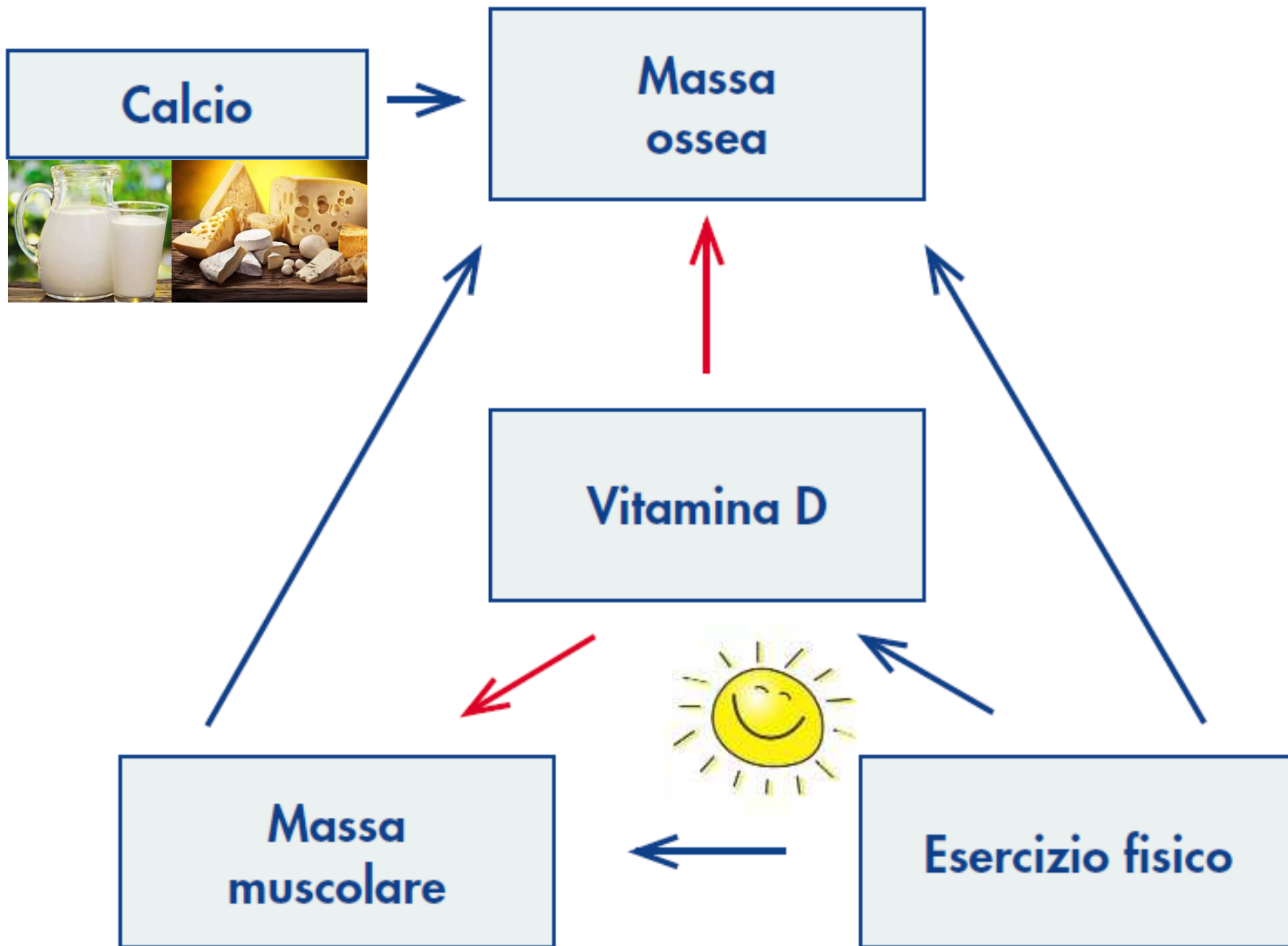
The Spectrum of Vitamin D Deficiency





(Reid IR, J Intern Med
2018 Sep 19)

- The concentrations of **25OHD** at which the various changes occur vary between studies so indication on the figure are only approximate, and the **y-axis is not linear**.
- **Secondary hyperparathyroidism** is reported when 25OHD is < **10-16 ng/ml**, and clinical **osteomalacia** is usually only reported when 25OHD is < **10 ng/ml**.
- The trials which have suggested that vitamin D supplements **increase falls and fractures** have achieved 25OHD concentrations > **48 ng/ml**.
- **Hypercalcaemia** is generally only found at very much higher 25OHD levels.





