Vitamin D

دکتر اکبر -علی عسگرزاده
متخصص داخلی، فوق تخصص غدد و متابولیسم
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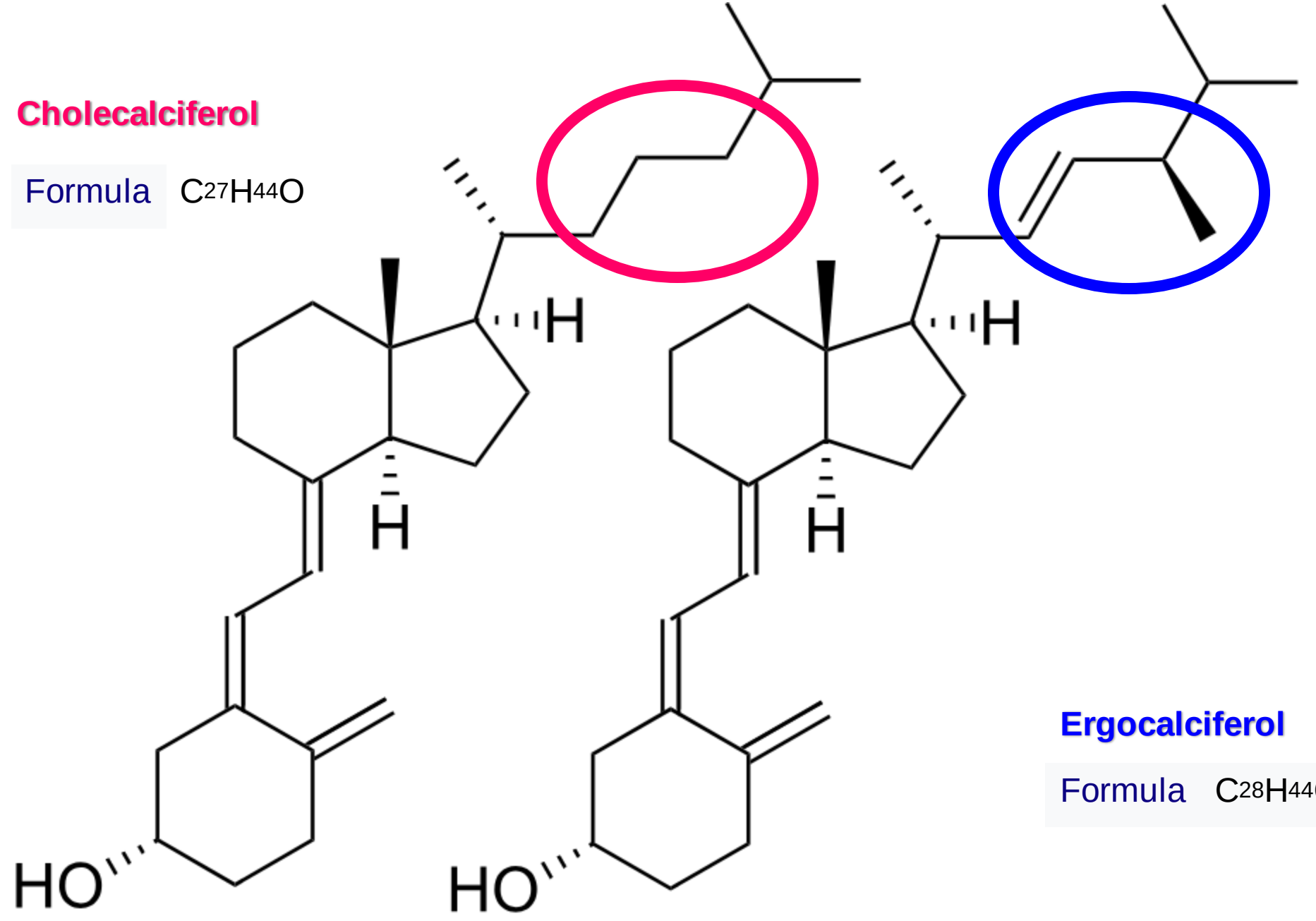
دوشنبه 91/10/22
2021/01/10

Cholecalciferol

Formula $C_{27}H_{44}O$

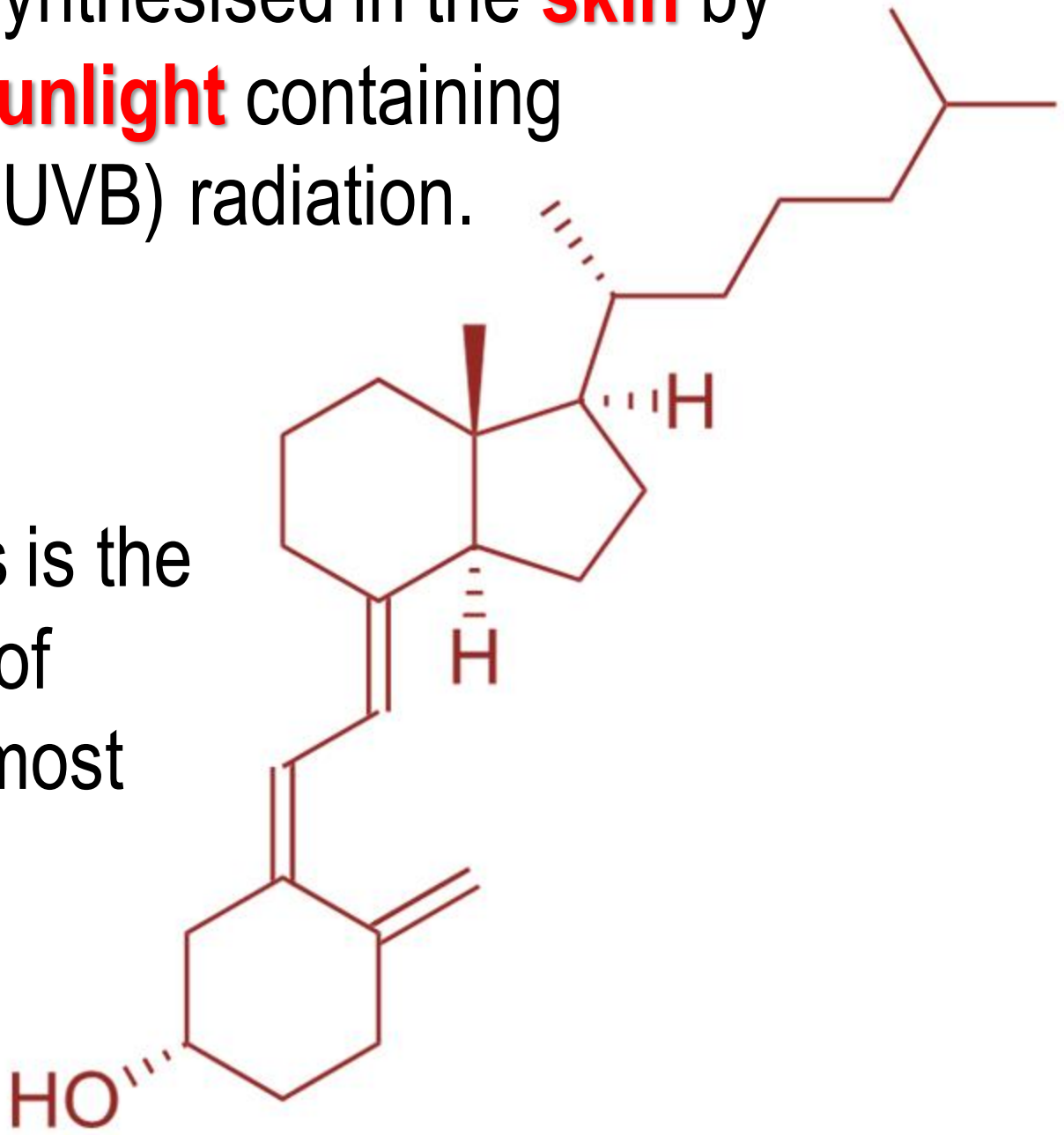


Ergocalciferol

Formula $C_{28}H_{44}O$

Vitamin D is synthesised in the **skin** by the action of **sunlight** containing **ultraviolet B** (UVB) radiation.

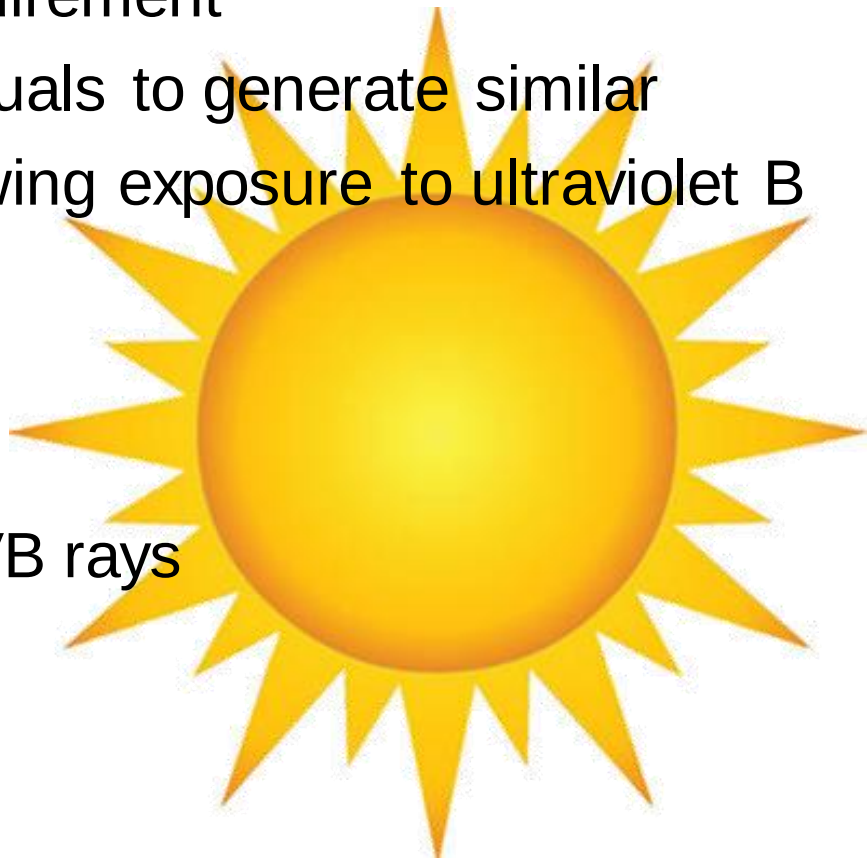
Skin synthesis is the **main source** of vitamin D for most people.



Exposure to sunlight is a major source of vitamin D for most people

- **BUT**

  - Risks of erythema
  - Potential skin cancer
  - 80% of daily vitamin D requirement
  - Different capacity of individuals to generate similar amounts of vitamin D following exposure to ultraviolet B (UVB) rays (280–315 nm)
  - Intensity of sunlight
  - Amount of skin exposed
  - Duration of exposure to UVB rays
  - The zenith angle of the sun
  - Thickness of the skin
  - The skin color



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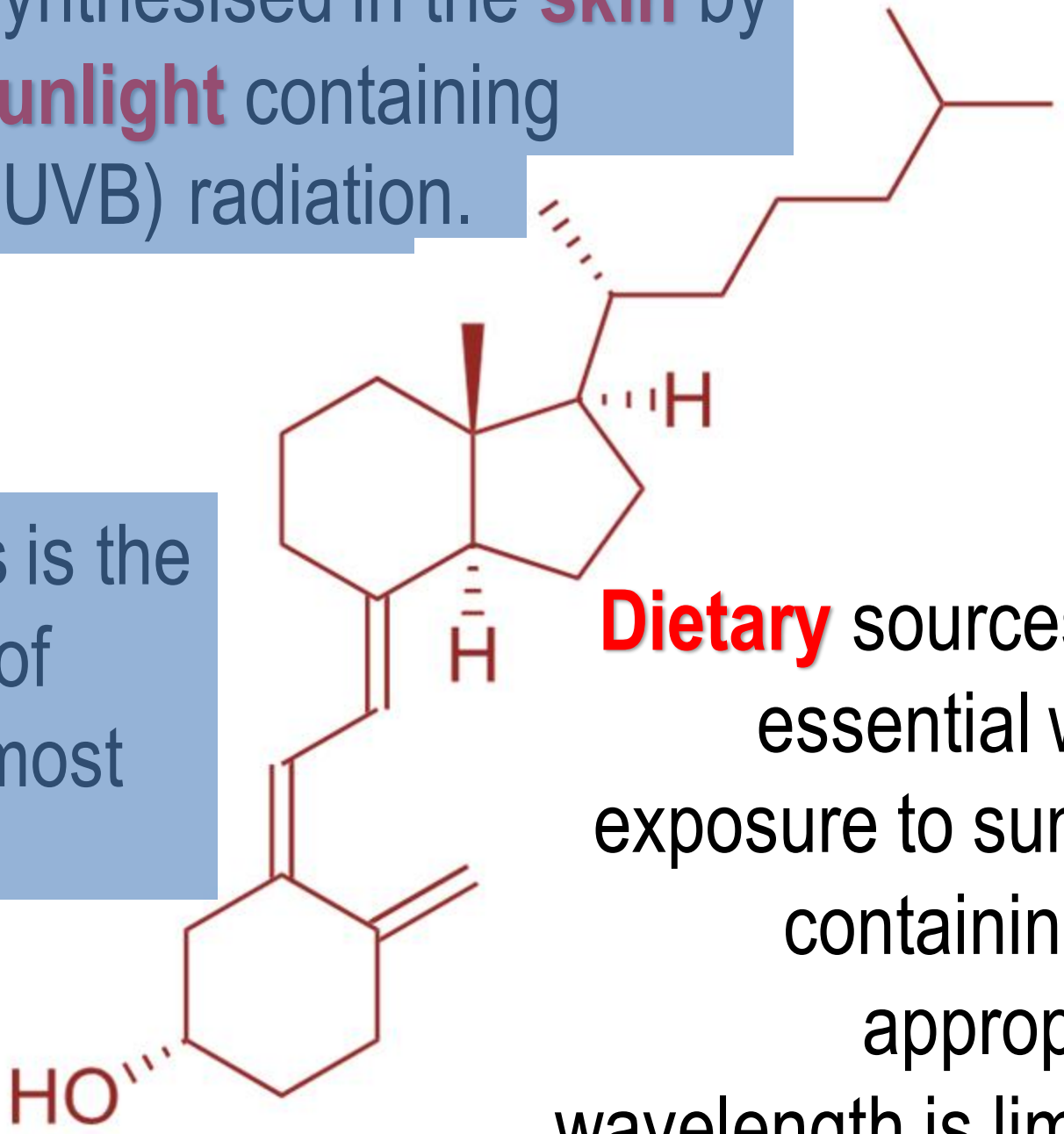
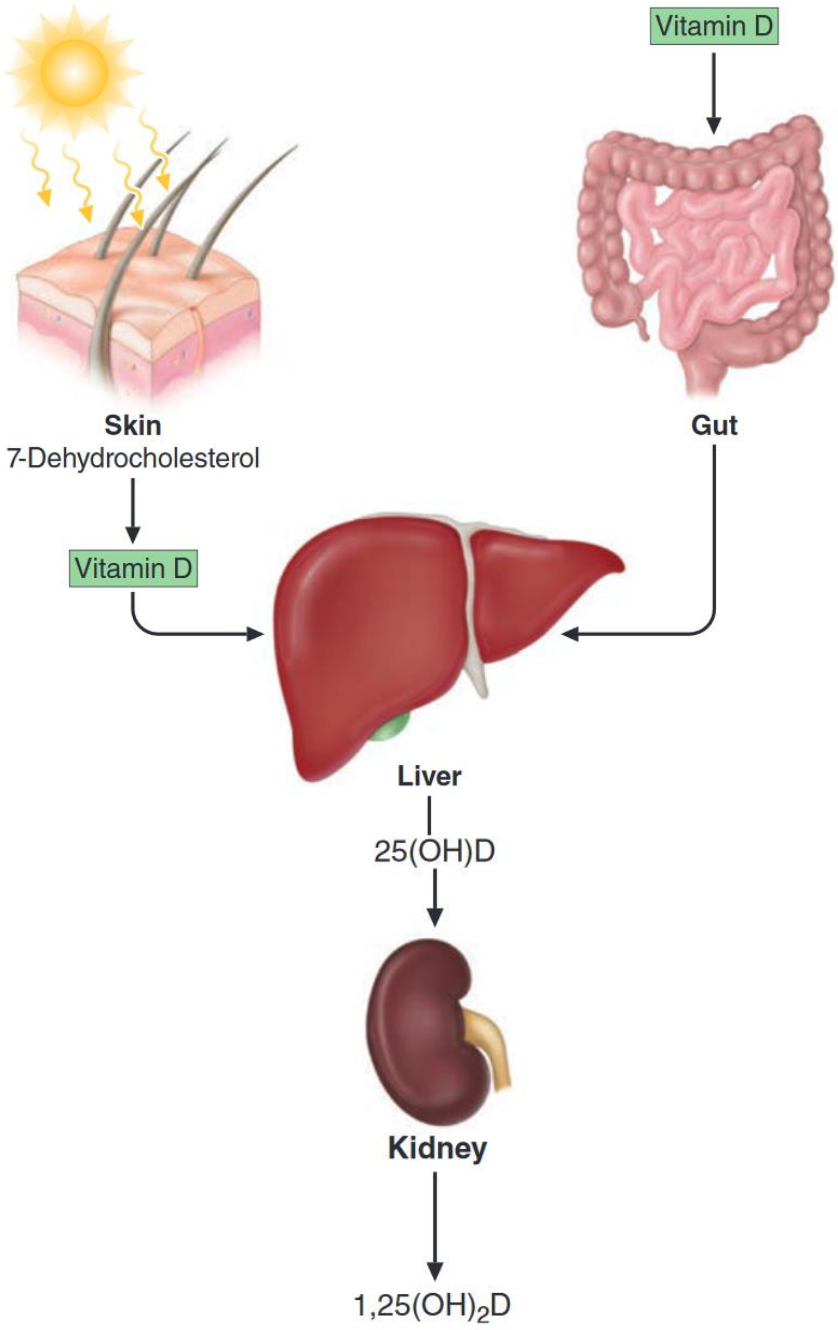
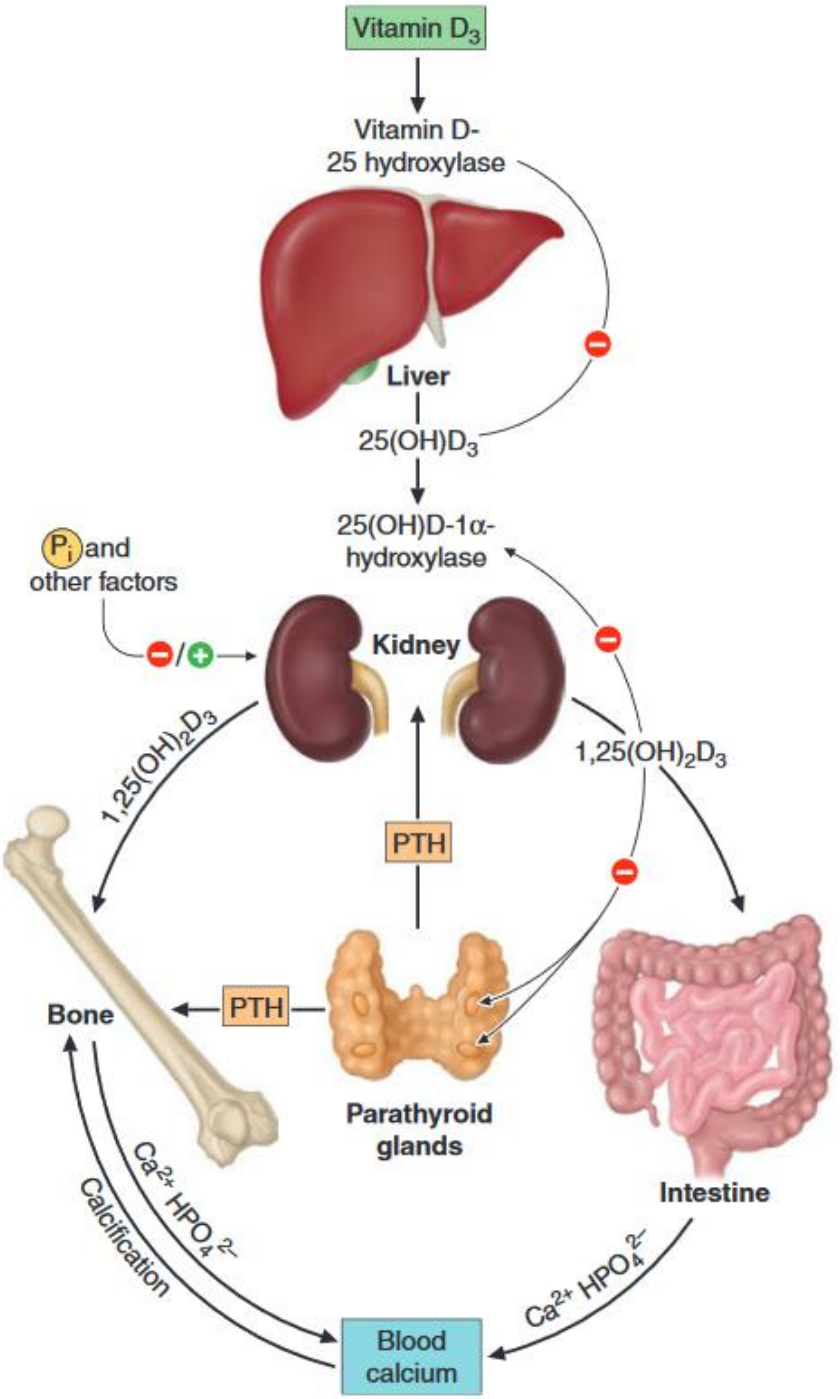


Dietary sources are essential when exposure to sunlight containing the appropriate wavelength is limited.



