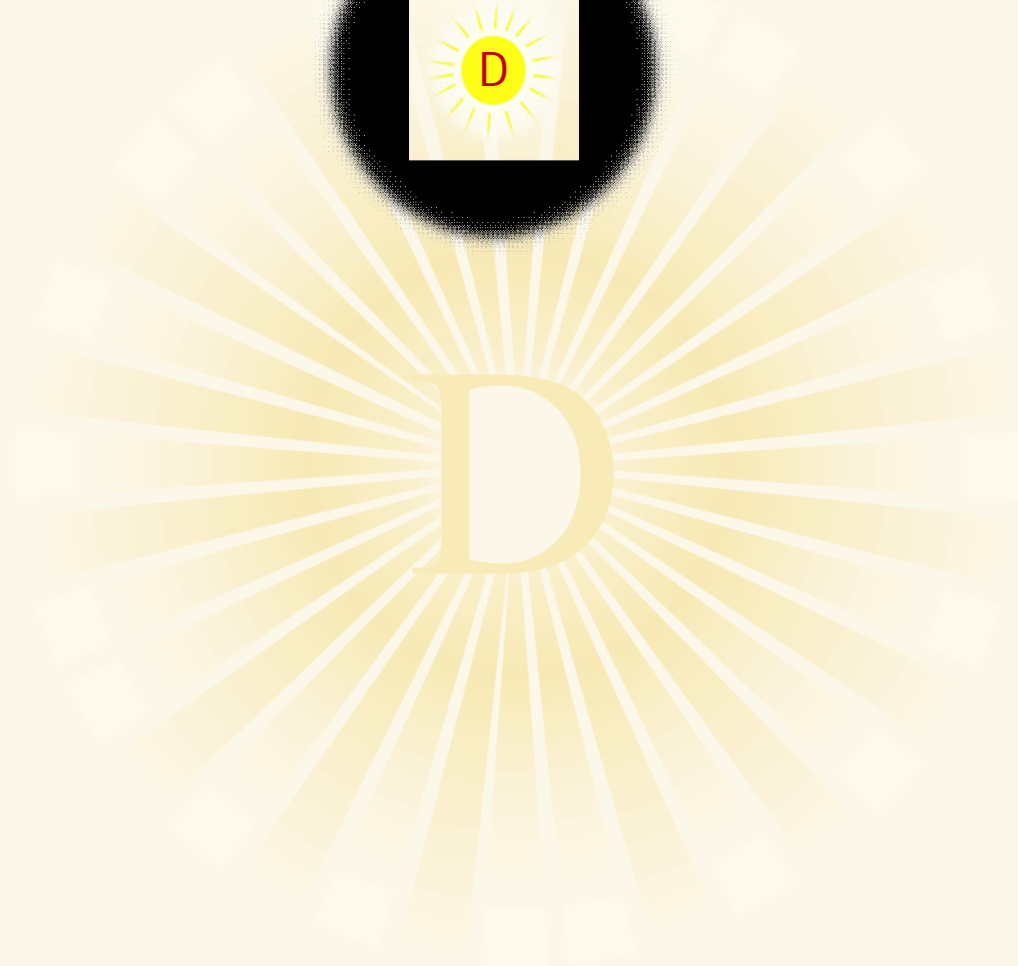
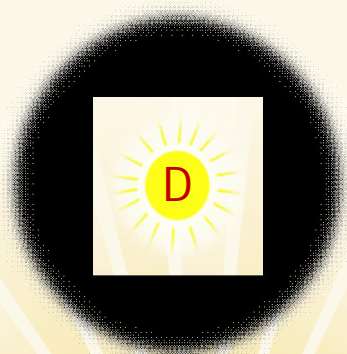


Global Vitamin D Deficiency And Its Role In Health And Disease

Dr. Afrozul Haq, Ph.D.
Senior Clinical Scientist
Pathology & Laboratory Medicine Institute
Sheikh Khalifa Medical City
Abu Dhabi, United Arab Emirates

1st Abu Dhabi International Conference on Vitamin D Deficiency
March 23, 2012, Rocco Forte Hotel, Abu Dhabi