400 UI



Fabbisogno giornaliero raccomandato di vit. D

Primo anno di vita

Dopo il primo anno di vita

Seconda infanzia

Terza infanzia

Adolescenza



400 UI



600 UI

Adequate intake

Recommended Dietary Allowance (RDA)

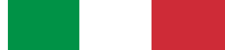
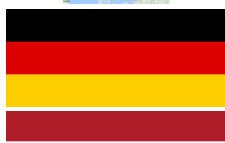
Tabella II. Valori dietetici di riferimento di vitamina D proposti da alcune Società e Organizzazioni internazionali per bambini, adolescenti, donne in gravidanza e donne che allattano (modificato da ⁶).

Società/ Organizzazione	Anno	Paese/i	Valori dietetici di riferimento utilizzati	0-12 mesi, UI/die	1-18 anni, UI/die	Donne in gravidanza	Donne che allattano
European Food Safety Authority	2016	Europa	AI	400 (7-11 mesi)	600 (1-17 anni)	600	600
Scientific Advisory Committee on Nutrition	2016	Regno Unito	Safe Intake (< 4 anni) RNI (4-18 anni)	340-400	400	400	400
Nordic Nutrition Recommendations	2012	Danimarca, Finlandia, Islanda, Norvegia, Svezia	RI	400	400	400	400
German Nutrition Society	2012	Germania, Austria, Svizzera	AI	400	800*	800*	800*
Health Council of the Netherlands	2012	Paesi Bassi	AI	400	400	400	400
LARN	2012	Italia	AI (6-12 mesi) PRI (1-18 anni)	400 (6-12 mesi)	600	600	600
Institute of Medicine	2011	Nord America, Canada	AI (< 12 mesi) RDA (1-18 anni)	400	600	600	600
The Endocrine Society	2011	Raccomandazione mondiale	Fabbisogni giornalieri ^o	400-1.000	600-1.000	1.500-2.000	1.500-2.000

AI: *Adequate Intake*: livello di assunzione di un nutriente che si assume adeguato a soddisfare i fabbisogni della popolazione. Safe Intake: Livello di assunzione di un nutriente che non si associa ad alcun rischio di carenza e al di sotto del quale sono possibili effetti indesiderati.

RNI: *Reference Nutrient Intake*; RI: *Recommended Intake*; PRI: *Population Reference Intake*; RDA: *Recommended Dietary Allowance*: livello di assunzione di un nutriente sufficiente a soddisfare il fabbisogno di quasi tutti (97,5%) i soggetti sani in uno specifico gruppo di popolazione.

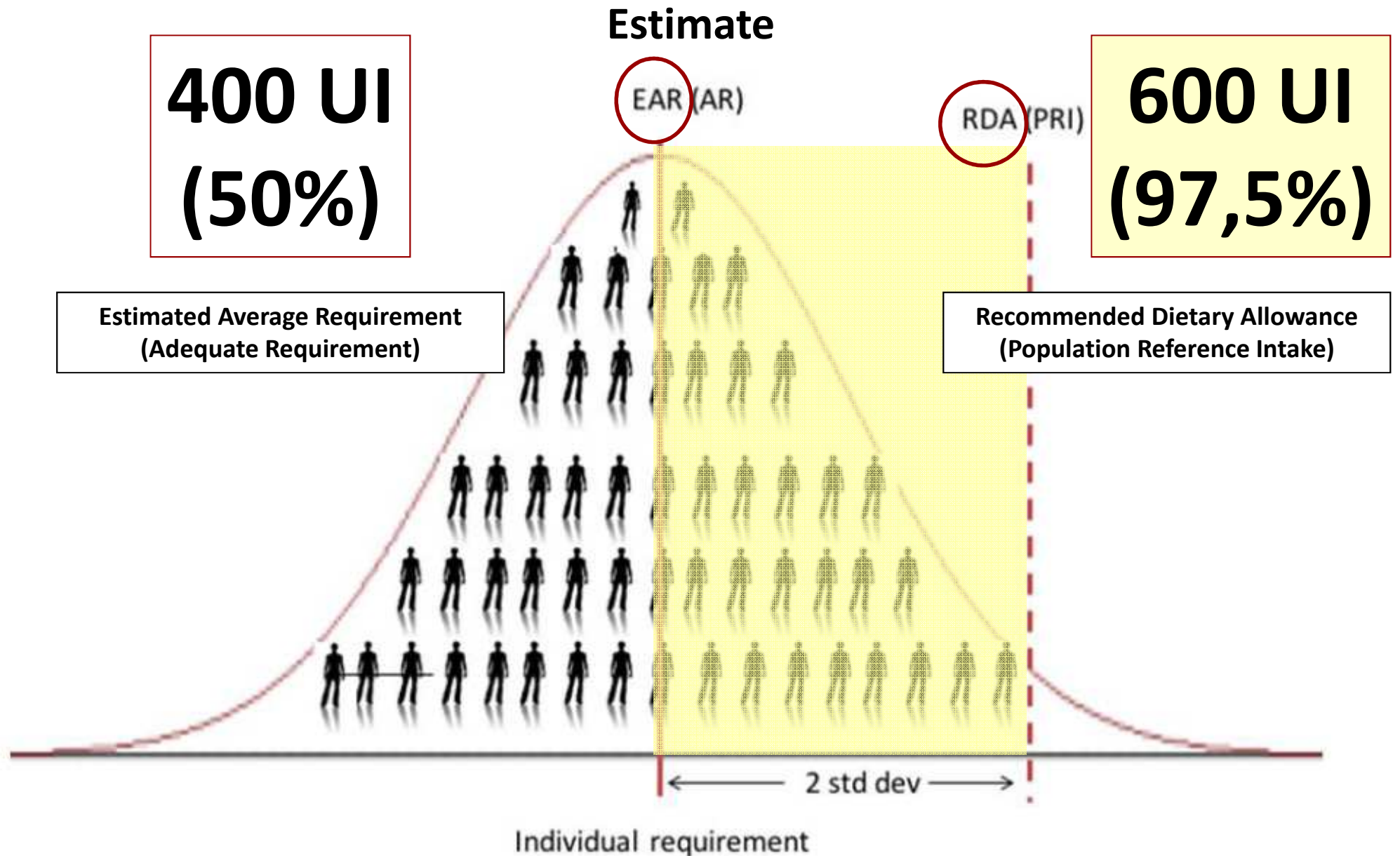
* Apporto di vitamina D ritenuto adeguato in caso di assente sintesi cutanea di vitamina D. ^o Fabbisogni giornalieri di vitamina D raccomandati nei soggetti a rischio di deficit.



INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES



Fabbisogno giornaliero raccomandato di vit. D



(Cashman KD. Nutrients Apr 2018)

Fattori di rischio di deficit di vitamina D

RIDOTTA ESPOSIZIONE SOLARE E/O USO COSTANTE DI FILTRI SOLARI

SOGGETTI DI ETNIA NON CAUCASICA CON ELEVATA PIGMENTAZIONE CUTANEA

OBESITÀ

BAMBINI NEL PRIMO ANNO DI VITA NATI DA MADRI CON FATTORI DI RISCHIO DI DEFICIT DI VITAMINA D DURANTE LA GRAVIDANZA NON SOTTOPOSTE A PROFILASSI CON VITAMINA D

INSUFFICIENZA EPATICA CRONICA

INSUFFICIENZA RENALE CRONICA

MALASSORBIMENTO (AD ESEMPIO FIBROSI CISTICA, MALATTIE INFIAMMATORIE CRONICHE INTESTINALI, CELIACHIA ALLA DIAGNOSI, ETC.)

TERAPIE CRONICHE: ANTIEPILETTICI (FENOBARBITAL, FENITOINA), CORTICOSTEROIDI PER VIA SISTEMICA, FARMACI ANTIRETROVIRALI, ANTIMICOTICI PER VIA SISTEMICA (KETOCONAZOLO)

FRATTURE RICORRENTI O CONDIZIONI ASSOCIATE A RIDOTTA DENSITÀ MINERALE OSSEA

IMMOBILIZZAZIONE (PARALISI CEREBRALE, MALATTIE NEUROMUSCOLARI)

MALATTIE GRANULOMATOSE (AD ESEMPIO TUBERCOLOSI)



0-12 mesi: 400-1.000 UI/die

1-18 anni: 600-1.000 UI/die

Obesità: 2-3 volte i fabb. per età

How can my child get vitamin D?

Exposure to direct sunlight
Sunlight converts a chemical in the skin to an active form of vitamin D.



Dietary sources

Fatty fishes and vitamin D-fortified foods, such as dairy products and cereals, are sources of vitamin D. Eggs also have a small amount of vitamin D.