Vitamin D synthesis and activation. Vitamin D is synthesized in the skin in response to ultraviolet radiation and also is absorbed from the diet. It is then transported to the liver, where it undergoes 25-hydroxylation. This metabolite is the major circulating form of vitamin D. The final step in hormone activation, 1α-hydroxylation, occurs in the kidney

Schematic representation of the hormonal control loop for vitamin D metabolism and function. A reduction in the serum calcium below ~2.2 mmol/L (8.8 mg/dL) prompts a proportional increase in the secretion of parathyroid hormone (PTH) and so mobilizes additional calcium from the bone. PTH promotes the synthesis of 1,25(OH)2D in the kidney, which in turn stimulates the mobilization of calcium from bone and intestine and regulates the synthesis of PTH by negative feedback.



Vitamin D Content of Some Common Foods

Food	Serving Size	Vitamin D (IU)
Vegetables and Fruit	This food group contains very little of this nutrient	
Orange juice, fortified with vitamin D	125 mL (½ cup)	50
Grain Products	This food group contains very little of this nutrient.	
Milk and Alternatives		
Soy beverage, fortified with vitamin D	250 mL (1 cup)	86
Milk (3.3 % homo, 2%, 1%, skim, chocolate milk)	250 mL (1 cup)	103-105
Skim milk powdered	24 g (will make 250 mL of milk)	103
Yogurt (plain, fruit bottom), fortified with vitamin D	175 g (3/4 cup)	58-71
Meat and Alternatives		
Egg, yolk, cooked	2 large	57-88
Pork, various cuts, cooked	75 g (2 ½ oz)	6-60
Deli meat (pork, beef, salami, bologna)	75 g (2 ½ oz)/ 3 slices	30-54
Beef liver, cooked	75 g (2 ½ oz)	36
Fish and Seafood		
Salmon, sockeye/red, canned, cooked or raw	75 g (2 ½ oz)	394-636
Salmon, humpback/pink, canned, cooked or raw	75 g (2 ½ oz)	392-447
Salmon, coho, raw or cooked	75 g (2 ½ oz)	338-422
Snapper, cooked	75 g (2 ½ oz)	392
Salmon, chinook, raw or cooked	75 g (2 ½ oz)	382-387
Whitefish, lake, cooked	75 g (2 ½ oz)	135
Mackerel, Pacific, cooked	75 g (2 ½ oz)	343
Salmon, Atlantic, raw or cooked	75 g (2 ½ oz)	206-245
Salmon, chum/keta, raw or cooked	75 g (2 ½ oz)	203-221
Mackerel, canned	75 g (2 ½ oz)	219
Herring, Atlantic, pickled	75 g (2 ½ oz)	202
Trout, cooked	75 g (2 ½ oz)	148-208
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Roe, raw	30 g (1 oz)	145
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Halibut, cooked	75 g (2 ½ oz)	144
Tuna, albacore, raw or cooked	75 g (2 ½ oz)	99-106
Mackerel, Atlantic, cooked	75 g (2 ½ oz)	78
Tuna, white, canned with water	75 g (2 ½ oz)	60
Fats and Oils		
Cod liver oil	5 mL (1 tsp)	427
Margarine	5 mL (1 tsp)	25-36
Other		
Goat's milk, fortified with Vitamin D	250 mL (1 cup)	100
Rice, oat, almond beverage, fortified with Vitamin D	250 mL (1 cup)	85-90

Vitamin D Content of Some Common Foods

Milk (3.3 % homo, 2%, 1%, skim, chocolate milk) 250 mL (1 cup) 103-105

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Standard multivitamin 200 IU

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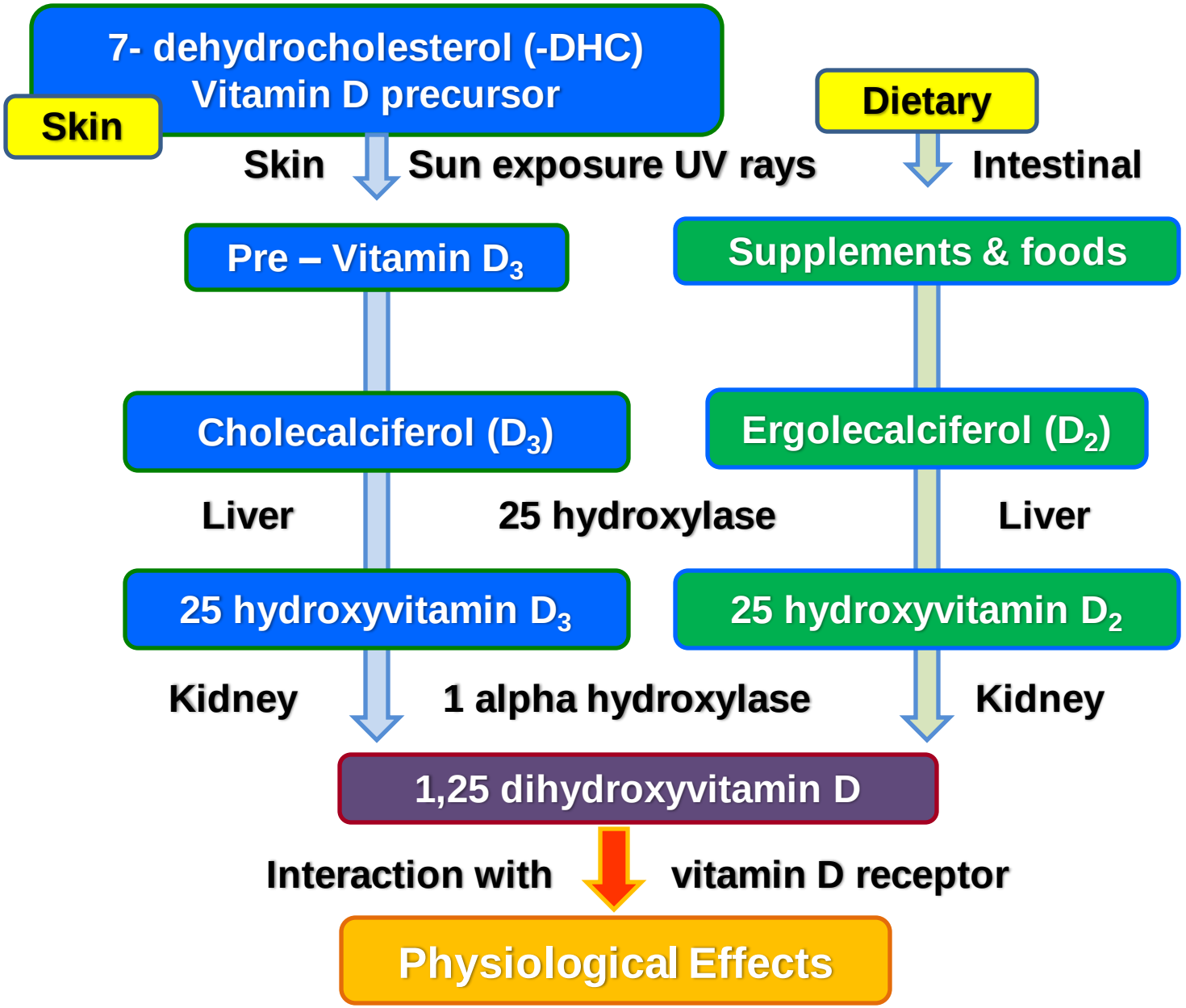
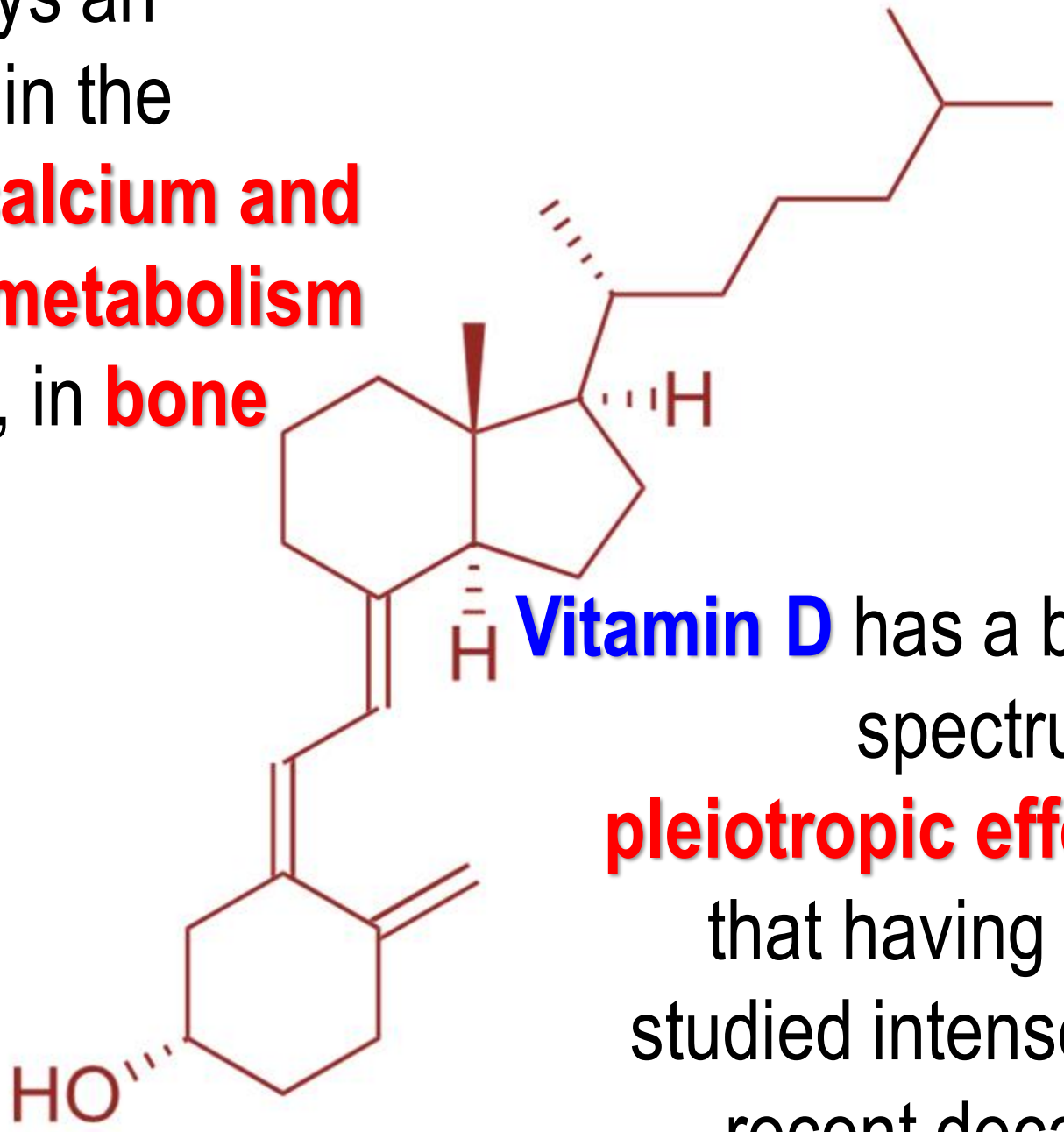
Most foods do not contain meaningful amounts of vitamin D. Despite stipulations and regulations, fortified food contains variable ad sub-optimal amounts of vitamin

Pathways of generation and activation of vitamin D



Vitamin D plays an important role in the regulation of **calcium and phosphorus metabolism** and, therefore, in **bone health**



Vitamin D has a broad spectrum of **pleiotropic effects**, that having been studied intensely in recent decades.

Studies that provided some insight to a variety of non-skeletal effects of vitamin D

- Epidemiological studies
- Clinical studies
- VDR knock-out mice cell-based models
- Genome-wide association

Physiological importance of vitamin D

Skeletal and non-skeletal effects of vitamin D	
Musculoskeletal effects	**Non-skeletal effects**
Essential for calcium homeostasis	Improved immunity
Enhanced GI absorption of calcium	Decrease severity of autoimmunity and neurological disorders
Enhanced osteoblast function	Prevention of type 1 and type 2 diabetes
Necessary for bone mineralization	Prevention of cancer
Prevent rickets and osteomalacia	Decreased cardiovascular diseases
Decrease sarcopenia	Decreased all-cause mortality
Improve balance and prevention of falls	Decreased pulmonary morbidities
Prevention of osteoporosis and fractures	Less morbidities and improved survival

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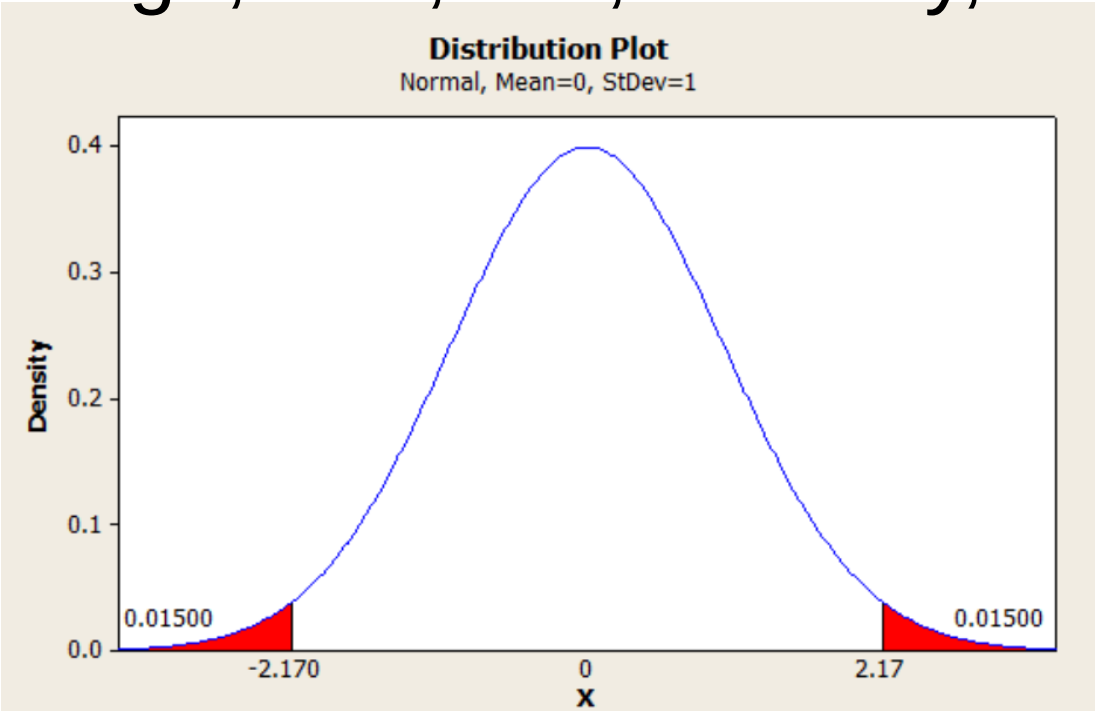
The physiological blood level of 25(OH)D

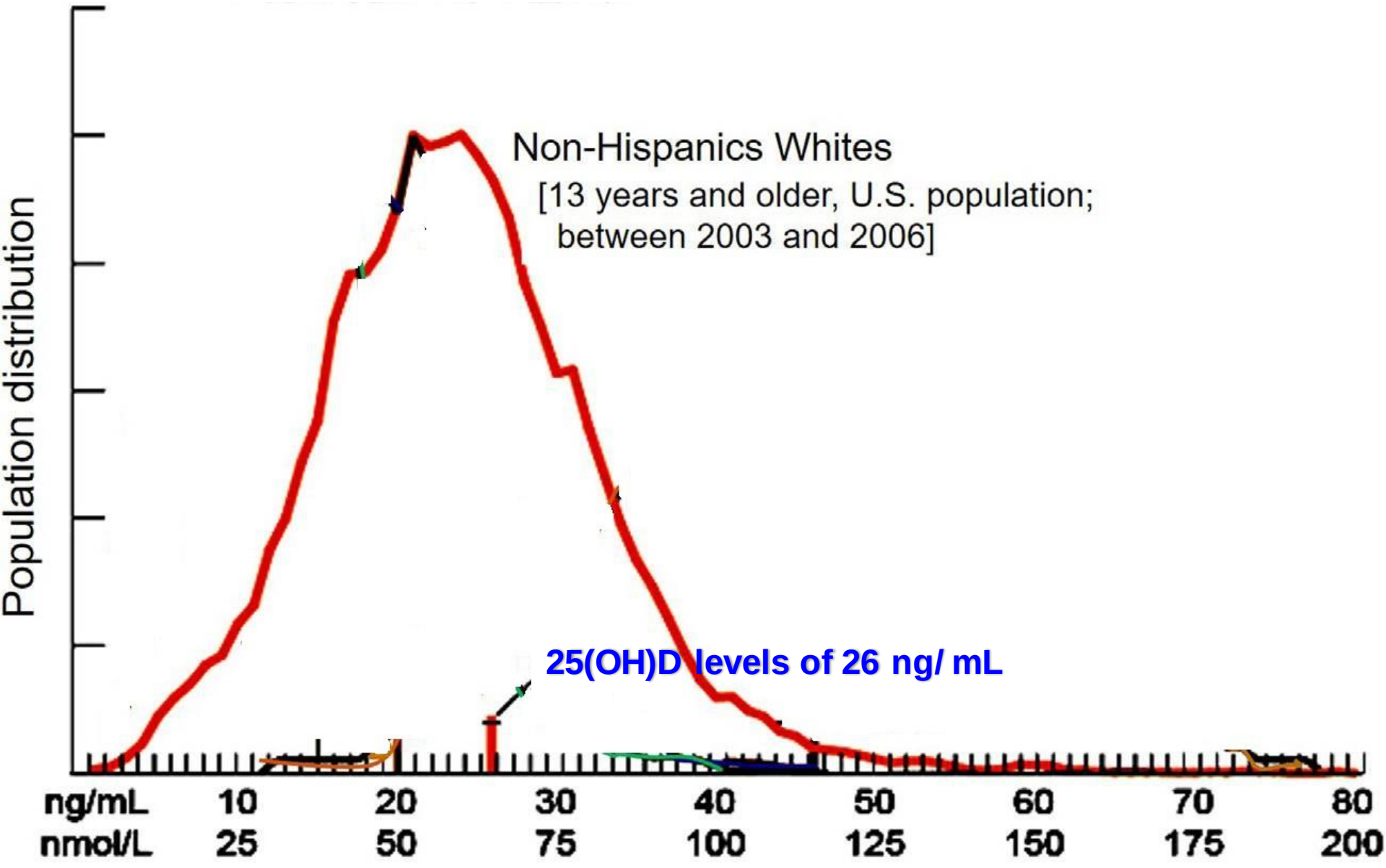
Having physiological levels of vitamin D over a long period,