Learning Objectives

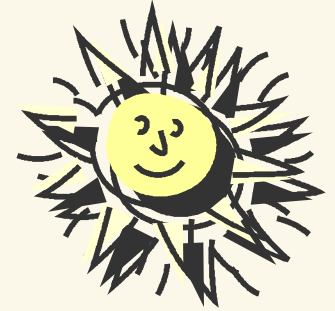
- ❖ Develop an understanding of Vitamin D what it is, how we get it, and why we need it
- ❖ Recall the basics of Vitamin D, its source, production, and metabolism
- ❖ Understand the difference between D3 & D2
- ❖ Prevalence of D deficiency in Abu Dhabi, in the middle east and other countries
- ❖ Current research on Vitamin D, major physiologic actions

Introduction

Many clinical laboratories in the world have seen requests for vitamin D testing increased by 100% or more in the last 5 years

The most common laboratory test to assess vitamin D nutritional status is total 25-(OH)D serum concentrations

Vitamin D ?



- ❖ Vitamin D is actually a steroidal hormone like estrogen or testosterone
- ❖ It stands alone as the only 'Vitamin' the body can produce on its own
- ❖ Vitamin D is called the 'Sunshine Vitamin' because the body naturally produces it through exposure of your skin to the sun

Vitamin D-Deficiency ?

- ❖ Vitamin D deficiency is- not having enough vitamin D that your body needs to function normally
- ❖ Vitamin D deficiency is an epidemic of such magnitude and seriousness that it is not only alarmingly widespread, but also a root cause of many serious diseases such as rickets, osteoporosis, MS, cancer, CVD tuberculosis and diabetes

Introduction

VDR

❖ Vitamin D receptors (VDR) have been found in almost every type of human cell, from brain to our bones. Vitamin D controls (directly or indirectly) more than 3000 genes that regulate calcium, phosphorus and bone metabolism, modulate innate & adaptive immunity, control cell growth and maturation, regulate the production of insulin and renin, induce apoptosis and inhibit angiogenesis