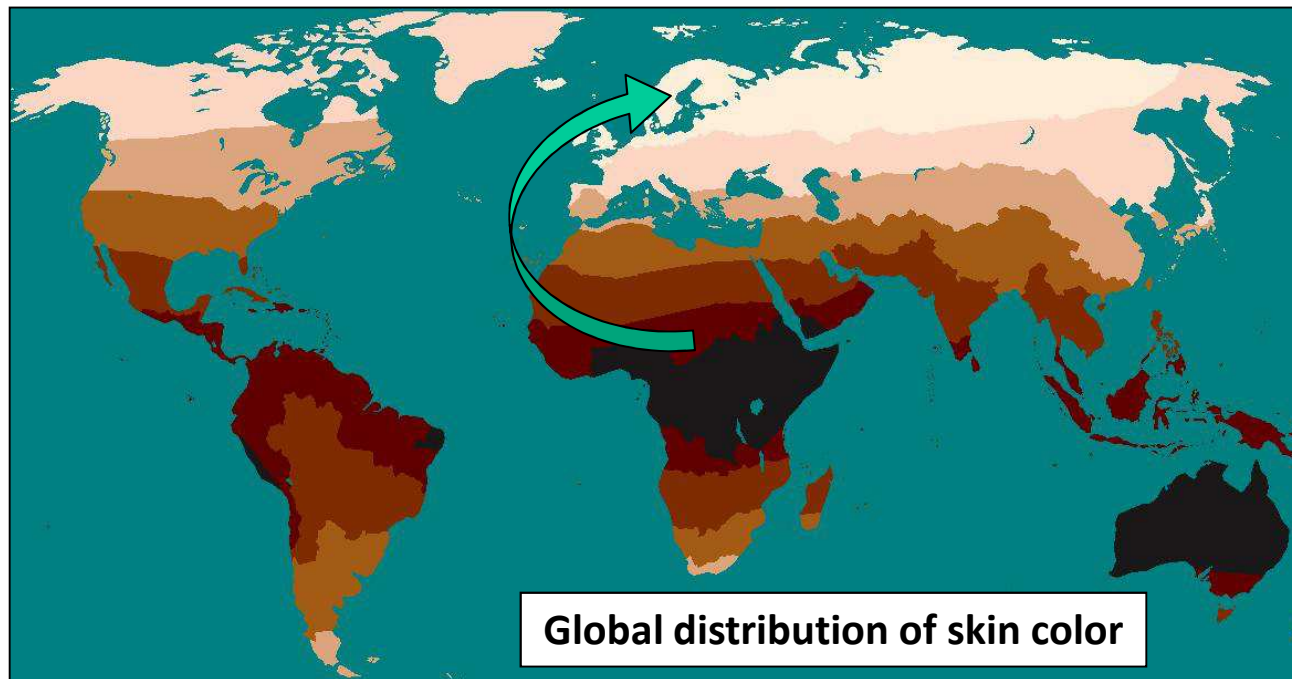
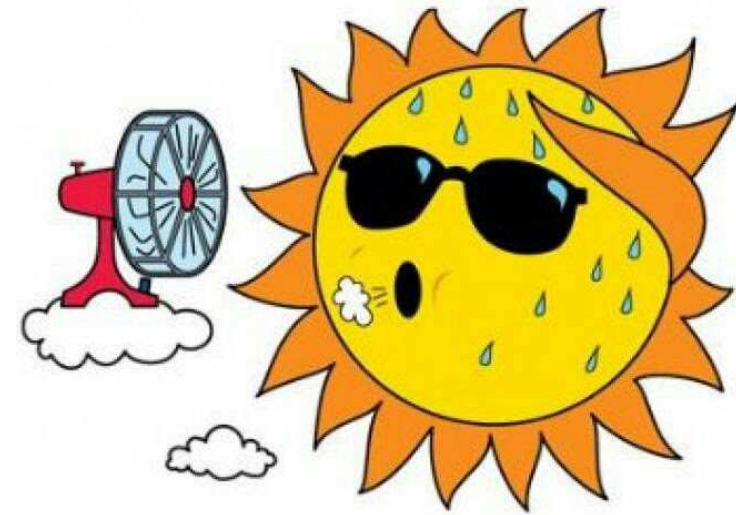