decreases the incidence and severity of

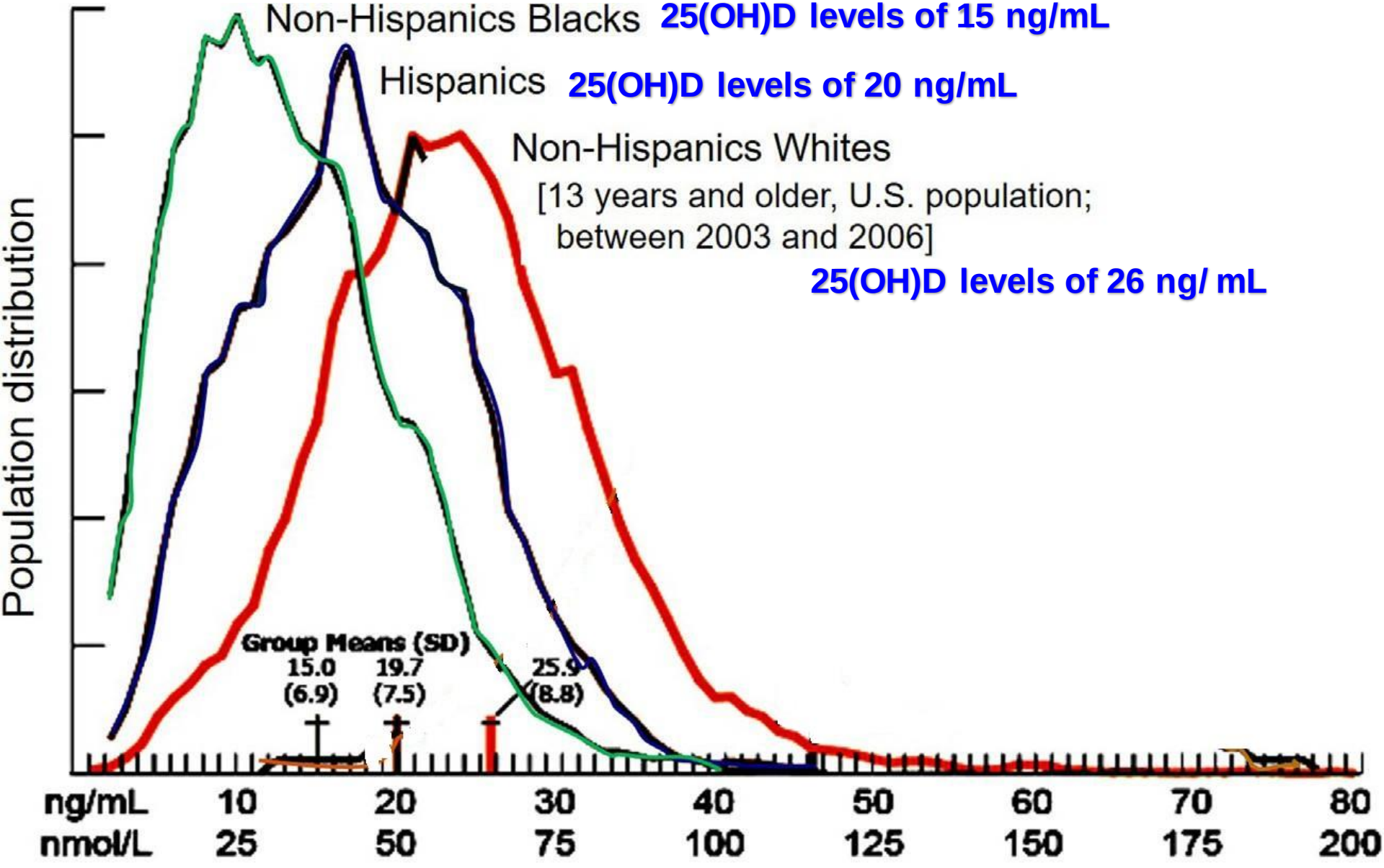
- Type 1 and Type 2 diabetes
- Insulin Resistance
- Metabolic Syndrome
- Cardiovascular Diseases
- Depression
- Certain Cancers
  - Breast
  - Colon
  - Prostate

Normal range: Characteristic of 95 percent of values from a normal population. The remaining normal results fall outside the normal range, as do any truly abnormal results. The normal range for a particular test result, condition, symptom, or behavior may differ, based on the patient's age, size, sex, ethnicity, or culture.





Distribution of serum 25(OH)D levels in four populations



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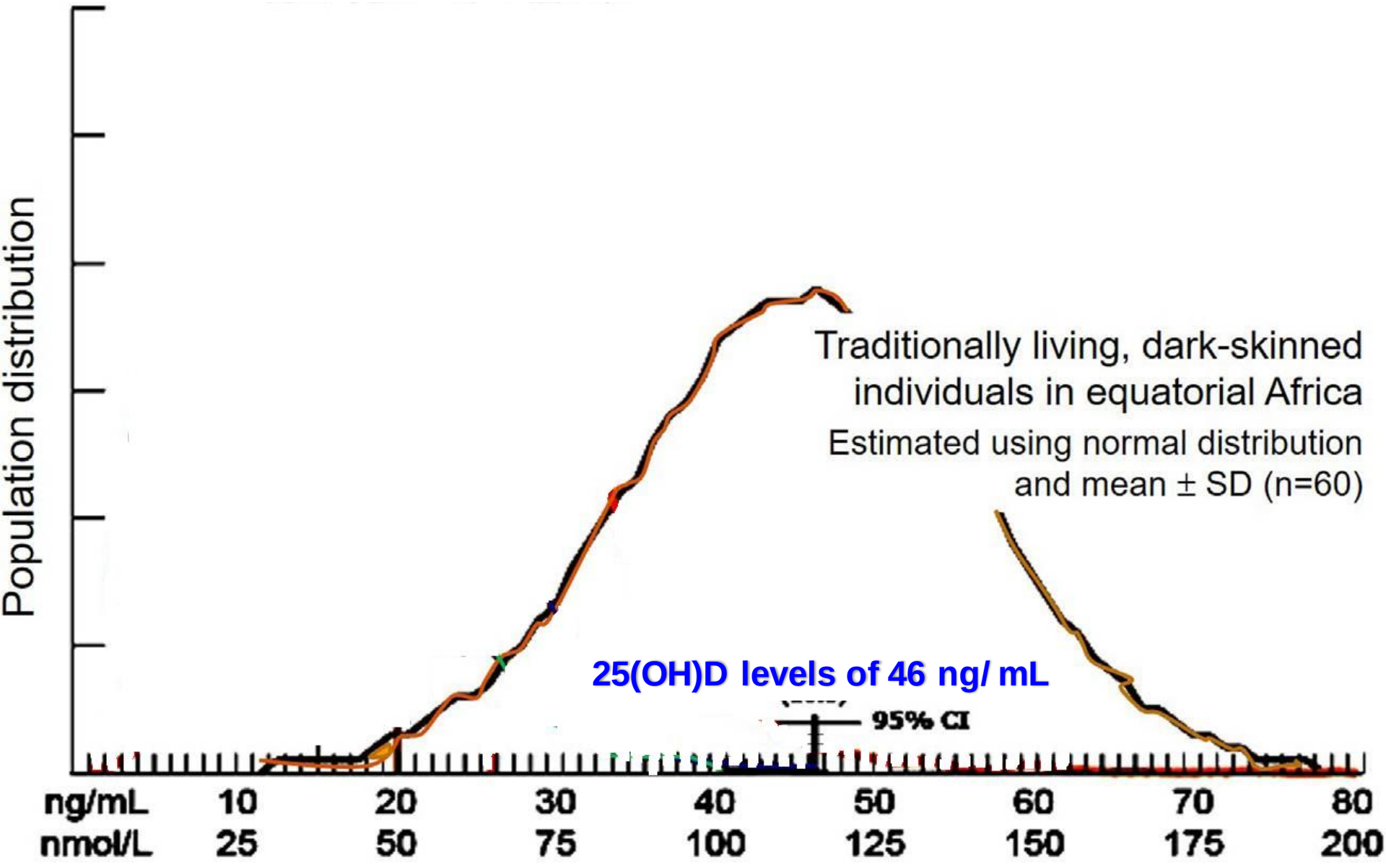

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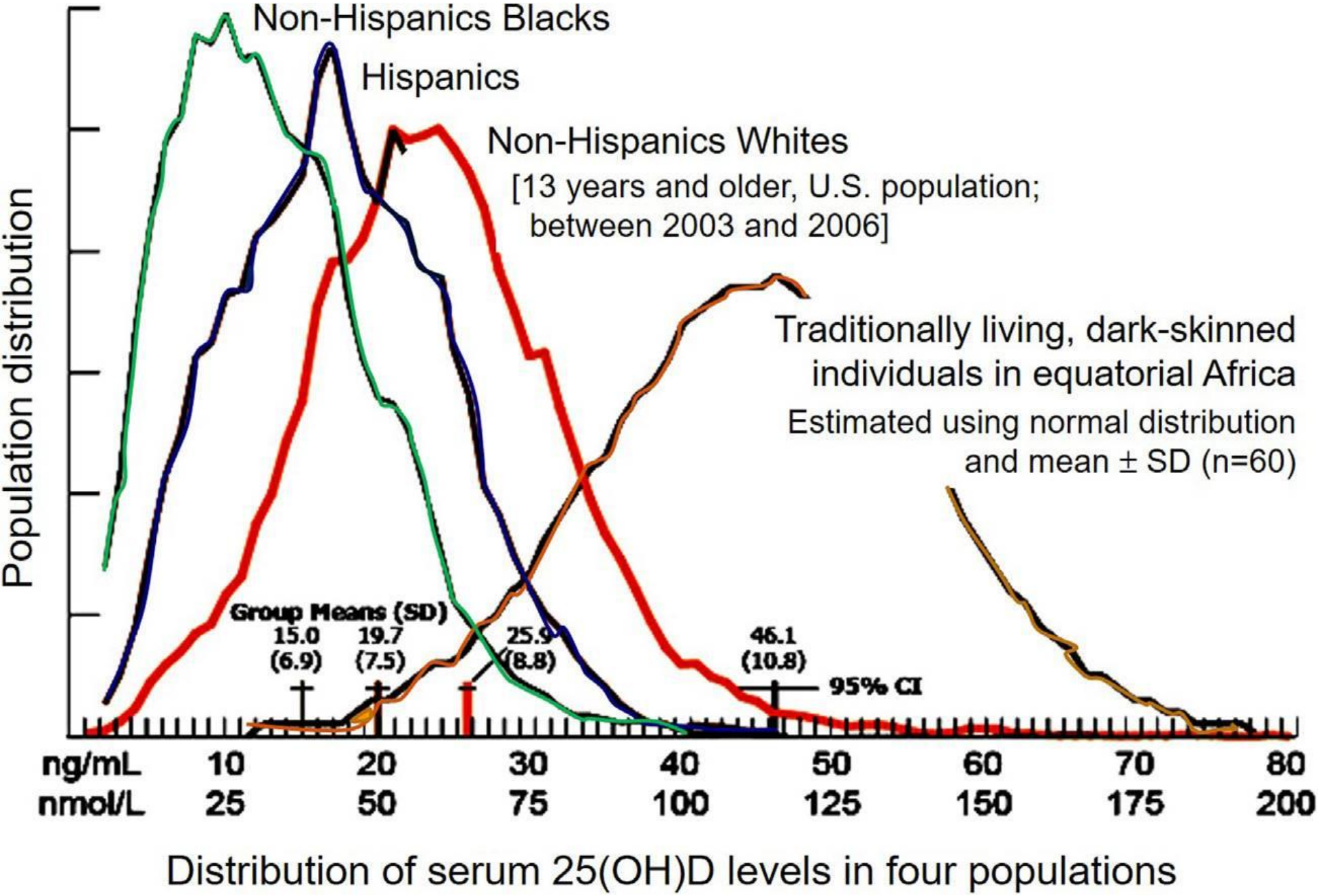

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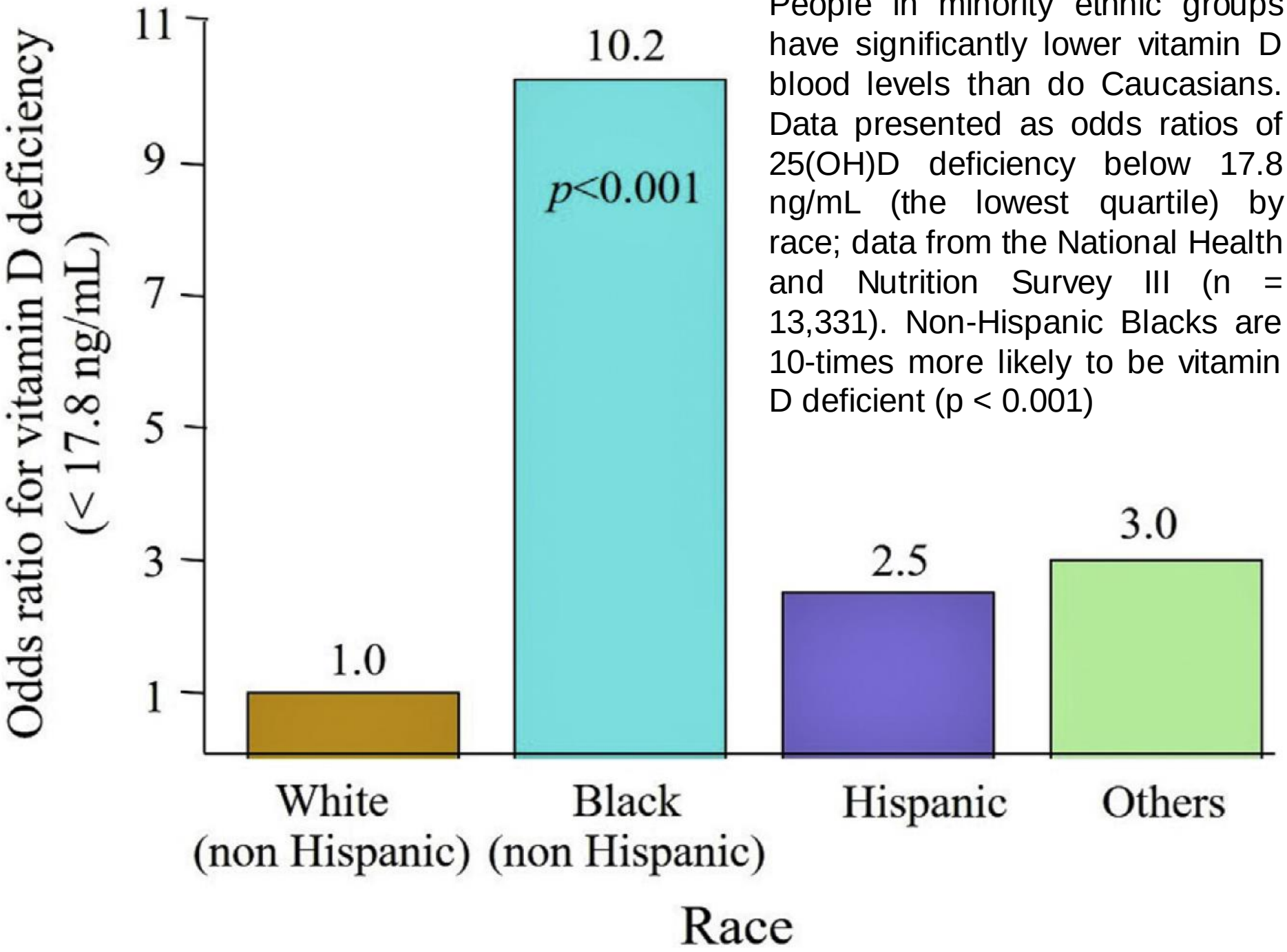


People in minority ethnic groups have significantly lower vitamin D blood levels than do Caucasians. Data presented as odds ratios of 25(OH)D deficiency below 17.8 ng/mL (the lowest quartile) by race; data from the National Health and Nutrition Survey III (n = 13,331). Non-Hispanic Blacks are 10-times more likely to be vitamin D deficient ($p < 0.001$)

Vitamin D deficiency

Vitamin D deficiency is typically diagnosed by measuring the concentration of the **25-hydroxyvitamin D** in the blood, which is the most accurate measure of stores of vitamin D in the body

Deficiency: <20 ng/mL

Insufficient: 20–29 ng/mL

Normal: 30–100 ng/mL

Mayo Medical Laboratories Reference Ranges for Total Serum 25-hydroxyvitamin D [25(OH)D]

Severe deficiency <10 ng/mL

Could be associated with osteomalacia or rickets.

Mild to moderate deficiency 10-24 ng/mL

May be associated with secondary hyperparathyroidism and/or osteoporosis

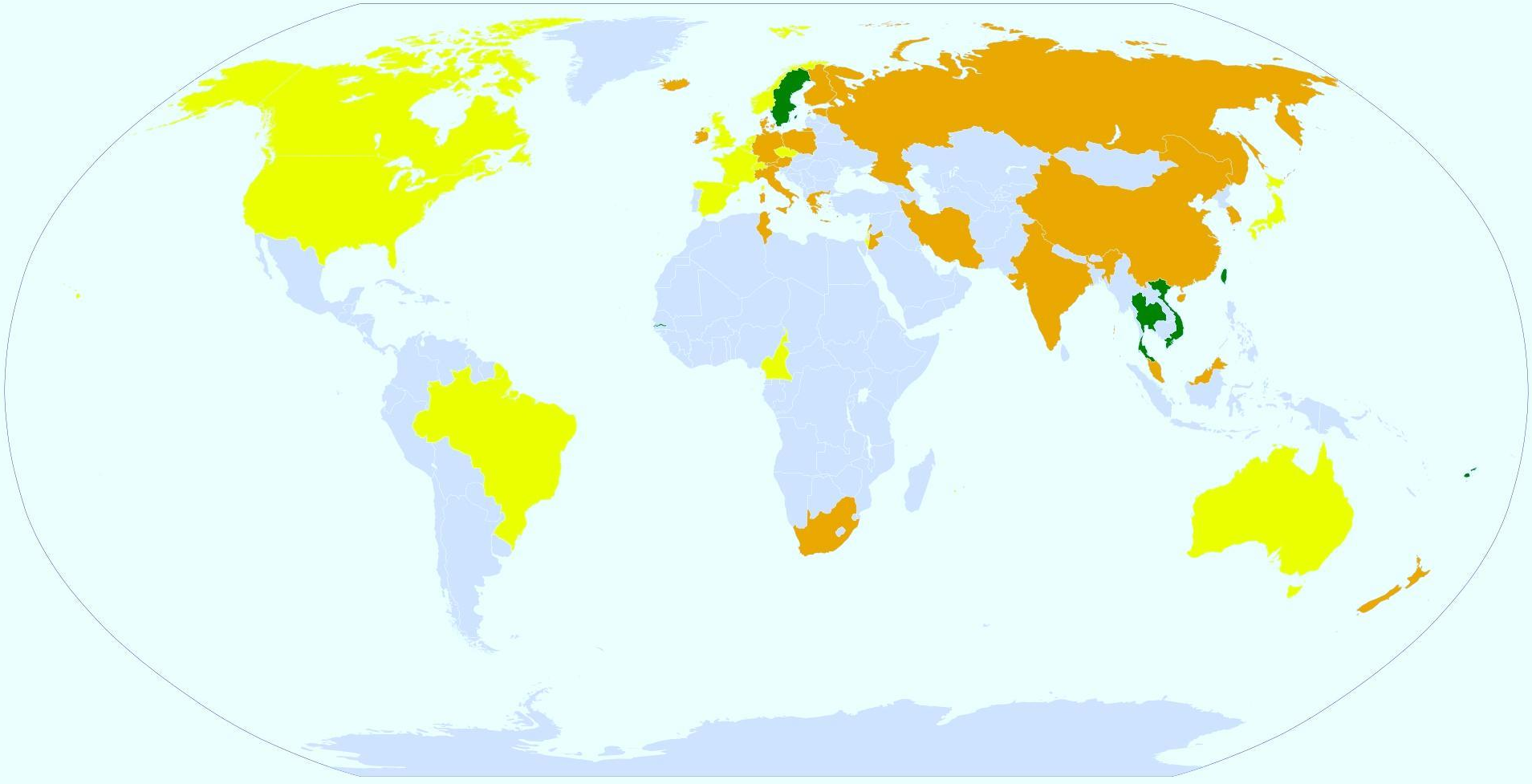
Optimald 25-80 ng/mL

Levels present in healthy populations

Possible toxicity >80 ng/mL

Mayo Clin Proc. • August 2010;85(8):752-758 • doi:10.4065/mcp.2010.0138

SI conversion factor: To convert 25(OH)D values to nmol/L, multipl by 2.496.