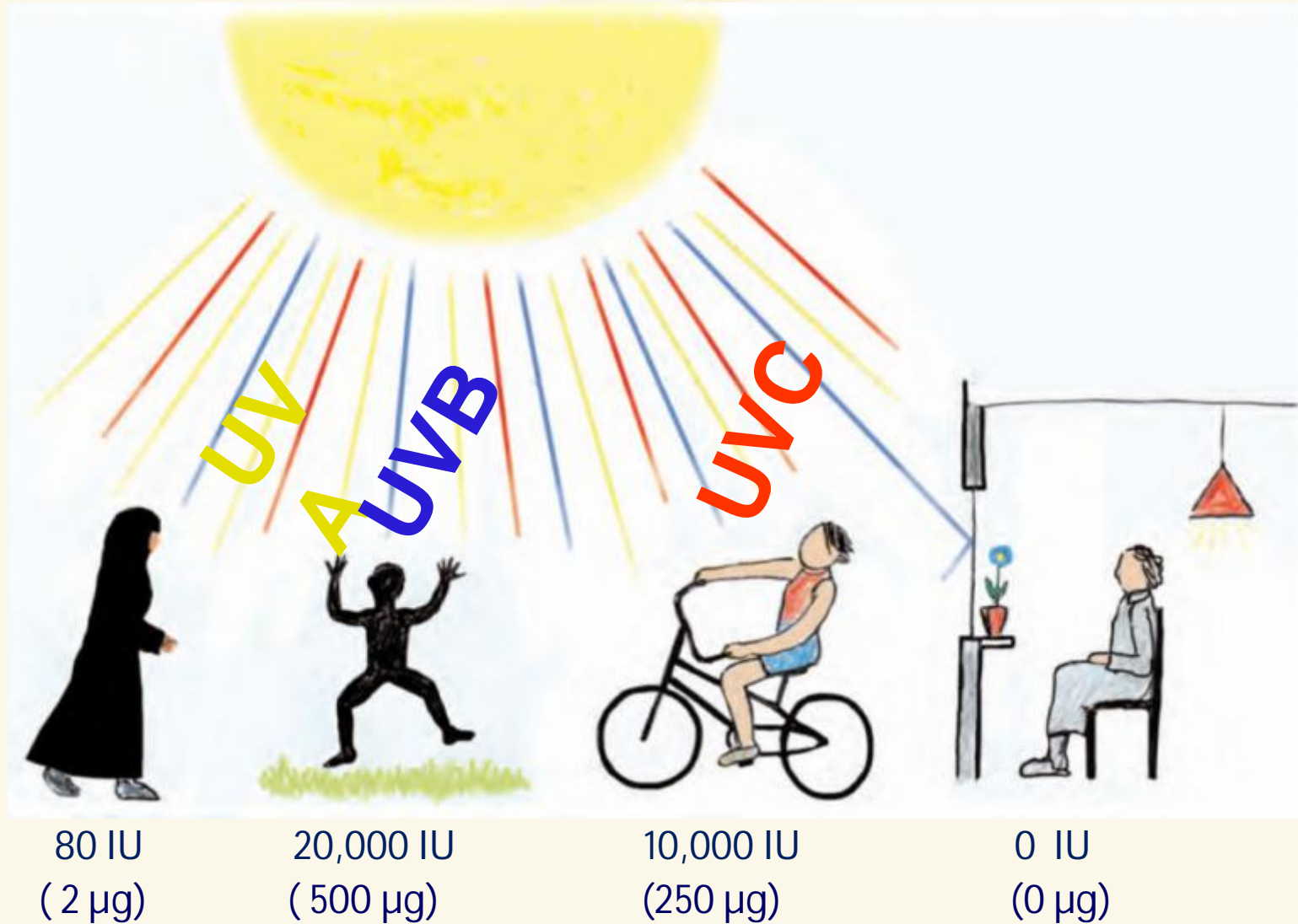
Dietary Sources of Vitamin D

Food	IUs per Serving*
Cod liver oil, 1 tablespoon	1360
Salmon (sockeye), cooked, 3 ounces	794
Mackerel, cooked, 3 ounces	388
Tuna fish, canned in water, drained, 3 ounces	154
Milk, vitamin D–fortified, 1 cup	115-124
Sardines, canned in oil, drained, 2 sardines	46
Liver, beef, cooked, 3.5 ounces	46
Egg, 1 whole (vitamin D is found in yolk)	25

*

Adapted from Selected Food Sources of Vitamin D. US Department of Agriculture, Agricultural Research Service USDA Nutrient Database for Standard Reference, Release 22; 2009.