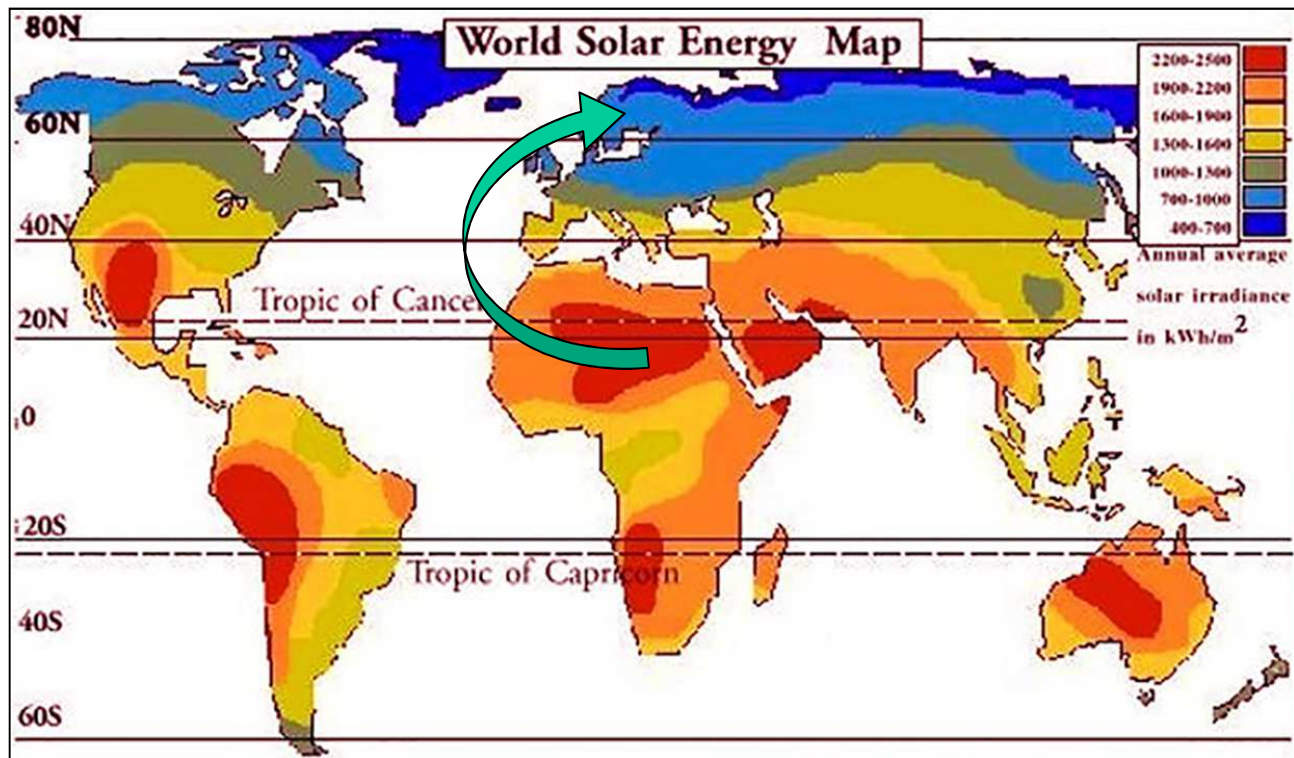
Vitamin D supplements