Global vitamin D serum levels among adults

> 75 nmol/L (> 30 ng/ml)

50-75 nmol/L (20-30 ng/ml)

25-50 nmol/L (10-20 ng/ml)

< 25 nmol/L (<10 ng/ml)

IJMS
Vol 43, No 2, March 2018

Review Article

High Prevalence of Vitamin D Deficiency among Iranian Population: A Systematic Review and Meta-Analysis

Reza Tabrizi, PhD, Mahmood Moosazadeh, PhD,Maryam Akbari, PhD, Mohammad Hossein Dabbaghmanesh, MD, Minoo Mohamadkhani, MS, Zatollah Asemi, PhD, Seyed Taghi Heydari, PhD, Mojtaba Akbari, PhD,[6] andKamran B Lankarani, MD

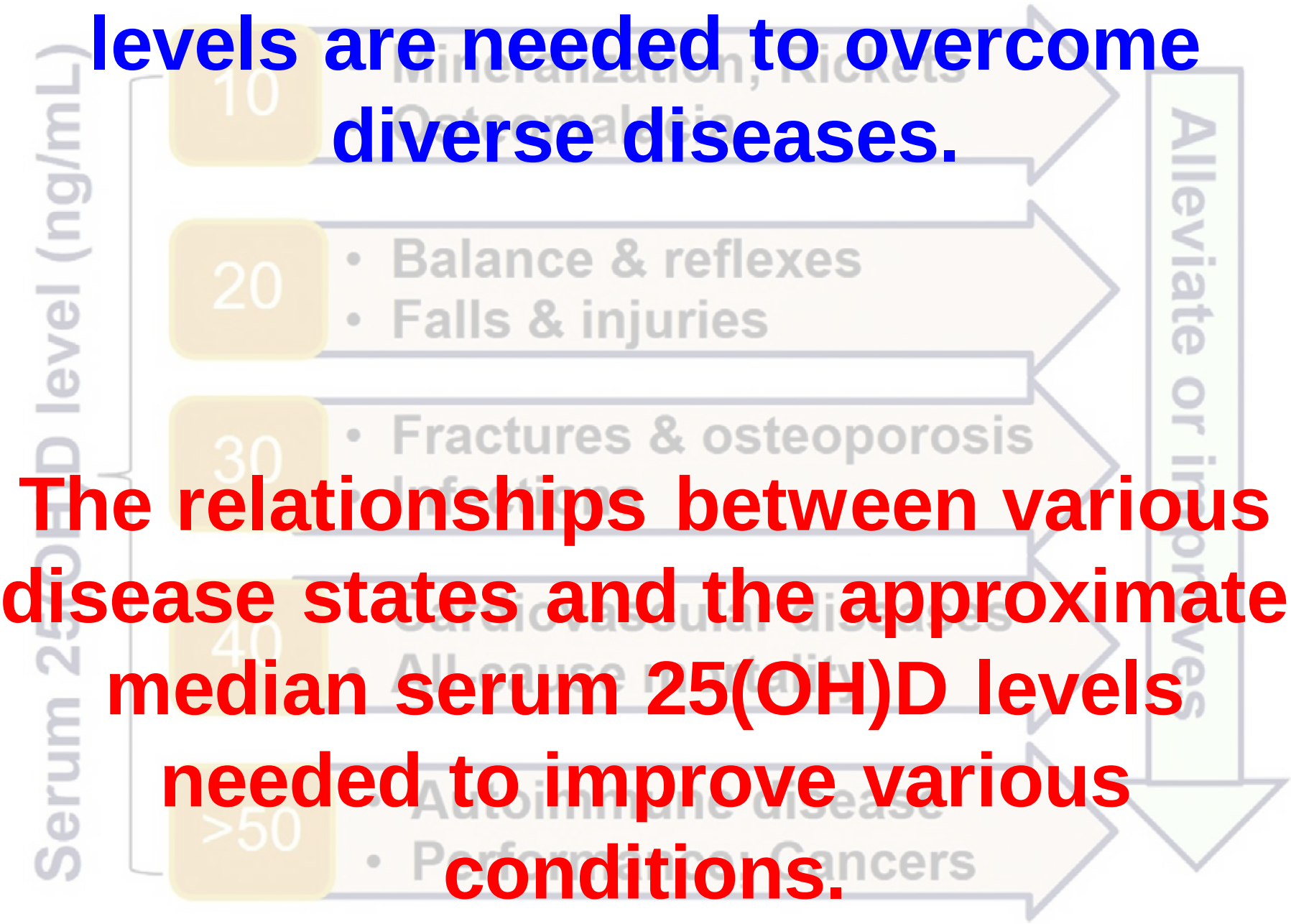
Articles published online in Persian and English between 2000 and November 1, 2016, were reviewed. The meta-analysis of 48 studies identified 18531 individuals with vitamin D deficiency.

Variables	Included studies	Sample size (n)	Pooled prevalence (%)	95% confidence interval	Heterogeneity (I^2-%)
Vitamin D deficiency (total)	48	18531	61.97	52.53-71.40	99.7
Vitamin D deficiency (males)	18	5854	45.64	29.63-61.65	99.6
Vitamin D deficiency (females)	32	10868	61.90	48.85-74.96	99.9

vitamin D deficiency was defined as serum 25(OH) D below 20 ng/mL (<50 nmol/L).

Conclusion
The results obtained showed a significant prevalence of vitamin D deficiency among the Iranian population, a condition to be addressed by appropriate planning.

Different minimum serum 25(OH)D levels are needed to overcome diverse diseases.



The relationships between various disease states and the approximate median serum 25(OH)D levels needed to improve various conditions.

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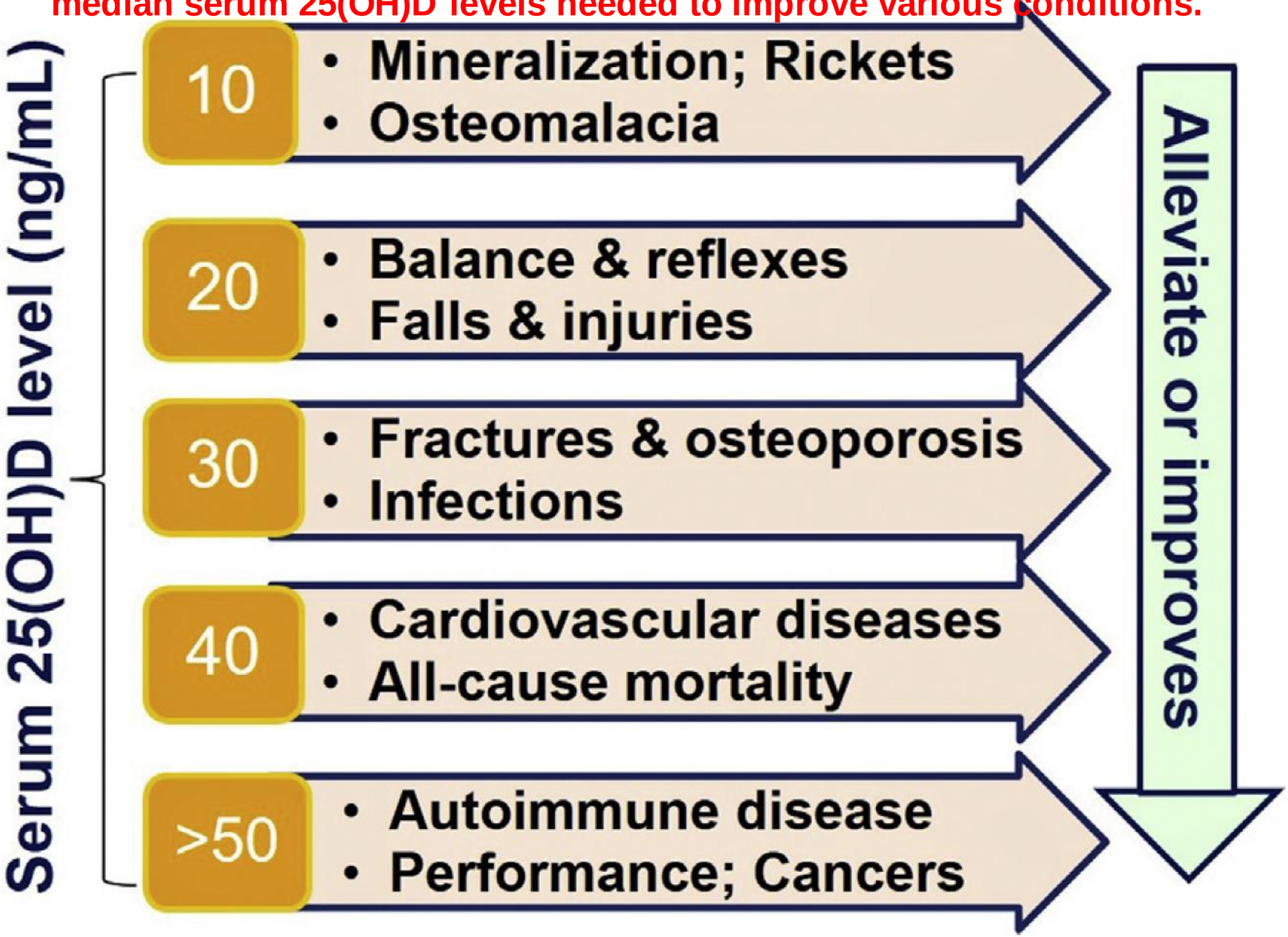
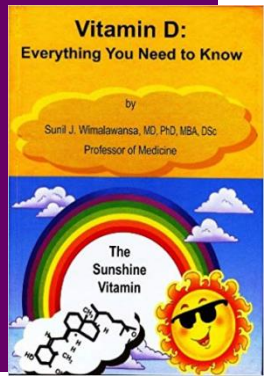


Diseases and conditions that are associated with or aggravated by vitamin D deficiency

- Osteomalacia/osteoporosis
- Parathyroid diseases
- Muscle function and falls
- Polymyalgia rheumatic
- Autoimmune disorders
- Autism
- Tuberculosis/infection
- Peripheral vascular disease
- Cancer (breast, colon, skin, pancreas, prostate)
- Chronic pain
- Fibromyalgia
- Celiac disease
- Chronic fatigue syndrome
- Cystic fibrosis
- Cardiovascular mortality
- Multiple sclerosis
- Demyelinating diseases

- Hypertension
- Infections
- Type 2 diabetes
- Athletic performance
- Inflammatory bowel disease
- Seasonal affective disorder
- Rheumatoid arthritis
- Depression
- Migraine headaches
- Obesity
- Incontinence
- Rheumatoid arthritis
- Macular degeneration (AMD)
- Parkinson's disease
- Cognitive impairment
- Psoriasis
- Cardiovascular events
- Overall mortality



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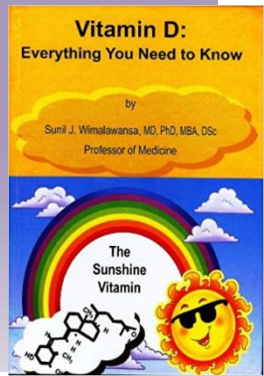

The NEW ENGLAND JOURNAL of MEDICINE

November 10, 2018
DOI: 10.1056/NEJMoa1809944

ORIGINAL ARTICLE

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

CONCLUSIONS

Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo

The NEW ENGLAND JOURNAL of MEDICINE

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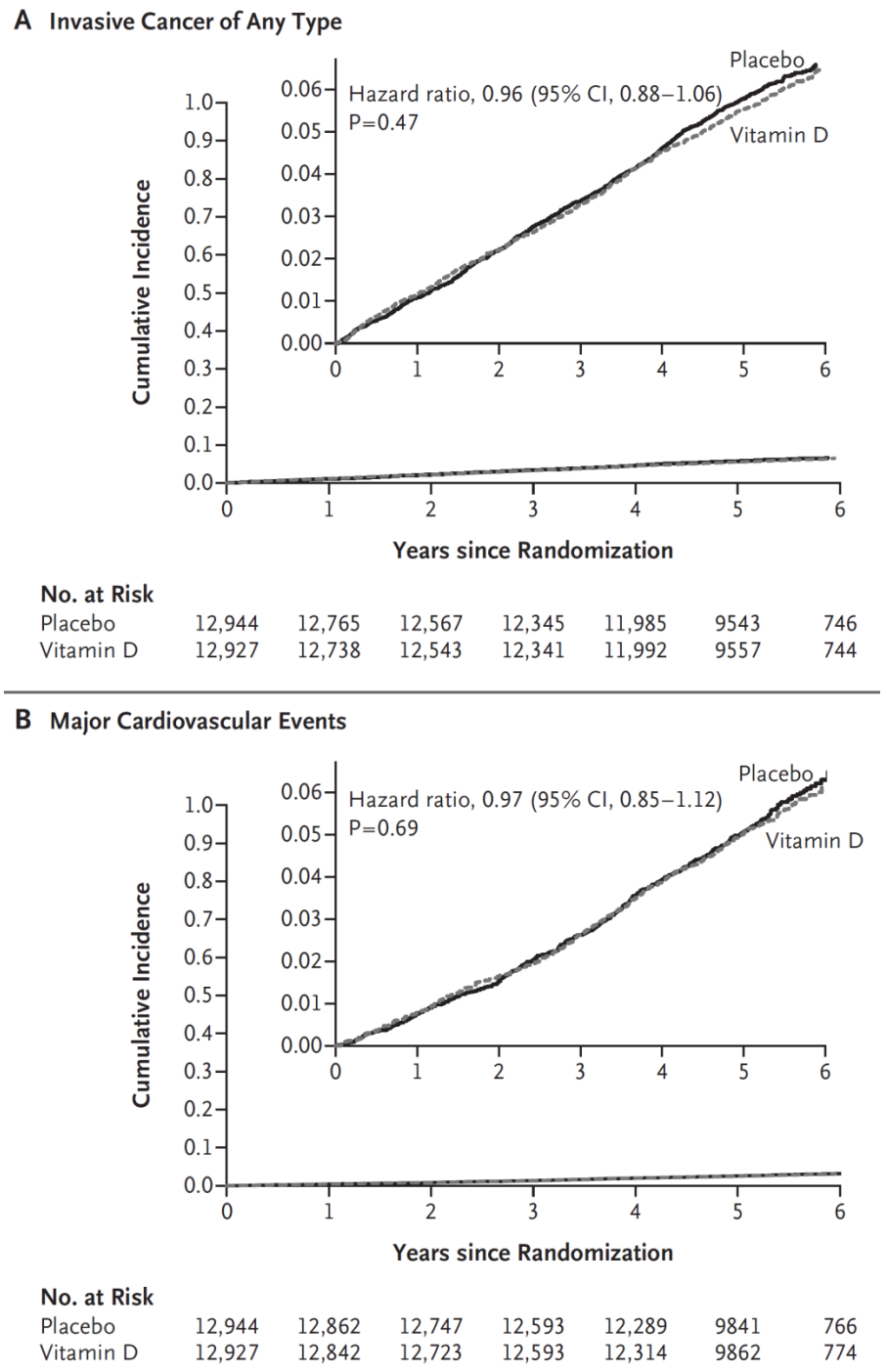

Cumulative Incidence Rates of Invasive Cancer of Any Type and Major Cardiovascular Events, According to Year of Follow-up, in the Vitamin D Group and Placebo Group.

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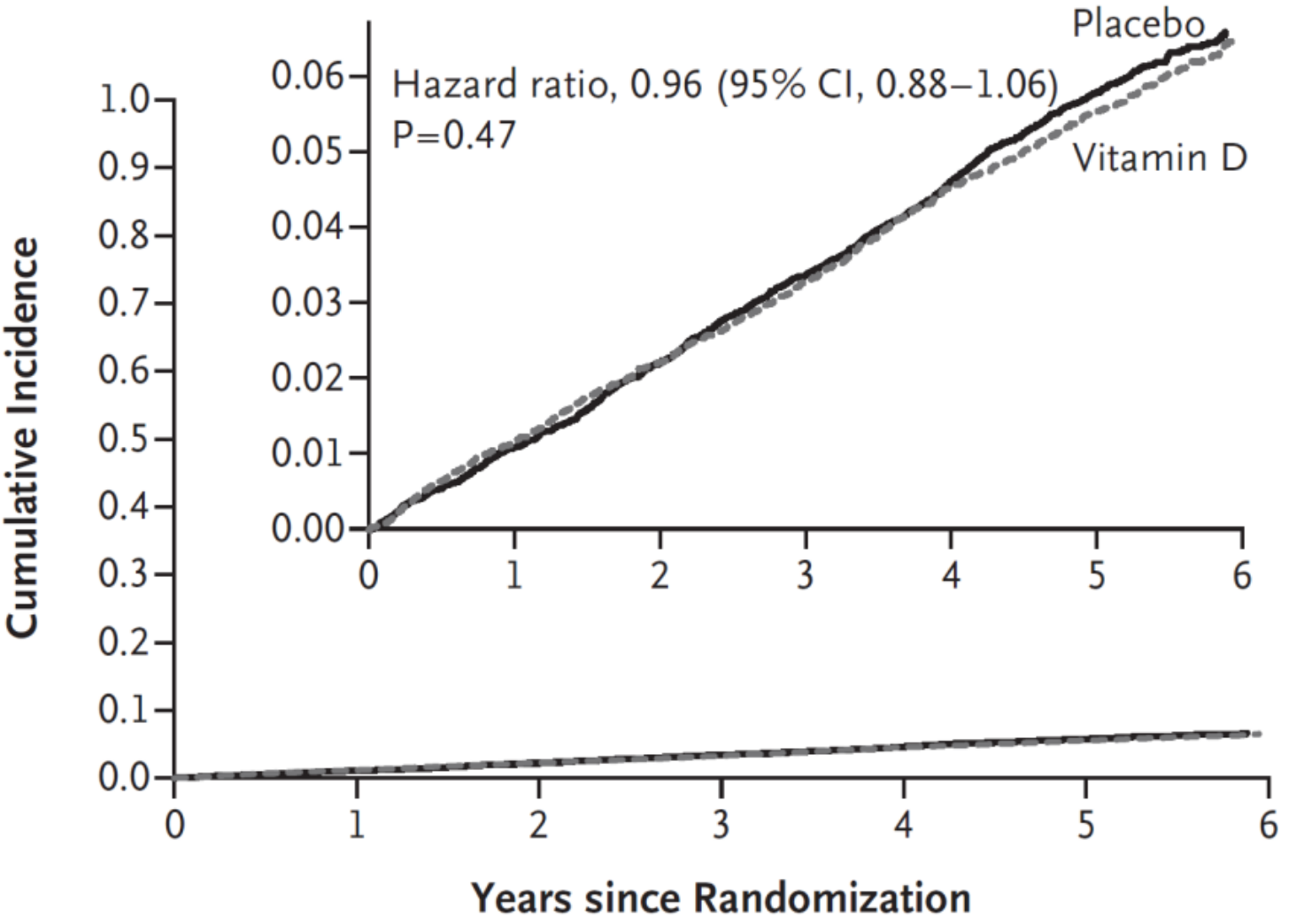