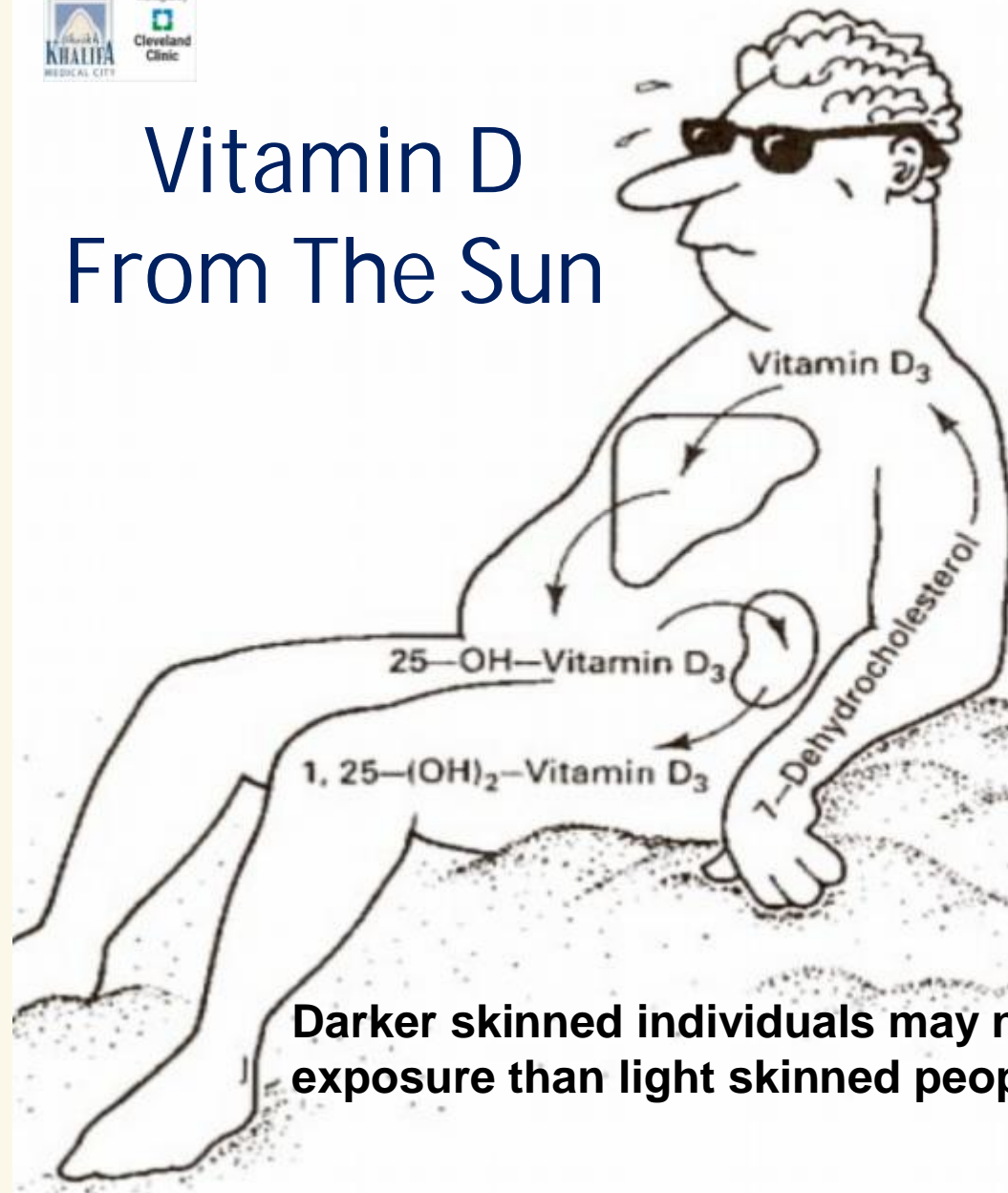
Daily Vitamin D Synthesis From The Sun



Sun Exposure

- ❖ 10-20 minutes, not less than 40% of body surface exposed between 10 am to 2 pm and 2 times a week.
- ❖ UVB light can not pass through glass
- ❖ Decreased cutaneous production of Vitamin D with:
 - Aging
 - Dark skin
 - Sun screen/clothes