Vitamin D is available as multivitamins with vitamin D and as vitamin D supplements.



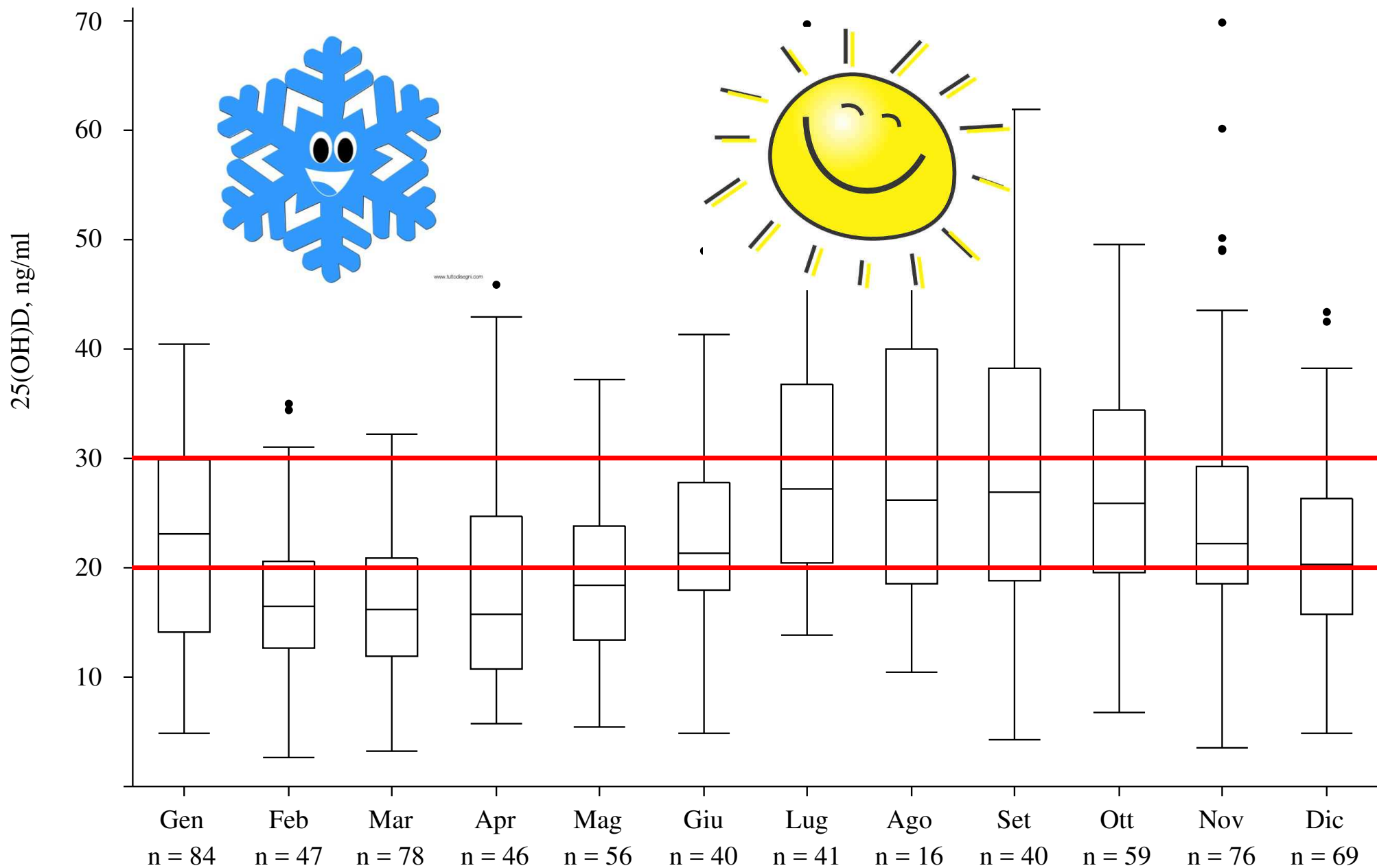
K. BUCHER

(JAMA Pediatrics July 2018)



(Hernigou P et al. Int Orthop Mar 2018)

Livelli mediani di 25(OH)D nei diversi mesi dell'anno valutati trasversalmente in 692 bambini e adolescenti toscani (età 2-21 anni) non sottoposti a profilassi con vitamina D ($p < 0,0001$)



Il deficit di vitamina D oggi



Do sufficient vitamin D levels at the end of summer in children and adolescents provide an assurance of vitamin D sufficiency at the end of winter?
(Iran; Longitudinal study; n = 68; 7-18 years; summer 2011-winter 2012)

End of summer
100% ≥ 30 ng/ml
25(OH)D: 46.5 ± 10.1 ng/ml

End of winter
14.7% < 20
36.8% 20-30
48.5% ≥ 30

Mean 25(OH)D decrease
 15.3 ± 12.4 ng/ml

Cutoff to provide sufficiency at the end of the winter: **40 ng/mL** at the end of the **summer**

UOVO

- Tuorlo: 20 UI / 100g

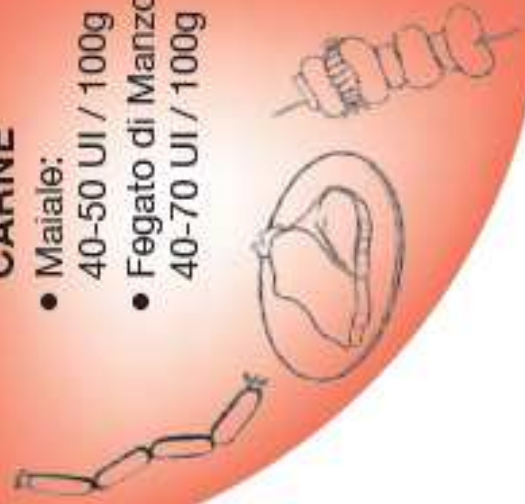


PESCE

- Dentice, Merluzzo, Orata, Palombo, Sogliola, Trota, Salmone, Aringhe: 300 - 1.500 UI / 100g
- Olio di fegato di Merluzzo: 400 UI / 5 ml

CARNE

- Maiale: 40-50 UI / 100g
- Fegato di Manzo: 40-70 UI / 100g



LATTE e LATTICINI

- Latte vaccino o di capra: 5-40 UI / l
- Burro: 30 UI / 100g
- Yogurt: 2,4 UI / 100g
- Panna: 30 UI / 100g
- Formaggio: 12-40 UI / 100g