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No. at Risk							
Placebo	12,944	12,765	12,567	12,345	11,985	9543	746
Vitamin D	12,927	12,738	12,543	12,341	11,992	9557	744

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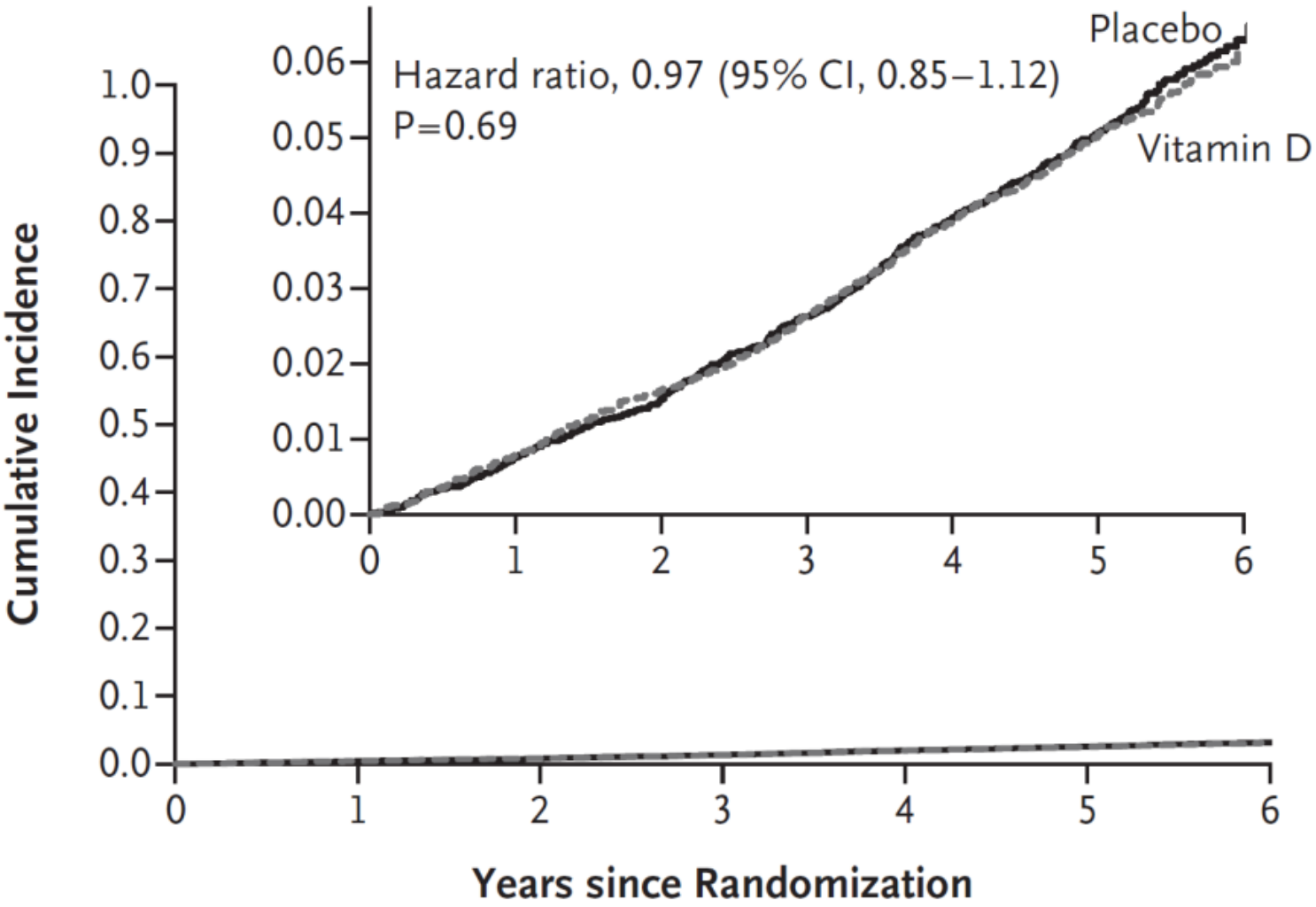

No. at Risk

Placebo	12,944	12,862	12,747	12,593	12,289	9841	766
Vitamin D	12,927	12,842	12,723	12,593	12,314	9862	774

Pharmaceutical Sciences
September 2017, 23, 189-192
doi: 10.15171/PS.2017.28
http://journals.tbzmed.ac.ir/PHARM

Research Article

Concentration of Maternal Serum 25-Hydroxy Vitamin D and Gestational Diabetes Mellitus Risk

Akbar Vosoughi[1], Akbar Aliasgarzadeh[1]*, Amir Bahrami[1], Fatemeh Abbasalizadeh[2], Mitra Niafar[1], Farzad Najafipour[1], Naser Aghamohammadzadeh[1], Zeinab Nikniaz[3]

[1]*Endocrinology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

[2]*Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

[3]*Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

Concentration of Maternal Serum 25-Hydroxy Vitamin D and Gestational Diabetes Mellitus Risk

Background: The present study was designed to primarily investigate the association between serum 25 (OH) vitamin D levels and gestational diabetes mellitus (GDM) in a sample of Iranian woman.

Concentration of Maternal Serum 25-Hydroxy Vitamin D and Gestational Diabetes Mellitus Risk

Methods: In the present cross-sectional study 136 pregnant women (68 with GDM and 68 non GDM) who were referred to a university hospital clinic of the Tabriz University of Medical Sciences during July to September 2016 were studied. All pregnant women were assessed for GDM and also serum vitamin D was assessed in all

Variable	Total	Non GDM (n=68)	GDM (n=68)	p-value*
Age (Years)	30.41±5.82	29.66±6.09	31.16±5.48	0.13
Gestational age (weeks)	22.57±8.52	24.88±6.76	20.26±9.50	0.001
BMI (kg/m^2)	29.42±5.45	29.06±5.66	29.78±5.23	0.14
Parity n (%)				0.11≠
Nulliparous	81 (56.9)	36 (52.9)	45 (66.2)	
parous	55 (40.4)	32 (47.1)	23 (33.8)	

*P-value of independent t-test
≠ p-value of chi-square

Concentration of Maternal Serum 25-Hydroxy Vitamin D and Gestational Diabetes Mellitus Risk

Results: The mean serum 25(OH) D of pregnant women was 13.42±7.78 ng/mL. In the term of the mean serum 25(OH) D level, there was not significant differences between GDM (14.45±8.73) and non-GDM (12.38±6.62) pregnant women (p=0.12). Totally 83.8% of participants were vitamin D deficient and 11.8% of them had insufficient amount of serum vitamin D. Only 4.4% of participants were vitamin D sufficient. The results of logistic regression analysis showed no significant association between GDM and vitamin D status in both unadjusted and adjusted (for mother`s age, parity, BMI and gestational week) models.

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Biochemical characteristics of participants (n=136).

Variable	Total	Non-GDM (n=68)	GDM (n=68)	p-unadjusted≠	p-adjusted*
FBS (mg/dl)	89.68±13.70	79.51±7.14	99.71±10.93	<0.001	<0.001
GTT 1h (mg/dl)	146.73±42.85	125.66±32.11	182.48±34.38	<0.001	<0.001
GGT 2h (mg/dl)	116.06±41.56	97.84±29.97	148.61±39.78	<0.001	<0.001
Serum vitamin D (ng/mL)	13.42±7.78	12.38±6.62	14.45±8.73	0.12	0.17

≠Independent t-test

* ANCOVA: Adjusted for, mothers age, BMI, parity, gestational week.

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Comparison of the vitamin D status in GDM and non-GDM mothers

Variables	Total	Non-GDM (n=68)	GDM (n=68)	Odds Ratio (95% CI)	
				Unadjusted model	Adjusted model*
Vitamin D deficiency	114 (83.8)	62 (91.2)	52 (76.5)	0.44 (0.04, 4.81)	0.28 (0.02, 3.54)
Vitamin D insufficiency	16 (11.8)	5 (7.4)	11 (16.2)	0.16 (0.01, 1.48)	0.15 (0.01, 1. 44)
Vitamin D sufficiency	6 (4.4)	1 (1.5)	5 (7.4)	1	1

*Logistic regression: Adjusted for, mothers age, BMI, parity, gestational week.

Concentration of Maternal Serum 25-Hydroxy Vitamin D and Gestational Diabetes Mellitus Risk

Conclusion: The results of the present study could not show any association between serum vitamin D and GDM. It seems that other factors rather than serum level of 25 (OH) vitamin D level likely explain the growing prevalence of GDM.

Causes of Impaired Vitamin D Action

Vitamin D deficiency	Impaired cutaneous production	**Impaired 1α-hydroxylation**	Hypoparathyroidism
	Dietary absence		Ketoconazole
	Malabsorption		1α-hydroxylase mutation
Accelerated loss of vitamin D	Increased metabolism (barbiturates, phenytoin, rifampin)	**FGF23 excess**	Oncogenic osteomalacia
	Impaired enterohepatic circulation		X-linked hypophosphatemic rickets
	Nephrotic syndrome		Renal Failure
Impaired 25-hydroxylation	Liver disease, isoniazid	**Target Organ Resistance**	Vitamin D receptor mutation
	25-hydroxylase mutation		Phenytoin
		Other	Obesity

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Who Should Be Tested For Vitamin D Deficiency?

Empiric vitamin D **supplementation** without testing can be justified for patients who have **no overt risk factors or evidence of deficiency** but are thought to have **inadequate sun exposure** or **dietary intake**

Who Should Be Tested For Vitamin D Deficiency?

Clinical Risk Factors for Vitamin D Deficiency

Decreased intake

Inadequate oral intake
Malnutrition (poor oral intake)
Limited sun exposure

Gastrointestinal

Malabsorption (eg, short bowel syndrome, pancreatitis, inflammatory bowel disease, amyloidosis, celiac sprue, and malabsorptive bariatric surgery procedures)

Hepatic

Some antiepileptic medications (increased 24-hydroxylase activity)
Severe liver disease or failure (decreased 25-hydroxylase activity)

Renal

Aging (decreased 1-α hydroxylase activity)
Renal insufficiency, glomerular filtration rate <60% (decreased 1-α hydroxylase activity)
Nephrotic syndrome (decreased levels of vitamin D–binding protein)

Who Should Be Tested For Vitamin D Deficiency?

Laboratory Findings That Suggest Possible Vitamin D Deficiency

Low 24-hour urine calcium excretion (in the absence of thiazide use)

Elevated parathyroid hormone level

Elevated total or bone alkaline phosphatase level

Low serum calcium and/or serum phosphorus level

Who Should Be Tested For Vitamin D Deficiency?

Radiographic Findings That Suggest Possible Vitamin D Deficiency

Decreased bone mineral density (osteopenia or osteoporosis)

Nontraumatic (fragility) fracture

Skeletal pseudofracture

Indications for assessment of 25(OH)D concentration in serum— groups at risk of vitamin D deficiency.

Disorders	examples of diagnoses
Disorders of the locomotor system	Rickets, osteomalacia, osteoporosis, bone pains, bone deformations, postural defects, recurrent low energy fractures and aseptic osteonecrosis
Disorders of calcium-phosphorus metabolism	Disorders of calcemia, calciuria, phosphatemia, phosphaturia, hypophosphatasia and hiperphosphatasia
Chronic treatment with some medications	Chronic corticosteridotherapy, treatment with ketoconazole, antiretroviral and antiepileptic therapy
Maldigestion and malabsorption	Maldigestion and malabsorption syndromes, cystic fibrosis and chronic inflammatory bowel disease Liver diseases Liver failure, cholestasis, posttrasplant state and non-alcoholic fatty liver disease (NAFLD) Kidney diseases Renal failure, posttransplant state and nephrocalcinosis
Endocrine disorders	Hyper- and hypoparathyroidism, hyper- and hypothyroidism, diabetes type 1, growth hormone deficiency, anorexia nervosa and autoimmune polyglandular syndromes
Disorders of somatic development	Short stature, tall stature, obesity and cachexia
Developmental delay	Delay of psychomotor development and intellectual disability
Diseases of the nervous system	Cerebral palsy, chronic immobilization, autism, multiple sclerosis, epilepsy, seizures of unknown etiology, miopathy and muscular dystrophy
Allergy	asthma, atopic dermatitis
Autoimmune diseases	Collagen diseases, rheumathoid arthritis, autoimmune diseases of the skin, diabetes type 1 and Hashimoto disease
Immune disorders	Recurrent infections of the respiratory tract, asthma, recurrent and chronic inflammatory states of other systems
Neoplasms	Blood cancer, malignancy of the lymphatic system and other organs, tumors and states after oncologic treatment
Cardiovascular diseases	Arterial hypertension and ischemic heart disease
Metabolic diseases	Diabetes type 2, lipid disorders, obesity and metabolic syndrome

Indications for assessment of 25(OH)D concentration in serum—groups at risk of vitamin D deficiency.

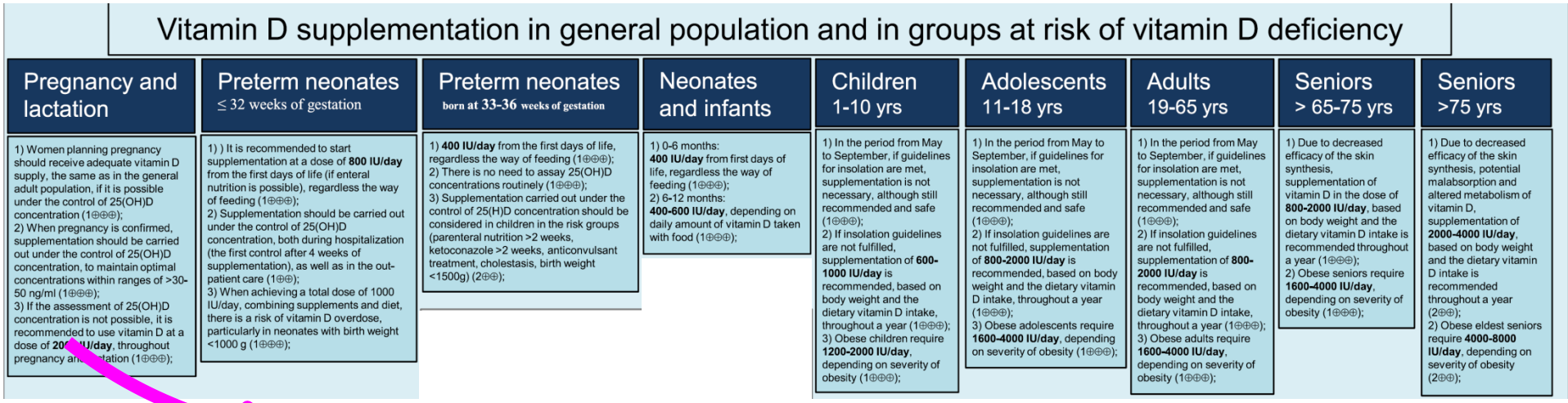
Disorders	examples of diagnoses
Disorders of the locomotor system	Rickets, osteomalacia, osteoporosis, bone pains, bone deformations, postural defects, recurrent low energy fractures and aseptic osteonecrosis
Disorders of calcium- phosphorus metabolism	Disorders of calcemia, calciuria, phosphatemia, phosphaturia, hypophosphatasia and hiperphosphatasia
Chronic treatment with some medications	Chronic corticosteridotherapy, treatment with ketoconazole, antiretroviral and antiepileptic therapy
Maldigestion and malabsorption	Maldigestion and malabsorption syndromes, cystic fibrosis and chronic
Endocrine disorders	
Disorders of somatic development	
Developmental delay	
Diseases of the nervous system	dystrophy
Allergy	asthma, atopic dermatitis
Autoimmune diseases	Collagen diseases, rheumathoid arthritis, autoimmune diseases of the skin, diabetes type 1 and Hashimoto disease
Immune disorders	Recurrent infections of the respiratory tract, asthma, recurrent and chronic inflammatory states of other systems
Neoplasms	Blood cancer, malignancy of the lymphatic system and other organs, tumors and states after oncologic treatment
Cardiovascular diseases	Arterial hypertension and ischemic heart disease
Metabolic diseases	Diabetes type 2, lipid disorders, obesity and metabolic syndrome

Vitamin D supplementation in general population and in groups at risk of vitamin D deficiency

Pregnancy and lactation	Preterm neonates ≤ 32 weeks of gestation	Preterm neonates born at 33-36 weeks of gestation	Neonates and infants	Children 1-10 yrs	Adolescents 11-18 yrs	Adults 19-65 yrs	Seniors > 65-75 yrs	Seniors >75 yrs
1) Women planning pregnancy should receive adequate vitamin D supply, the same as in the general adult population, if it is possible under the control of 25(OH)D concentration (1⊕⊕⊕); 2) When pregnancy is confirmed, supplementation should be carried out under the control of 25(OH)D concentration, to maintain optimal concentrations within ranges of >30-50 ng/ml (1⊕⊕⊕); 3) If the assessment of 25(OH)D concentration is not possible, it is recommended to use vitamin D at a dose of **2000 IU/day**, throughout pregnancy and lactation (1⊕⊕⊕);	1)) It is recommended to start supplementation at a dose of **800 IU/day** from the first days of life (if enteral nutrition is possible), regardless the way of feeding (1⊕⊕⊕); 2) Supplementation should be carried out under the control of 25(OH)D concentration, both during hospitalization (the first control after 4 weeks of supplementation), as well as in the out-patient care (1⊕⊕); 3) When achieving a total dose of 1000 IU/day, combining supplements and diet, there is a risk of vitamin D overdose, particularly in neonates with birth weight <1000 g (1⊕⊕⊕);	1) **400 IU/day** from the first days of life, regardless the way of feeding (1⊕⊕⊕); 2) There is no need to assay 25(OH)D concentrations routinely (1⊕⊕⊕); 3) Supplementation carried out under the control of 25(H)D concentration should be considered in children in the risk groups (parenteral nutrition >2 weeks, ketoconazole >2 weeks, anticonvulsant treatment, cholestasis, birth weight <1500g) (2⊕⊕);	1) 0-6 months: **400 IU/day** from first days of life, regardless the way of feeding (1⊕⊕⊕); 2) 6-12 months: **400-600 IU/day**, depending on daily amount of vitamin D taken with food (1⊕⊕⊕);	1) In the period from May to September, if guidelines for insolation are met, supplementation is not necessary, although still recommended and safe (1⊕⊕⊕); 2) If insolation guidelines are not fulfilled, supplementation of **600-1000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕); 3) Obese children require **1200-2000 IU/day**, depending on severity of obesity (1⊕⊕⊕);	1) In the period from May to September, if guidelines for insolation are met, supplementation is not necessary, although still recommended and safe (1⊕⊕⊕); 2) If insolation guidelines are not fulfilled, supplementation of **800-2000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕); 3) Obese adolescents require **1600-4000 IU/day**, depending on severity of obesity (1⊕⊕⊕);	1) In the period from May to September, if guidelines for insolation are met, supplementation is not necessary, although still recommended and safe (1⊕⊕⊕); 2) If insolation guidelines are not fulfilled, supplementation of **800-2000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕); 3) Obese adults require **1600-4000 IU/day**, depending on severity of obesity (1⊕⊕⊕);	1) Due to decreased efficacy of the skin synthesis, supplementation of vitamin D in the dose of **800-2000 IU/day**, based on body weight and the dietary vitamin D intake is recommended throughout a year (1⊕⊕⊕); 2) Obese seniors require **1600-4000 IU/day**, depending on severity of obesity (1⊕⊕⊕);	1) Due to decreased efficacy of the skin synthesis, potential malabsorption and altered metabolism of vitamin D, supplementation of **2000-4000 IU/day**, based on body weight and the dietary vitamin D intake is recommended throughout a year (2⊕⊕); 2) Obese eldest seniors require **4000-8000 IU/day**, depending on severity of obesity (2⊕⊕);