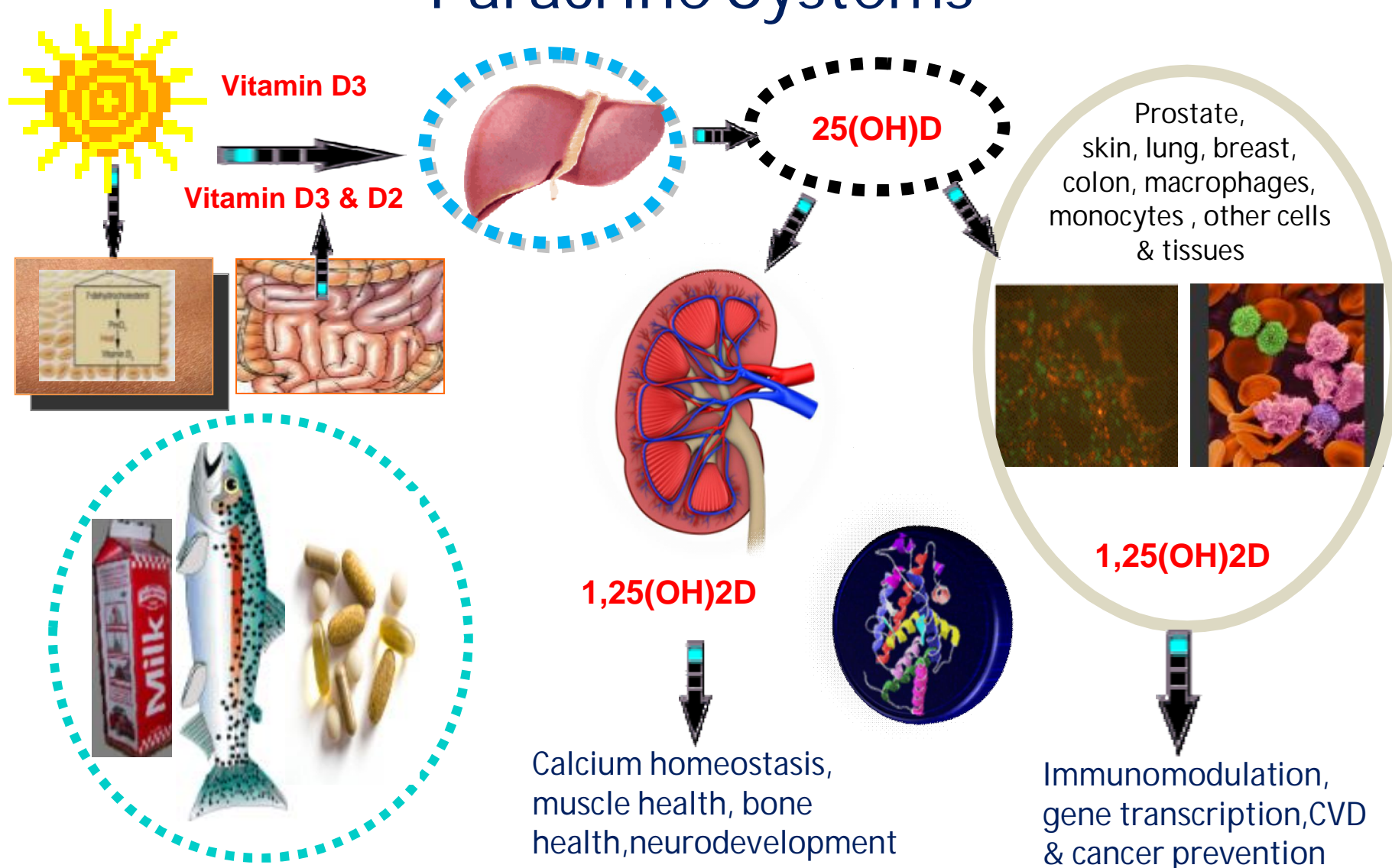
Vitamin D From The Sun



1 MED of UVBR will release
approx 10,000 -25,000 IU of
Vitamin D₃ into the circulation
within 24hrs

**Darker skinned individuals may need 6-10 times more UVB
exposure than light skinned people**

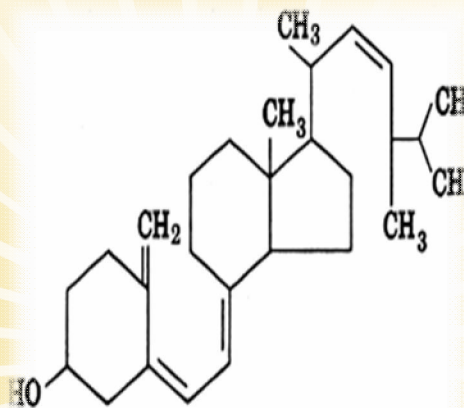
Vitamin D Endocrine, Autocrine / Paracrine Systems



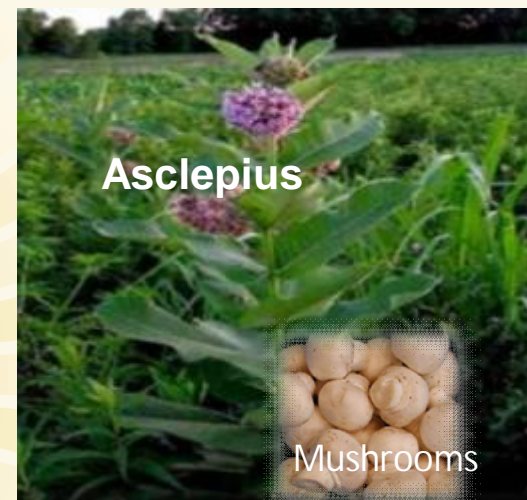
Types and Sources of Vitamin D

❖ Vitamin D2 (Ergocalciferol)

From plants/mushrooms/yeast leads to the formation of Vitamin D2 (calciferol). Biologically inert & conversion (OH) in the liver and then in kidneys produces active form. D2 is less potent than vitamin D3



Vitamin D₂ (calciferol)