Con Calcio + Vit B₂ B₁₂ D₂



con calcio, fosforo,
vit. D e K

Dichiarazione Nutrizionale per 100g

Energia	374 kJ
	88 kcal
Grassi	0,9 g
di cui:	
acidi grassi saturi	
acidi grassi monoinsaturi	
acidi grassi polinsaturi	
Carboidrati	
di cui: zuccheri	16 g
Fibre	0,7 g
Proteine	2,7 g
Sale	0,13 g
Calcio	120 (*) mg
Riboflavina (Vit B ₂)	0,21 (*) mg
Vitamina B ₁₂	0,30 (*) µg
Vitamina D	1,5 (**) µg

(*) 15%-(**) 30% dell'Assunzione di Riferimento Giornaliera

1 budino (115 gr):
69 UI vit. D2

VALORI MEDI PER 100 ML

ENERGIA	
kJ	175
kcal	41
GRASSI	1,0 g
di cui acidi grassi saturi	0,7 g
CARBOIDRATI	4,9 g
di cui zuccheri	4,9 g
FIBRE	0,0 g
PROTEINE	3,2 g
VITAMINE	
Vitamina D	1 µg
MINERALI	
Calcio	160 mg
Fosforo	115 mg
Sodio	0,13 g

1 bicchiere di latte
(200 ml): 80 UI vit. D



Consensus SIPPS 2018: dopo il primo anno

- We recommend vitamin D supplementation in children and adolescents with **risk factors for vitamin D deficiency**.

A CHI

- We recommend **daily** vitamin D supplementation ranging from **600 IU/day** (i.e. in presence of reduced sun exposure) up to **1000 IU/day** (i.e. in presence of multiple risk factors for vitamin D deficiency).
- In cases of poor compliance, supplementation with **intermittent** dosing (**weekly** or **monthly** doses for a cumulative monthly dose of **18000–30000 IU** of vitamin D) can be considered, starting from children aged **5–6 years** and particularly during **adolescence**.

COME

- We suggest vitamin D supplementation from the end of fall to the beginning of spring (**Nov–Apr**) in children and adolescents with **reduced sun exposure** during summer.
- We suggest **continuous** vitamin D supplementation in cases of **permanent risk factors** for vitamin D deficiency.

PER QUANTO

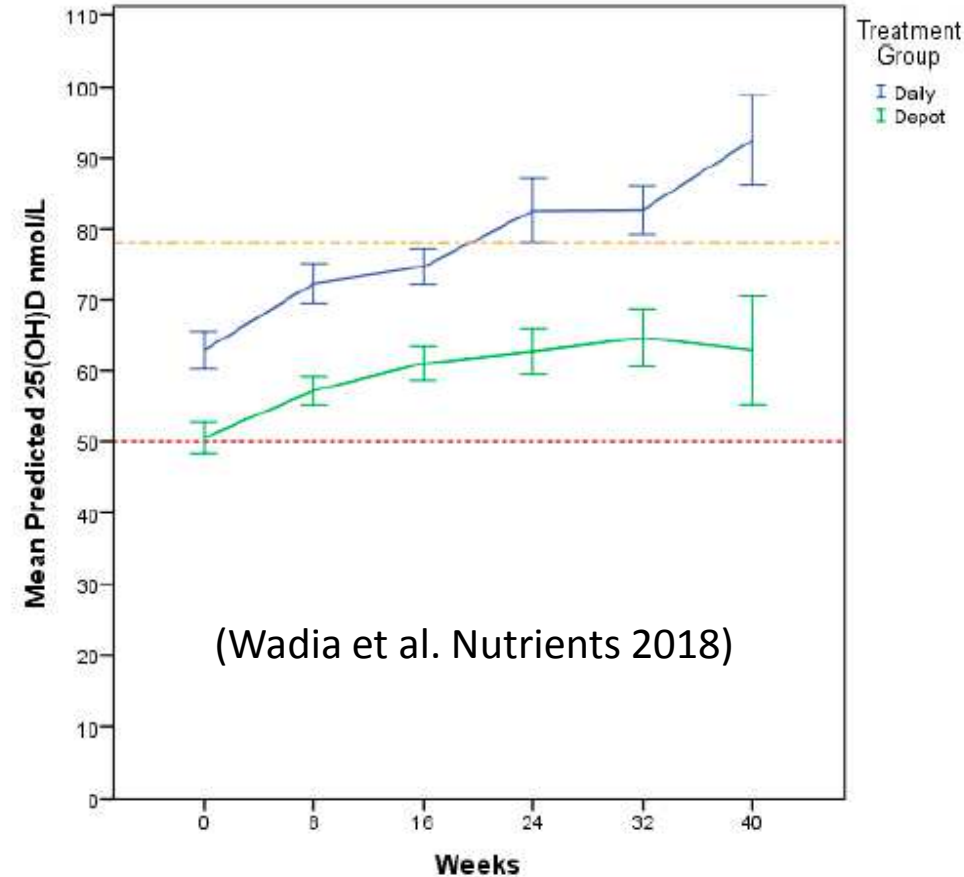
Somministrazione giornaliera o intermittente?