1 μg = 40 IU

1 ng/mL = 2.5 nmol/L

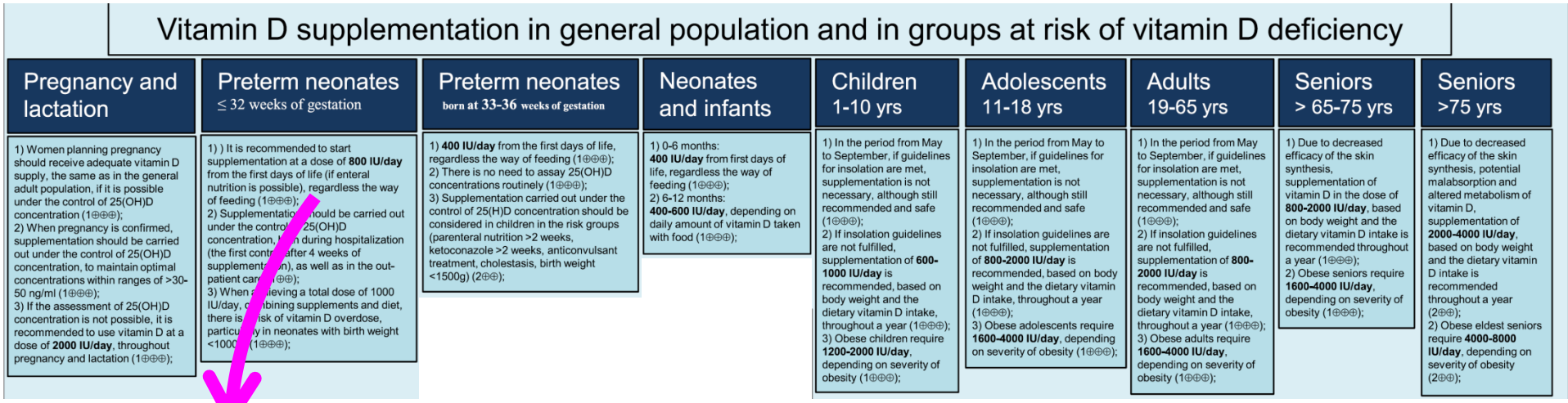


Pregnant and Lactating Women

I. **Women planning pregnancy** should receive adequate vitamin D supply, the **same as in the general adult population**, if it is possible under the control of 25(OH)D concentration (1⊕⊕⊕);

II. **When pregnancy is confirmed**, supplementation should be carried out under the control of 25(OH)D concentration, to maintain optimal concentrations within ranges of **>30–50 ng/ ml** (1⊕⊕⊕);

III. **If the assessment of 25(OH)D concentration is not possible**, it is recommended to use vitamin D at a dose of **2,000 IU/day**, throughout pregnancy and **lactation** (1⊕⊕⊕);



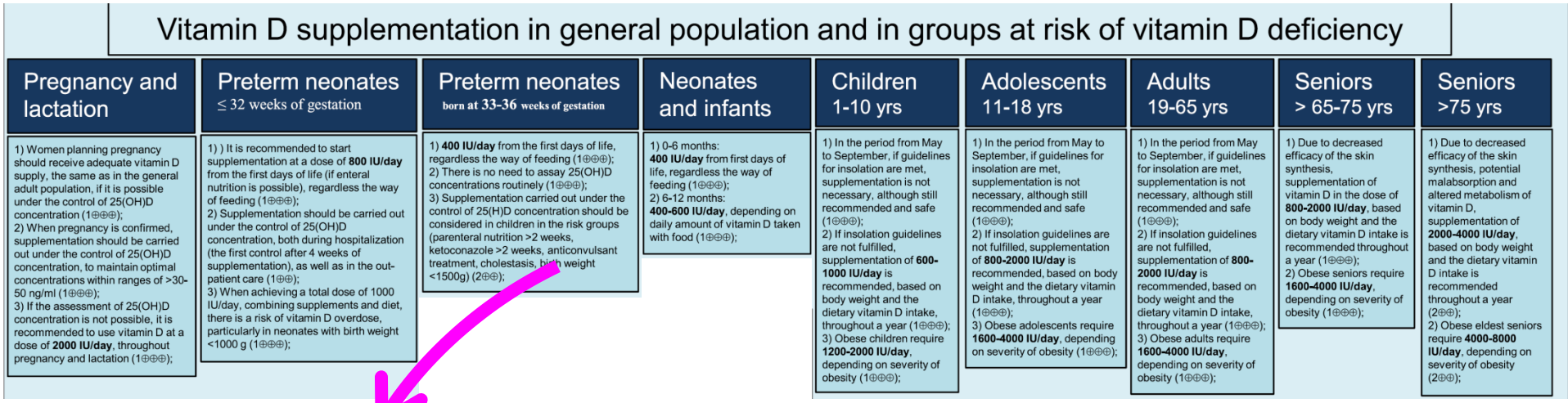
Preterm Neonates

Neonates Born at ≤32 Weeks of Gestation

I. It is recommended to start supplementation at a dose of **800 IU/day** from the **first days of life** (if enteral nutrition is possible), regardless the way of feeding (1⊕⊕⊕);

II. Supplementation should be carried out under the control of 25(OH)D concentration, both during hospitalization (the first control after 4 weeks of supplementation), as well as in the out-patient care (1⊕⊕);

III. When achieving a total dose of 1,000 IU/day, combining supplements and diet, there is a risk of vitamin D overdose, particularly in neonates with birth weight <1,000 g (1⊕⊕⊕);



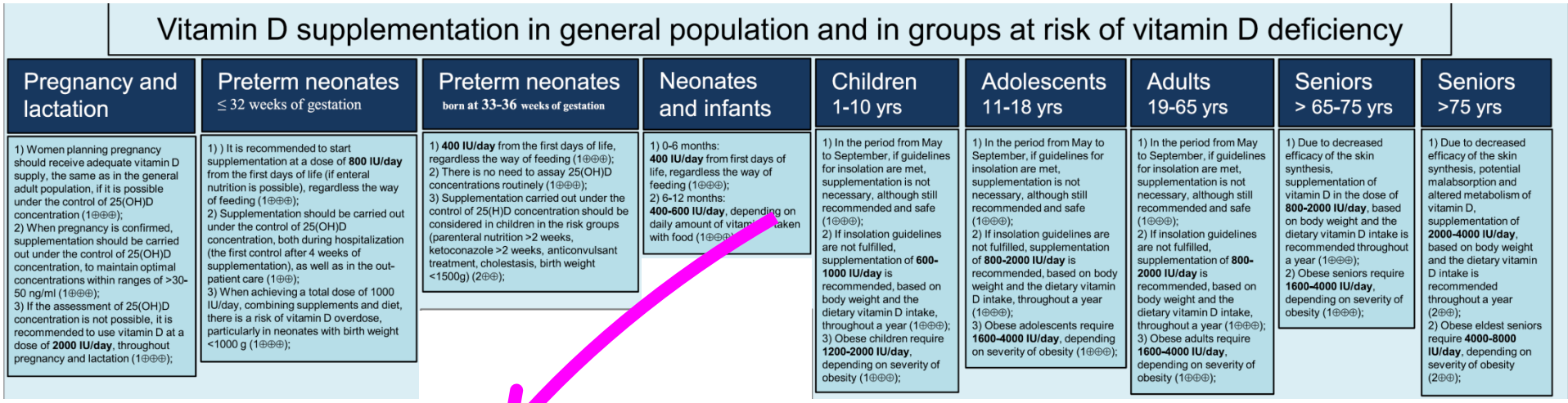
Preterm Neonates

Neonates Born at 33–36 Weeks of Gestation

I. **400 IU/day** from the **first days of life**, regardless the way of feeding (1⊕⊕⊕);

II. There is no need to assay 25(OH)D concentrations routinely (1⊕⊕⊕);

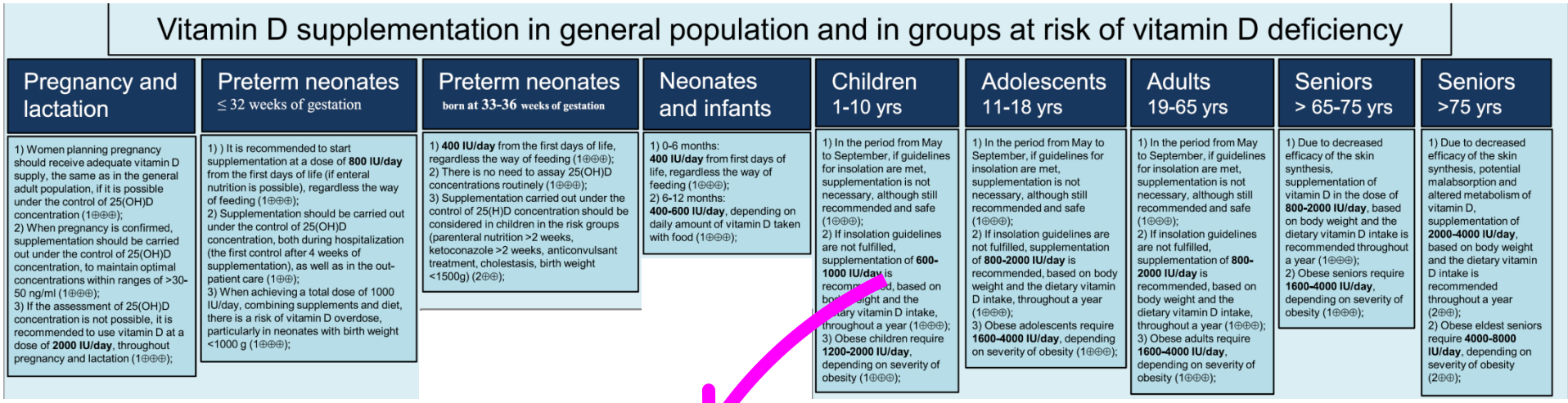
III. Supplementation under the control of 25(H)D concentration should be considered in children in the risk groups (parenteral nutrition >2 weeks, ketoconazole >2 weeks, anticonvulsant treatment, cholestasis and birth weight <1,500 g) (2⊕⊕);



Neonates Born at Term and Infants

i. **0–6 months**: **400 IU/day** from first days of life, regardless the way of feeding (1⊕⊕⊕);

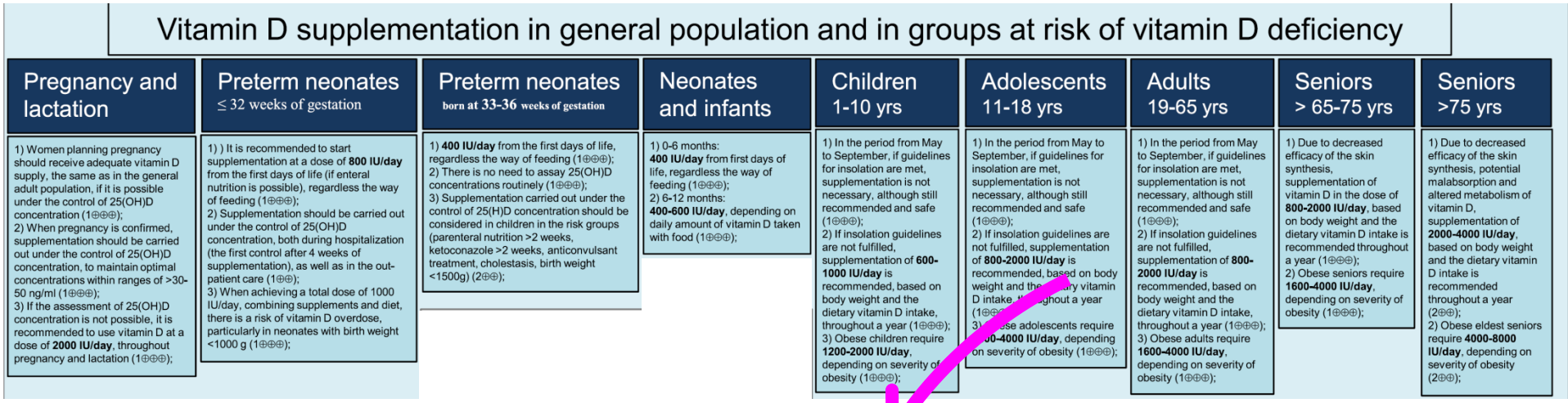
ii. **6–12 months**: **400–600 IU/day**, depending on daily amount of vitamin D taken with food (1⊕⊕⊕);



Children (1–10 Years)

i. In healthy children **sunbathing** with uncovered forearms and legs for at least 15 min between 10.00 and 15.00 h, without sunscreen in the period from **May to September**, supplementation is **not necessary**, although still recommended and safe (1⊕⊕⊕);

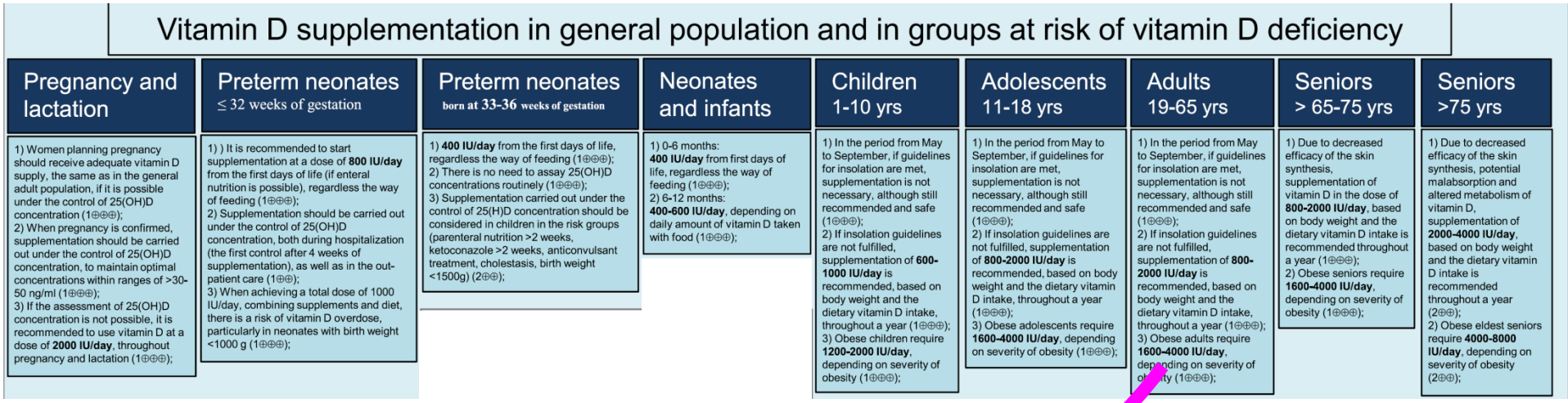
ii. If above insolation guidelines are not fulfilled, supplementation of **600–1000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕);



Adolescents (11–18 Years)

i. In healthy adolescents **sunbathing** with uncovered forearms and legs for at least 15 min between 10.00 and 15.00 h, without sunscreen in the period from **May to September**, supplementation is **not necessary**, although still recommended and safe (1⊕⊕⊕);

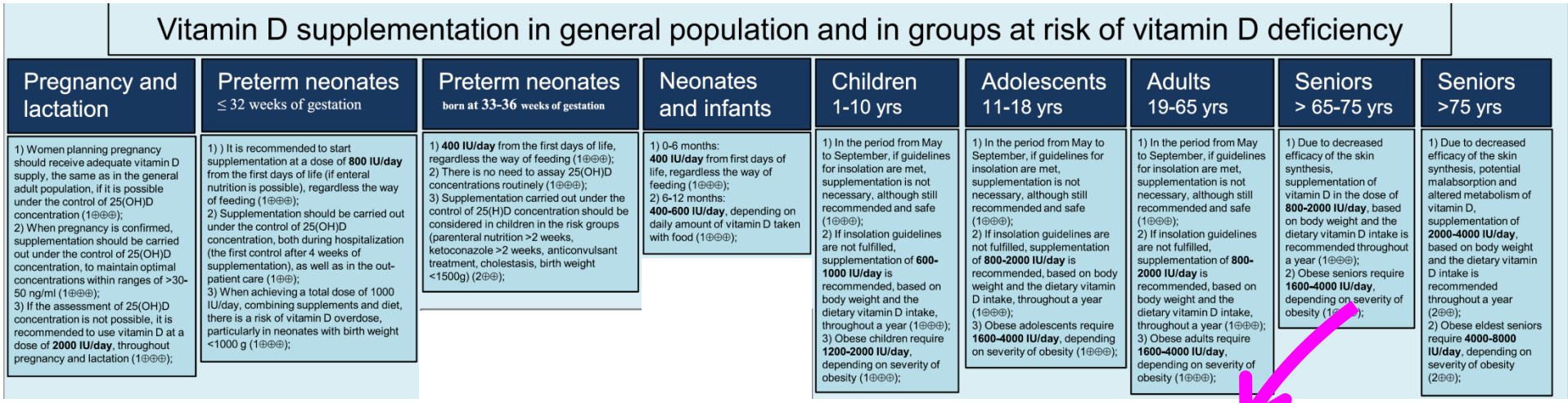
ii. If above insolation guidelines are not fulfilled, supplementation of **800–2000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕);



Adults (19–65 Years)

i. In healthy adults **sunbathing** with uncovered forearms and legs for at least 15 min between 10.00 and 15.00 h, without sunscreen in the period from **May to September**, **supplementation is not necessary**, although still recommended and safe (1⊕⊕⊕);

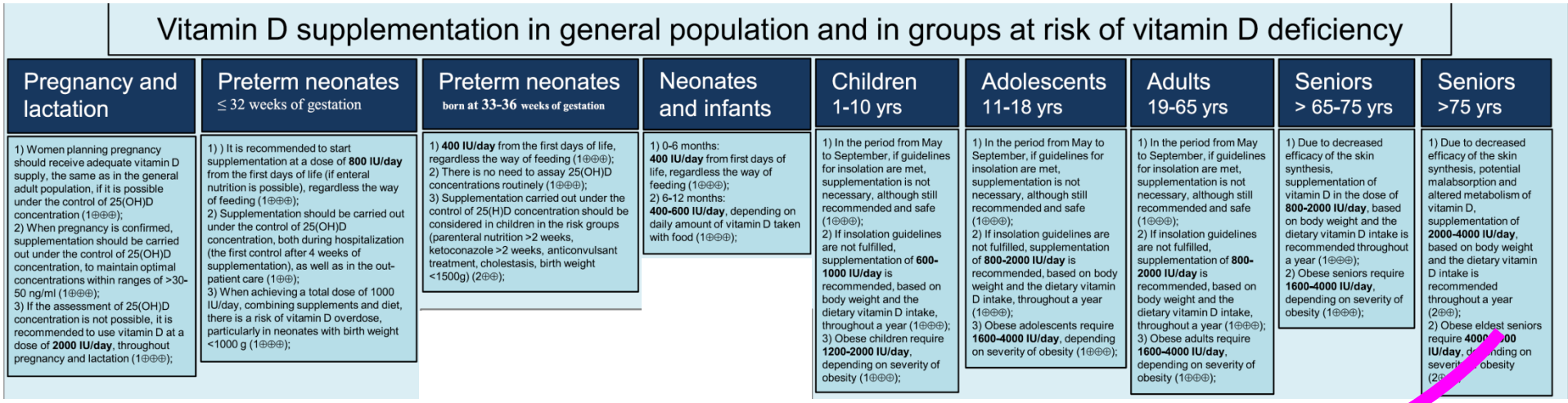
ii. If above insolation guidelines are not fulfilled, supplementation of **800–2000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕);