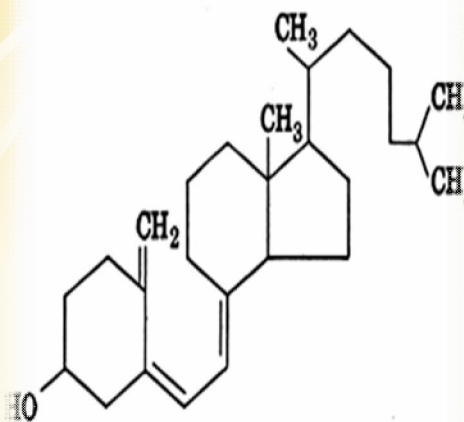


Asclepius

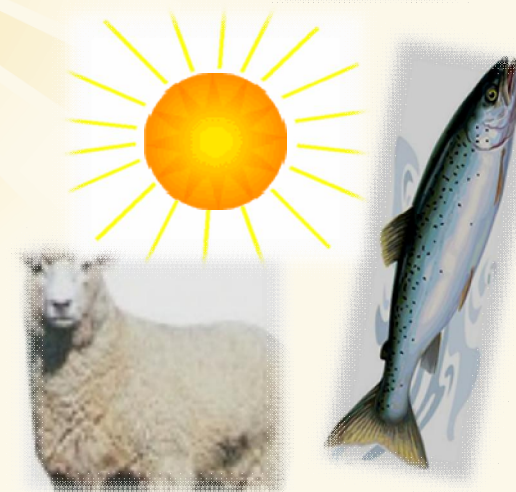
Mushrooms

❖ Vitamin D3 (Cholecalciferol)

Naturally occurring form in humans, formed by the action of ultraviolet light (UVB) on Vitamin D precursors in the skin (7-DHC). Lanolin is often used as a raw material for producing vitamin D3. Present in fish (salmon), other sea food. Biologically inert & conversion (OH) in the liver and then in kidneys produces active form



Vitamin D₃



Functions Of Vitamin D

- ❖ **Calcium Metabolism:** Vitamin D enhances calcium absorption in the gut and renal tubules
- ❖ **Cell Differentiation:** Particularly of collagen and epithelium
- ❖ **Immunity:** Immune system modulator and prevent excessive expression of pro-inflammatory cytokines

Classical And Non-Classical Functions Of Vitamin D

Classical

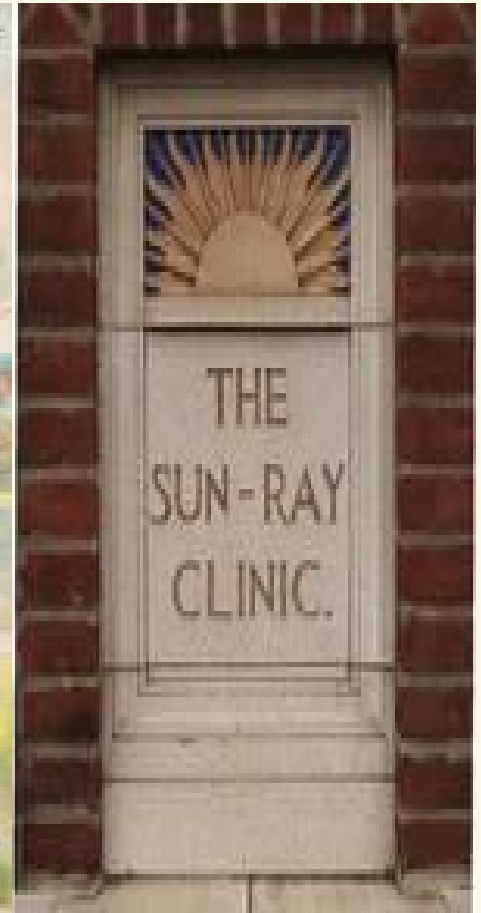
- ❖ Vitamin D was originally discovered for its ability to prevent the childhood bone disease Rickets which is characterized by softening of the bones leading to deformity
- ❖ The major physiological function of vitamin D is to maintain intracellular and extra cellular calcium concentrations within a physiologically acceptable range