Giornaliera

- Più studi disponibili
- Primo anno di vita
- Minor rischio di «errore»
- Livelli circolanti di 25(OH)D più «stabili»
- Minor dose totale richiesta
- Azioni extrascheletriche?

Intermittente

- Settimanale-bisettimanale-mensile
- Scarsa compliance con somm. giornaliera
- Dopo il 5°-6° anno di vita
- Non somministrare boli > 300.000 UI



Trattamento deficit

300.000 UI/6 sett vs. 84.000 UI/6 sett.

Age	Preparation and Dose ^a
Infants, 0–12 mo	Vitamin D ₂ or D ₃ 50 000 IU weekly for 6 wk or Vitamin D ₂ or D ₃ 2000 IU daily for 6 wk Followed by a maintenance dose of 400–1000 IU daily
Children and adolescents, 1–18 y	Vitamin D ₂ or D ₃ 50 000 IU weekly for 6–8 wk or Vitamin D ₂ or D ₃ 2000 IU daily for 6–8 wk Followed by a maintenance dose of 600–1000 IU daily

(Golden et al. Pediatrics 2014)

Vitamin D₂, ergocalciferol; vitamin D₃, cholecalciferol.

^a Vitamin D₃ may be more potent than vitamin D₂.

400.000 UI/6 sett vs. 112.000 UI/8 sett.

Vitamin D vs. metabolites

	Cholecalciferol	Calcidiol	Calcitriol
Hydroxylation	No	25	1,25
Properties	Lipophilic	Hydrophilic*	Hydrophilic
Circulating half-life	2 days	2-3 weeks	12 hours
Tissue distribution	Adipose/Muscle	Blood/Adipose/Muscle	Blood/Tissues
VDR** activation	?	-/+	++
↑in serum 25(OH)D levels	+	+	-

* Relatively lipophilic too

** Vitamin D Receptor

*** Cholecalciferol 1 mcg = 40 IU

(Courtesy of Prof. Sandro Giannini)



An initiative of the ABIM Foundation

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™



Section on Endocrinology

Five Things Physicians and Patients Should Question

Avoid ordering Vitamin D concentrations routinely in otherwise healthy children, including children who are overweight or obese.

Although a 25-hydroxyvitamin D concentration, reflecting both vitamin D synthesis and intake, is the correct screening lab to monitor for vitamin D deficiency, current evidence is not sufficient to suggest that screening in otherwise healthy including children who are overweight or obese is necessary or safe.

(October 2, 2017)

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

We recommend against routine 25(OH)D testing in children and adolescents. We suggest to measure serum 25(OH)D levels in presence of multiple risk factors for vitamin D deficiency. Vitamin D status should be monitored at least yearly in subjects that require supplementation during the whole year because affected from pathological conditions or receiving drugs affecting vitamin D metabolism

(May 8, 2018)

Quando dosare la vitamina D?

- Sospetto deficit sintomatico/**rachitismo** carenziale
- Sospetto deficit **grave** di vit. D (fattori di rischio multipli) tale da richiedere trattamento
- Sospetta patologia del metabolismo **calcio-fosforo** (es. “osteoporosi”)
- Patologie **croniche** e/o **farmaci** interferenti con il metabolismo della vit. D

Casi particolari (da individualizzare)

- Asma grave, steroideo-resistente (prevenzione esacerbazioni)
- Infezioni respiratorie ricorrenti (prevenzione)



Sospetto deficit di vit. D

Quando NON dosare la vitamina D?

- Nel bambino “altrimenti sano”
- Nel bambino con scarsa esposizione alla luce solare
- Nel bambino di colore “altrimenti sano”
- Nel bambino obeso “altrimenti sano”

Stile di vita

PROFILASSI

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Vitamin D and Your Child

Vitamin D is essential for building and maintaining healthy bones. While many know that calcium is a primary component of bone growth and development, not everyone knows that calcium can only be absorbed by your body when vitamin D is present.

- While **daily multivitamins are not recommended as necessary for children**, supplementing with **vitamin D** may be helpful for those not getting their daily vitamin D allowance through **foods** or who have limited **sun exposure**.
- If you are unsure if your child is getting enough vitamin D, [talk with your pediatrician](#).

(JAMA Pediatrics July 2018)



**KEEP
CALM
GET YOUR
VITAMIN D
ON**



Grazie per l'attenzione