Seniors (>65–75 Years) and People With a Dark Complexion

i. Due to decreased efficacy of the skin synthesis, supplementation of vitamin D in the dose of **800–2,000 IU/day**, based on body weight and the dietary vitamin D intake is recommended throughout a year (1⊕⊕⊕);

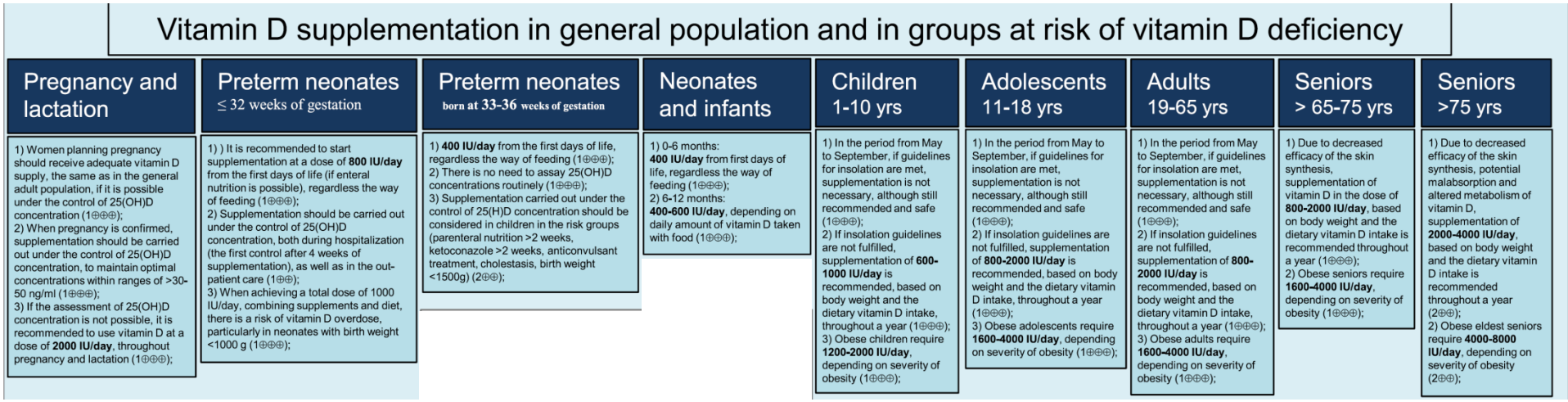
ii. **Obese seniors** require **1600-4000 IU/day** depending on severity of obesity (1⊕⊕⊕);



Eldest Seniors (>75 Years)

i. Due to decreased efficacy of the skin synthesis, potential malabsorption and altered metabolism of vitamin D, supplementation of **2,000–4,000 IU/day**, based on body weight and the dietary vitamin D intake is recommended throughout a year (2⊕⊕);

ii. **Obese eldest seniors** require **4000-8000 IU/day** depending on severity of obesity (1⊕⊕⊕);

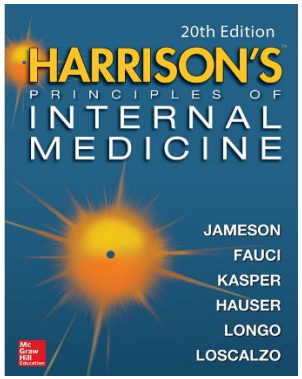


Supplementation in Groups at Risk of vitamin D Hypersensitivity

1. Prior to initiating the supplementation, the probability of vitamin D hypersensitivity should be assessed if feasible (hypercalcemia, hypercalciuria, nephrocalcinosis, nephro-lithiasis, *CYP24A1* gene mutation, *SLC34A1* gene mutation or history of other types of vitamin D hypersensitivity in an individual or family members).

This recommendation applies to all age groups as well as to groups at the risk of vitamin D deficiency (1⊕⊕⊕);

2. In groups at the risk of vitamin D hypersensitivity, supplementation should be supervised and carried out carefully and in an individual manner, preferably under the control of calcium-phosphate variables, particularly calcemia, calciuria, parathormone (PTH), 25(OH)D and 1,25(OH)2D (1⊕⊕);



Based on the National Academy of Medicine 2010 report, the recommended daily intake of vitamin D is 600 IU from 1 to 70 years of age, and 800 IU for those over 70.

Based on the observation that 800 IU of vitamin D, with calcium supplementation, decreases the risk of hip fractures in elderly women, this higher dose is thought to be an appropriate daily intake for prevention of vitamin D deficiency in adults.

Vitamin D supplementation and treatment regimes in relation to 25(OH)D concentration

Severe Deficiency 0-10 ng/ml (1⊕⊕⊕);

1) Therapy in relation to age and body weight; control assay of 25(OH)D concentration should be performed after 1 to 3 months of therapy (1⊕⊕⊕);
2) Recommended therapeutic doses:
- **0-12 months of age: 2000 IU/day (1⊕⊕⊕);**
- **1-10 years: 3000-6000 IU/day (1⊕⊕⊕);**
- **>10 years: 6000 IU/day (1⊕⊕⊕);**

3) Treatment should be carried out for 3 months or until the 25(OH)D concentration of >30-50 ng/ml is reached, then it is recommended to use consecutive maintenance dose i.e. a prophylactic dose recommended for general population, in relation to age and body weight (1⊕⊕⊕);
4) In patients with skeletal symptoms and bone mineral disorders (bone deformations, bone pain, history of fragility fractures), it is necessary to assess and monitor parameters of calcium-phosphate metabolism (Ca, PO_4 ALPL, PTH, Ca/creatinine ratio in urine), and if available – to examine bone mineral density using DXA (2⊕⊕);

Deficiency >10-20 ng/ml (1⊕⊕⊕);

1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
2) If vitamin D supplementation was appropriate, it is recommended to increase the dose by 100% and to assess 25(OH)D concentration in 3 months' time (2⊕⊕);
3) If vitamin D was not supplemented previously, it is recommended to start vitamin D intake at maximal doses recommended for peers from the general population and to assess 25(OH)D concentration in 3 months' time (2⊕⊕);
4) In patients with skeletal symptoms (bone deformations, bone pain, history of fragility fractures), it is indicated to assess calcium-phosphate metabolism (Ca, PO_4 ALPL, PTH, Ca/creatinine ratio in urine), and, if available – bone mineral density using DXA (2⊕⊕);

Suboptimal >20-30 ng/ml (1⊕⊕⊕);

1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
2) If vitamin D supplementation was appropriate, it is recommended to increase the dose by 50% and to consider the assessment of 25(OH)D concentration in 6 months' time (2⊕⊕);
3) If vitamin D was not supplemented previously, it is recommended to start vitamin D intake at doses recommended for peers from the general population (2⊕⊕);

Optimal >30-50 ng/ml (1⊕⊕⊕);

1) Continue previous management (1⊕⊕⊕);

High >50-75 ng/ml (2⊕⊕);

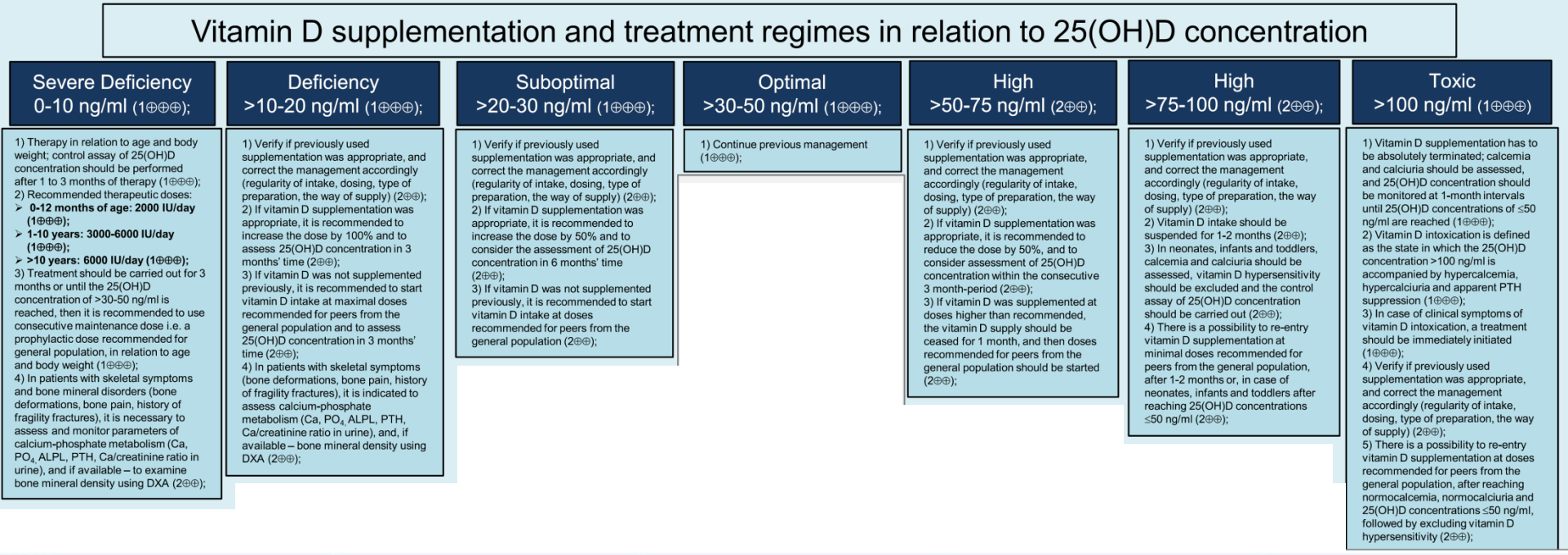
1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
2) If vitamin D supplementation was appropriate, it is recommended to reduce the dose by 50%, and to consider assessment of 25(OH)D concentration within the consecutive 3 month-period (2⊕⊕);
3) If vitamin D was supplemented at doses higher than recommended, the vitamin D supply should be ceased for 1 month, and then doses recommended for peers from the general population should be started (2⊕⊕);

High >75-100 ng/ml (2⊕⊕);

1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
2) Vitamin D intake should be suspended for 1-2 months (2⊕⊕);
3) In neonates, infants and toddlers, calcemia and calciuria should be assessed, vitamin D hypersensitivity should be excluded and the control assay of 25(OH)D concentration should be carried out (2⊕⊕);
4) There is a possibility to re-entry vitamin D supplementation at minimal doses recommended for peers from the general population, after 1-2 months or, in case of neonates, infants and toddlers after reaching 25(OH)D concentrations ≤50 ng/ml (2⊕⊕);

Toxic >100 ng/ml (1⊕⊕⊕)

1) Vitamin D supplementation has to be absolutely terminated; calcemia and calciuria should be assessed, and 25(OH)D concentration should be monitored at 1-month intervals until 25(OH)D concentrations of ≤50 ng/ml are reached (1⊕⊕⊕);
2) Vitamin D intoxication is defined as the state in which the 25(OH)D concentration >100 ng/ml is accompanied by hypercalcemia, hypercalciuria and apparent PTH suppression (1⊕⊕⊕);
3) In case of clinical symptoms of vitamin D intoxication, a treatment should be immediately initiated (1⊕⊕⊕);
4) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
5) There is a possibility to re-entry vitamin D supplementation at doses recommended for peers from the general population, after reaching normocalcemia, normocalciuria and 25(OH)D concentrations ≤50 ng/ml, followed by excluding vitamin D hypersensitivity (2⊕⊕);

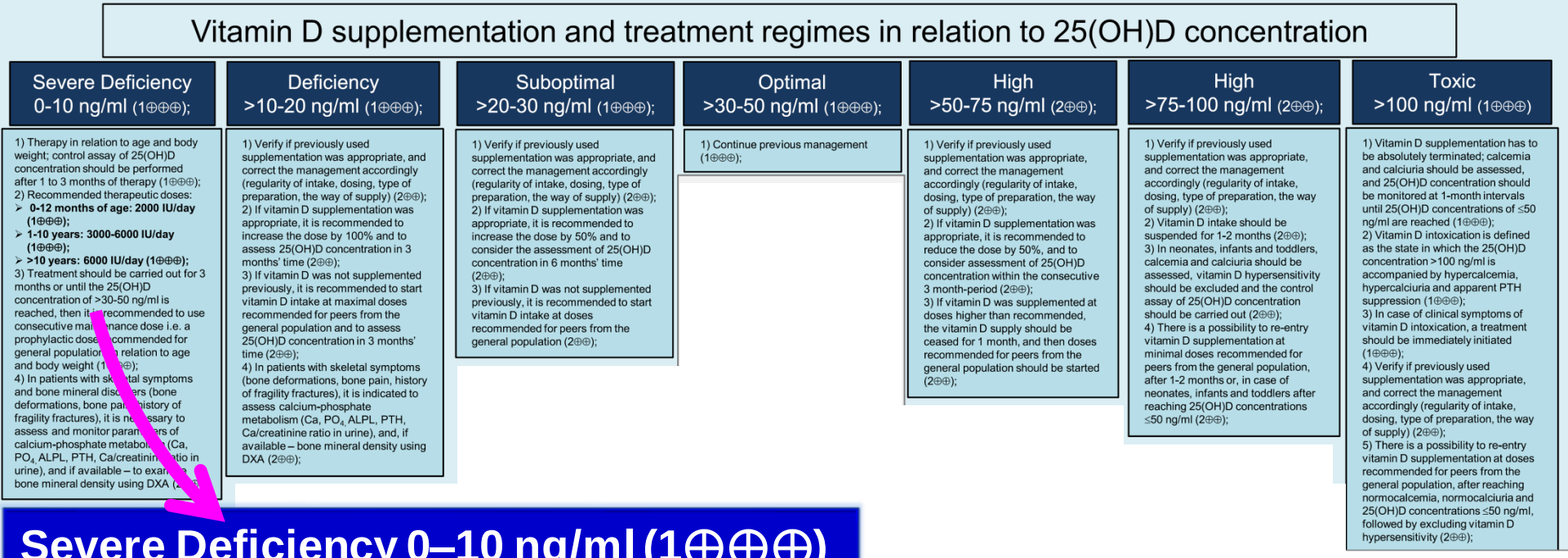


Principles of Supplementation and Treatment with vitamin D based on 25(OH)D Concentrations

i. A single loading dose of vitamin D is not recommended (2⊕⊕);

ii. Vitamin D dosing should be based on 25(OH)D concentrations and antecedent prophylactic management (2⊕⊕);

iii. The diagnostic standards include simultaneous assays of 25(OH)D2 and 25(OH)D3 [25(OH)D TOTAL], with intraassay variation <5% and interassay variation <10%, being subject to quality assurance by the certifying system DEQAS (2⊕⊕);



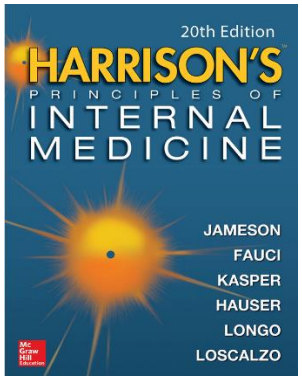
Severe Deficiency 0–10 ng/ml (1⊕⊕⊕)

1. Therapeutic doses should be implemented, based on age and body weight; the repeated control assay of 25(OH)D concentration should be performed after 1–3 months of therapy (1⊕⊕⊕);

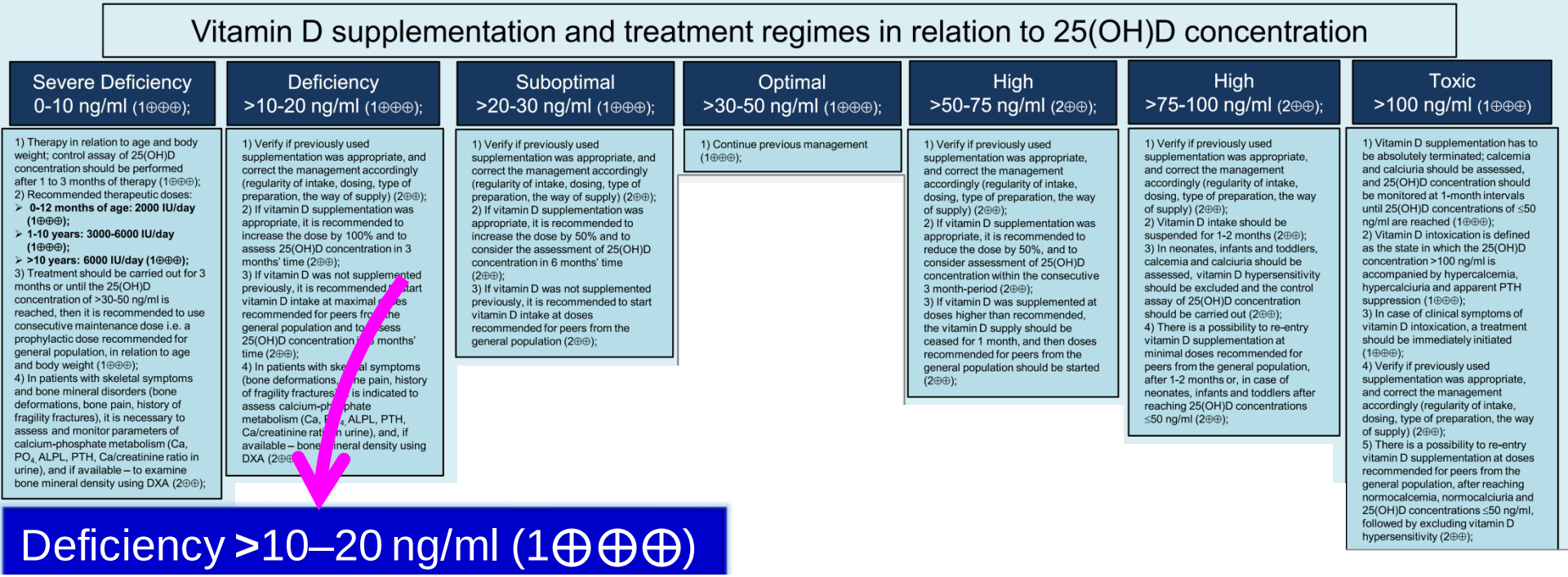
   a. **From birth to 12 months** of age: **2,000 IU/day** (1⊕⊕⊕);
   b. **1–10 years**: **3,000–6,000 IU/day** (1⊕⊕⊕);
   c. **>10 years**: **6,000 IU/day** (1⊕⊕⊕);

2. Treatment of severe deficiency should be carried out for 3 months or until the 25(OH)D concentration of **>30–50 ng/ml** is reached, then it is recommended to use consecutive maintenance dose, i.e., a prophylactic dose recommended for general population, in relation to age and body weight (1⊕⊕⊕);

3. In patients with skeletal symptoms and bone mineral disorders (bone deformations, bone pain, history of fragility fractures), it is necessary to assess and monitor parameters of calcium-phosphate metabolism (Ca, PO4, ALPL, PTH and Ca/creatinine ratio in urine), and if available to examine bone mineral density using DXA (2⊕⊕);



severe vitamin D deficiency can be treated with pharmacologic repletion initially (50,000 IU weekly for 3–12 weeks), followed by maintenance therapy (800 IU daily).