Non-Classical

- ❖ Multiple Sclerosis
- ❖ Cardiovascular disease
- ❖ Hypertension
- ❖ Muscle weakness and pain
- ❖ Autoimmune Diseases
- ❖ Type 1 & Type II diabetes
- ❖ Inflammatory bowel diseases
- ❖ Reduction in all cancers
- ❖ Allergy

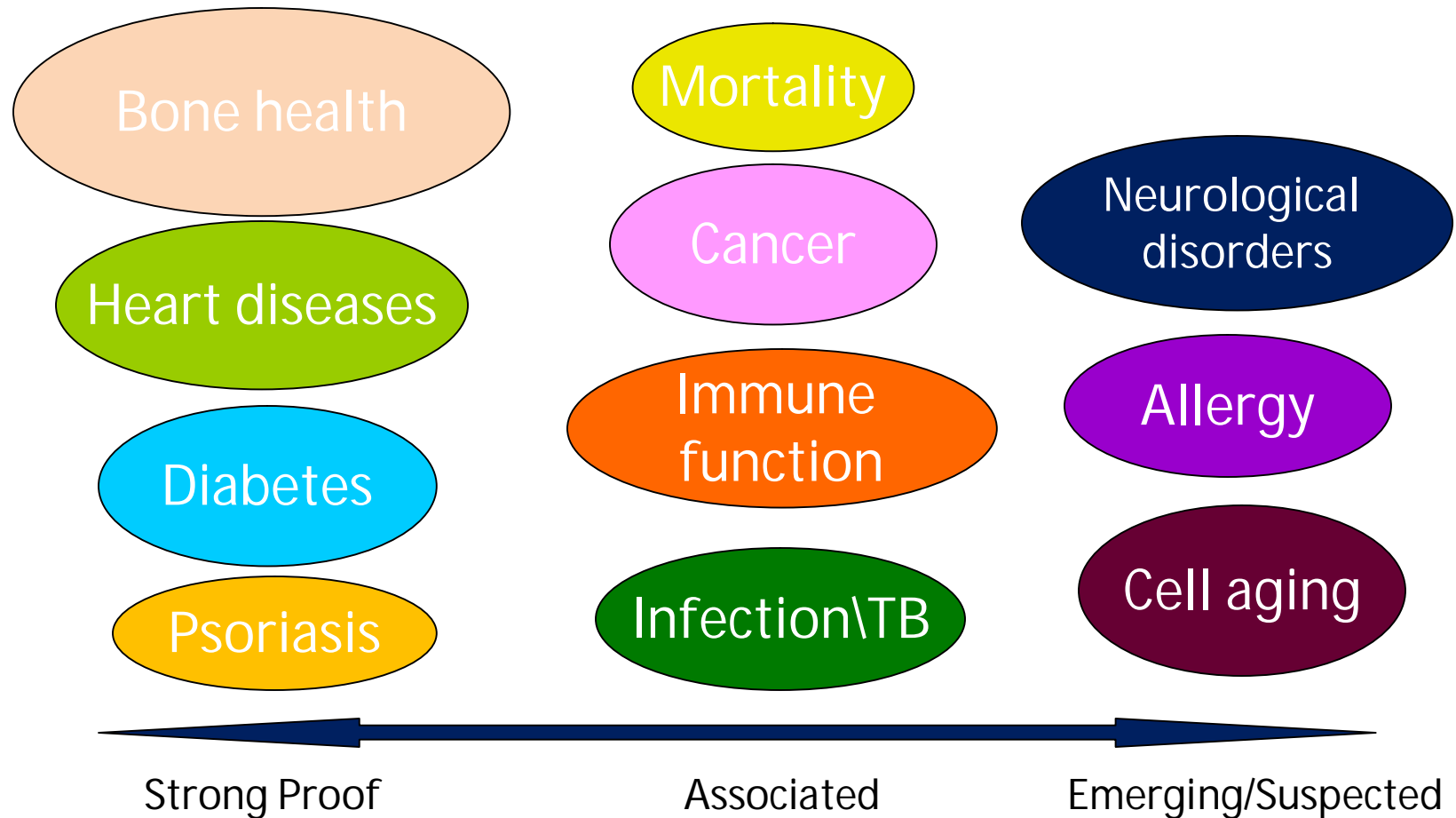
Bangladeshi children with rickets (left), and prevention and cure for rickets with cod-liver oil or with sun-rays (right)