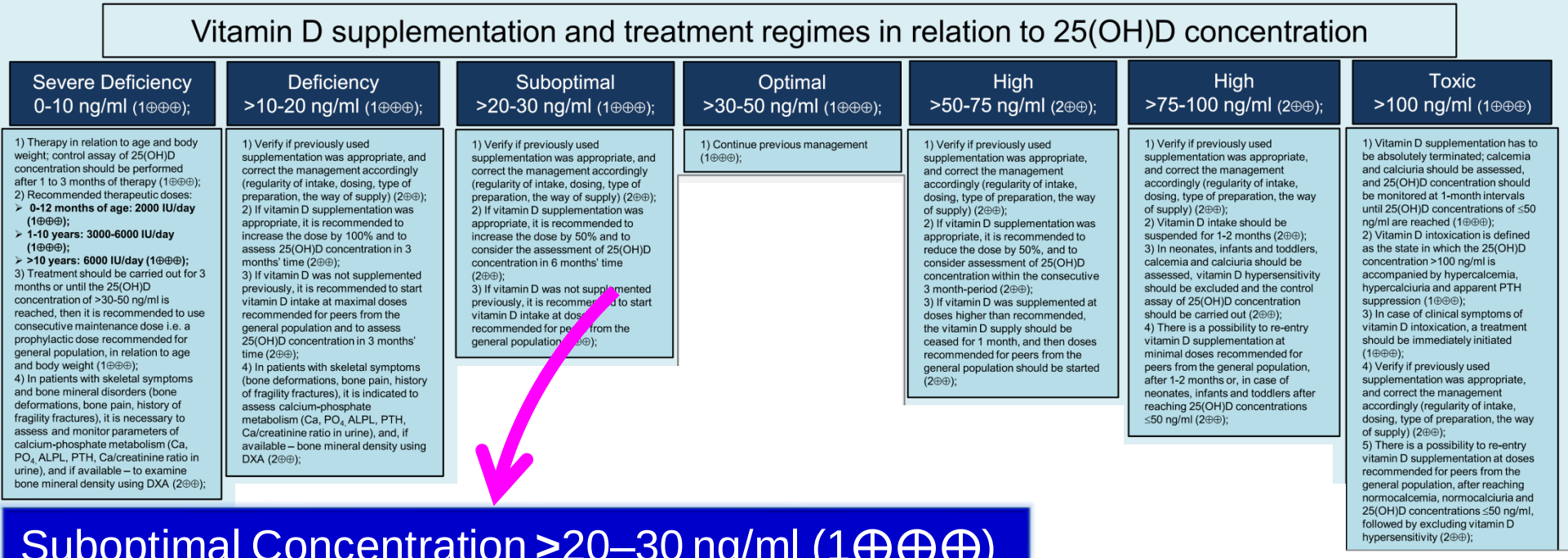
Deficiency >10–20 ng/ml (1⊕⊕⊕)

1. Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation and the way of supply) (2⊕⊕);

2. If vitamin D supplementation was appropriate, it is recommended to increase the dose by 100% and to assess 25(OH)D concentration in 3-month time (2⊕⊕);

3. If vitamin D was not supplemented previously, it is recommended to start vitamin D intake **at maximal doses recommended for peers from the general population** and to assess 25(OH)D concentration in 3-month time (2⊕⊕);

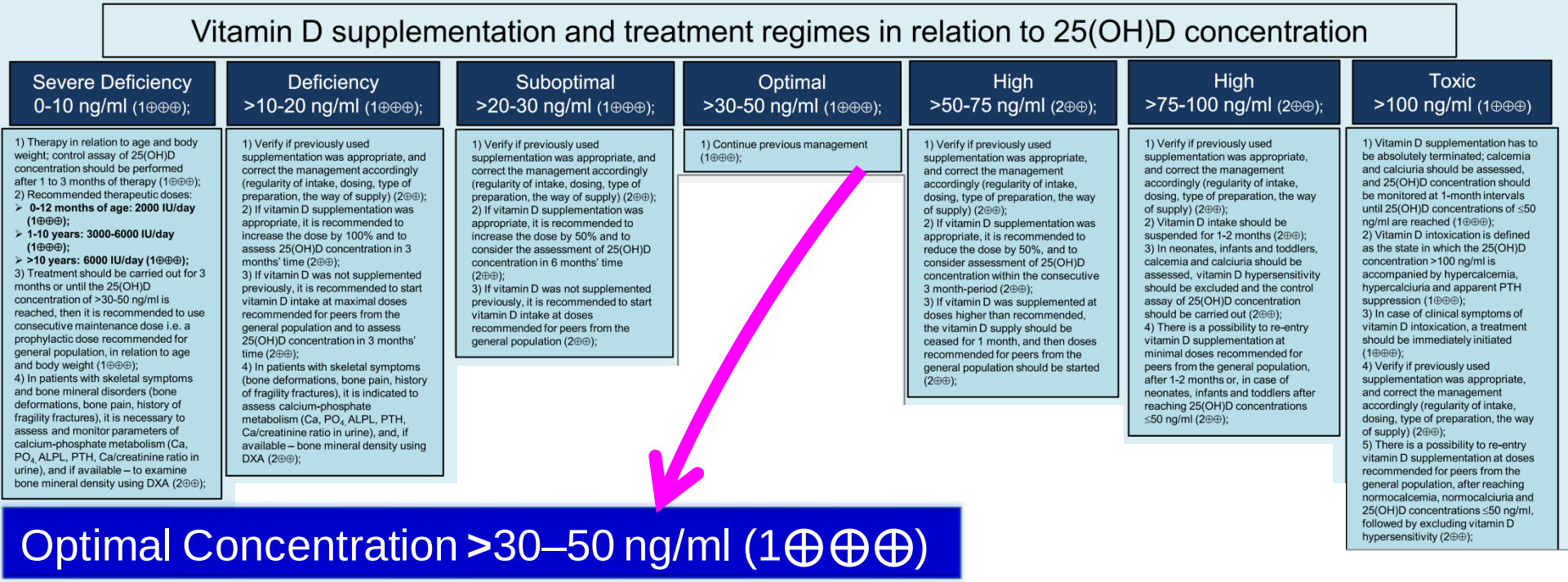
4. In patients with skeletal symptoms (bone deformations, bone pain, history of fragility fractures), it is indicated to assess calcium-phosphate metabolism [Ca, PO4, alkaline phos-phatase activity (ALPL), PTH, Ca/creatinine ratio in urine], and, if available—bone mineral density using dual-energy X-ray absorptiometry (DXA) (2⊕⊕);



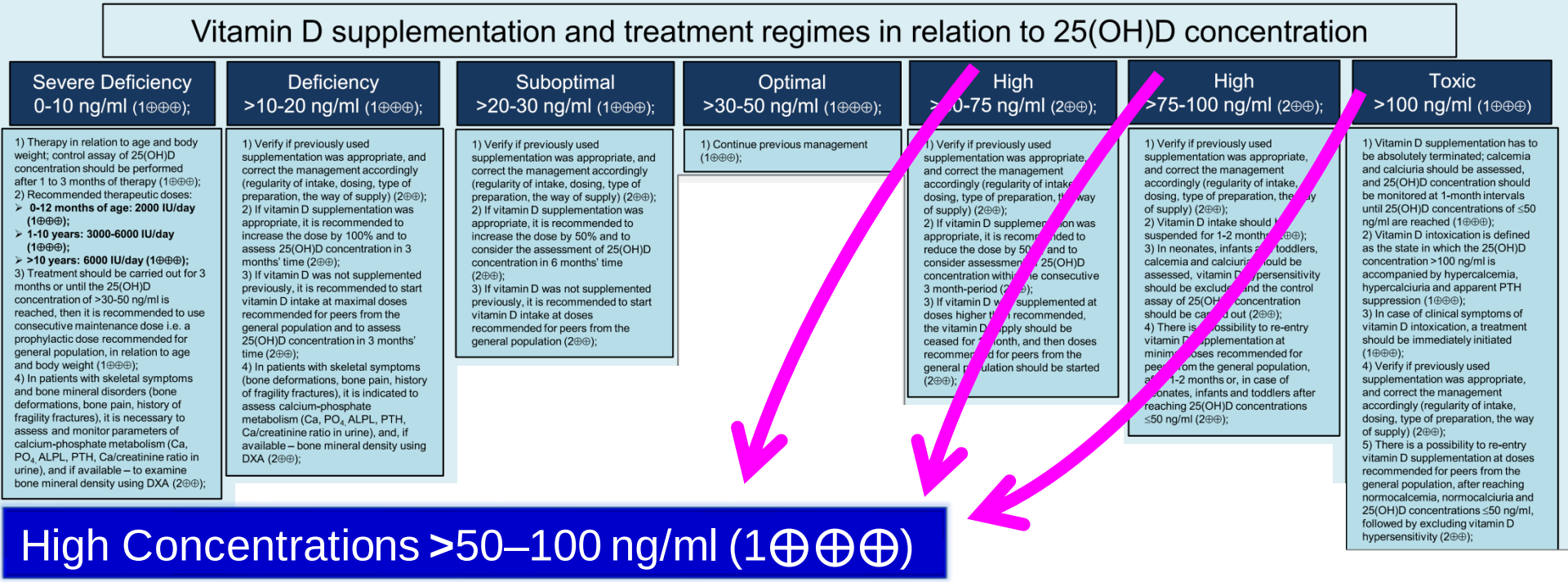
1. Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation and the way of supply) (2⊕⊕);

2. If vitamin D supplementation was appropriate, it is recommended to increase the dose by 50% and to consider the assessment of 25(OH)D concentration in 6-month time (2⊕⊕);

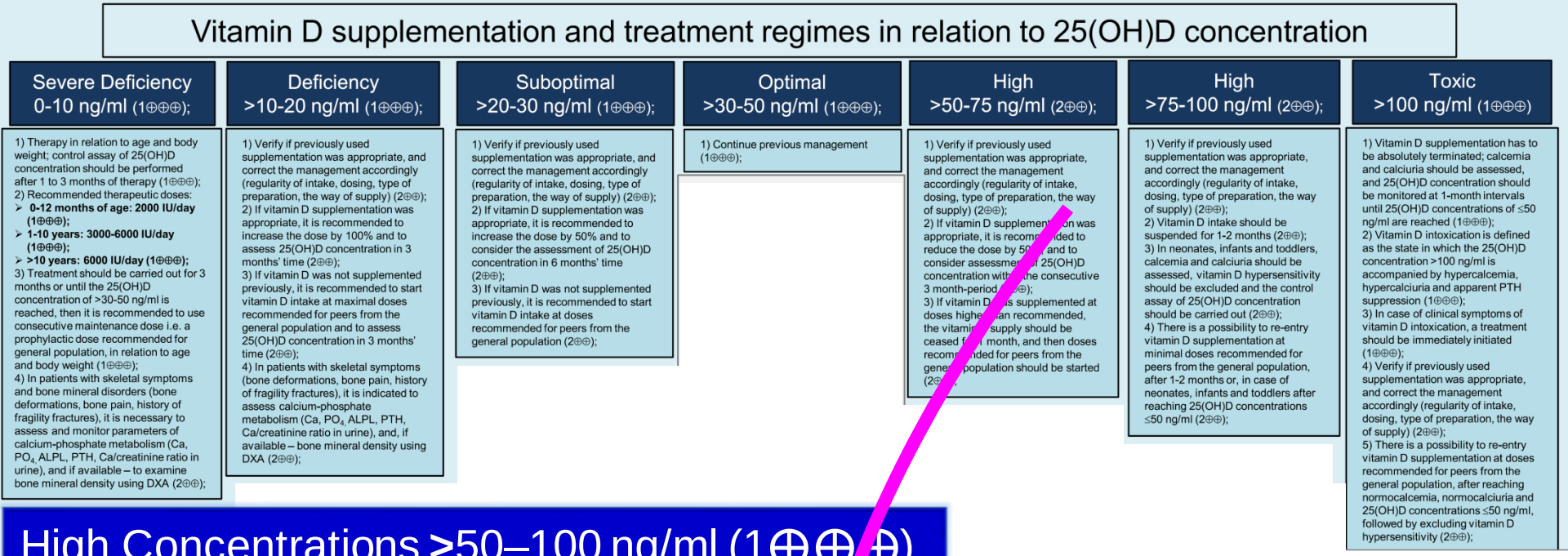
3. If vitamin D was not supplemented previously, it is recommended to start vitamin D intake at **doses recommended for peers from the general population** (2⊕⊕);



1. i. Continue previous management (1⊕⊕⊕);



1. Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation and the way of supply) (2⊕⊕);

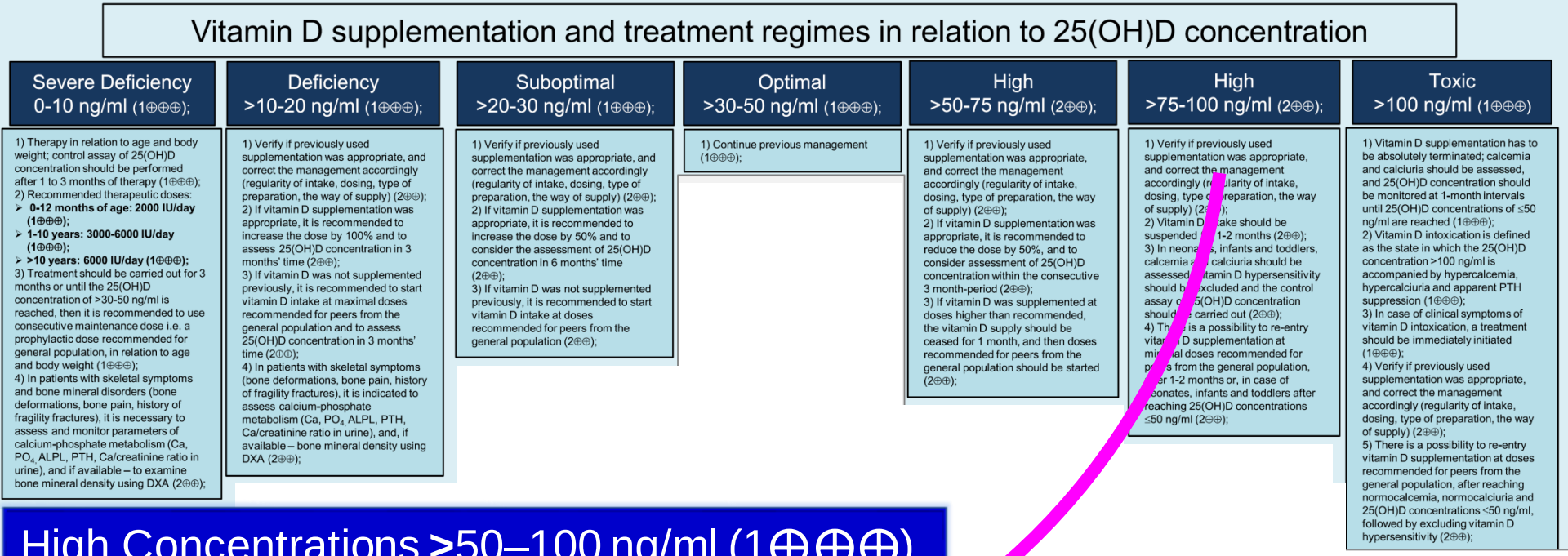


High Concentrations >50–100 ng/ml (1⊕⊕⊕)

Concentrations >50–75 ng/ml (2⊕⊕)

If vitamin D supplementation was appropriate, it is recommended to **reduce the dose by 50%,** and to consider assessment of 25(OH)D concentration within the consecutive 3-month period (2⊕⊕);

If vitamin D was supplemented at doses higher than recommended, the vitamin D supply should be ceased for 1 month, and then doses recommended for peers from the general population should be started (2⊕⊕);



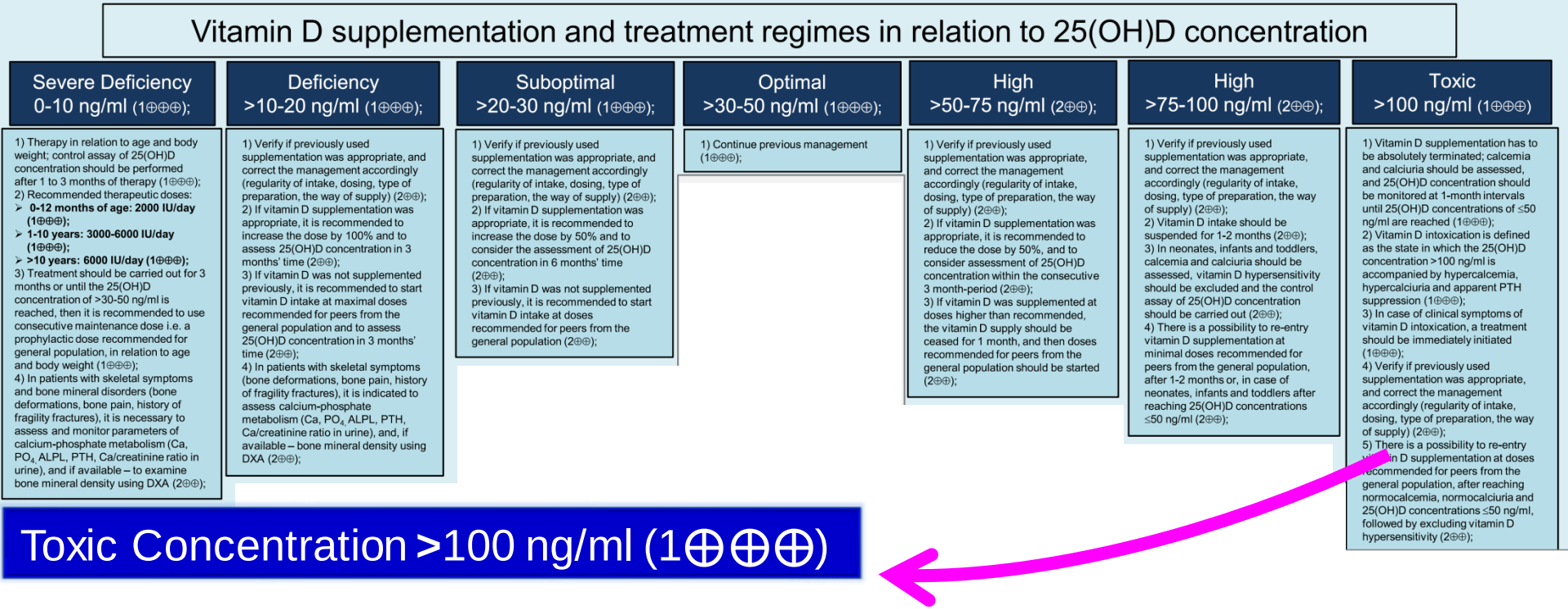
High Concentrations >50–100 ng/ml (1⊕⊕⊕)

Concentrations >75–100 ng/ml (2⊕⊕)

1. **Vitamin D intake should be suspended for 1–2 months (2⊕⊕);**

2. In neonates, infants and toddlers, calcemia and calciuria should be assessed, vitamin D hypersensitivity should be excluded and the control assay of 25(OH)D concentration should be carried out (2⊕⊕);

3. There is a possibility to re-entry vitamin D supplementation at minimal doses recommended for peers from the general population, after 1–2 months or, in case of neonates, infants and toddlers after reaching 25(OH)D concentrations ≤50 ng/ ml (2⊕⊕);



1. **Vitamin D supplementation has to be stopped forthwith**; calcemia and calciuria should be assessed, and 25(OH)D concentration should be monitored at 1-month intervals until 25(OH)D concentrations of ≤50 ng/ml are reached (1⊕⊕⊕);

2. **Vitamin D intoxication is defined as the state in which the 25 (OH)D concentration >100 ng/ml is accompanied by hypercalcemia, hypercalciuria and apparent PTH suppression** (1⊕⊕⊕);

3. In case of clinical symptoms of vitamin D intoxication, treatment should be immediately initiated (1⊕⊕⊕);

4. Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation and the way of supply) (2⊕⊕);

5. There is a possibility to re-entry vitamin D supplementation at doses recommended for peers from the general population, after reaching normocalcemia, normocalciuria and 25(OH)D concentrations ≤50 ng/ml, followed by excluding vitamin D hypersensitivity (2⊕⊕);

THE LANCET
Diabetes & Endocrinology

COMMENT | VOLUME 8, ISSUE 9, P735-736, SEPTEMBER 01, 2020

Vitamin D for COVID-19: a case to answer?

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Published: August 03, 2020 • DOI: https://doi.org/10.1016/S2213-8587(20)30268-0 •

Pending results of such trials, it would seem uncontroversial to enthusiastically promote efforts to achieve reference nutrient intakes of vitamin D, which range from 400 IU/day in the UK to 600–800 IU/day in the USA. These are predicated on benefits of vitamin D for bone and muscle health, but there is a chance that their implementation might also reduce the impact of COVID-19 in populations where vitamin D deficiency is prevalent; there is nothing to lose from their implementation, and potentially much to gain.


Thank You