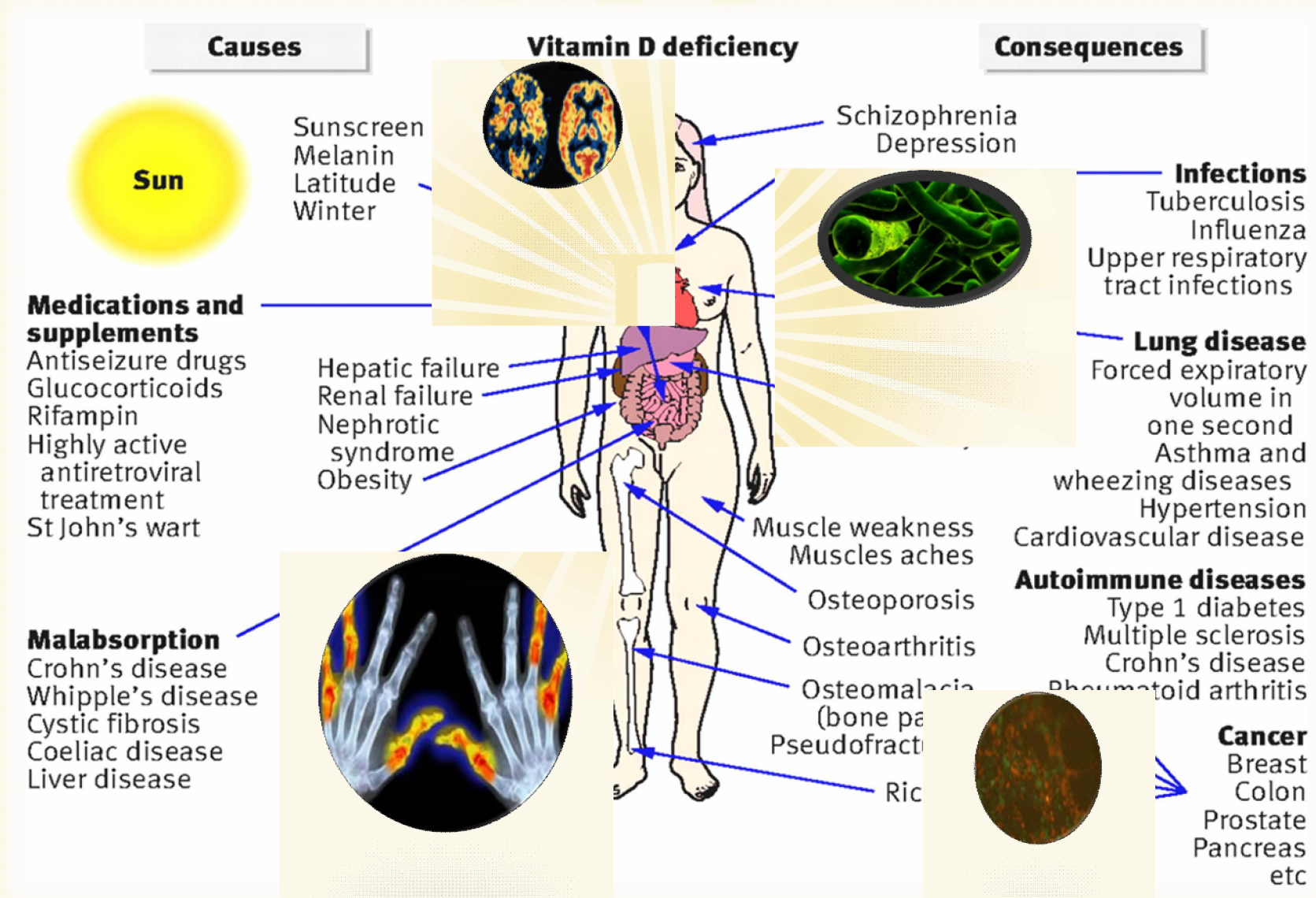
The sun itself is the best remedy

World Nutrition Volume 2, Number 7, August 2011
Journal of the World Public Health Nutrition Association

Why Vitamin D Has Become So Important ?

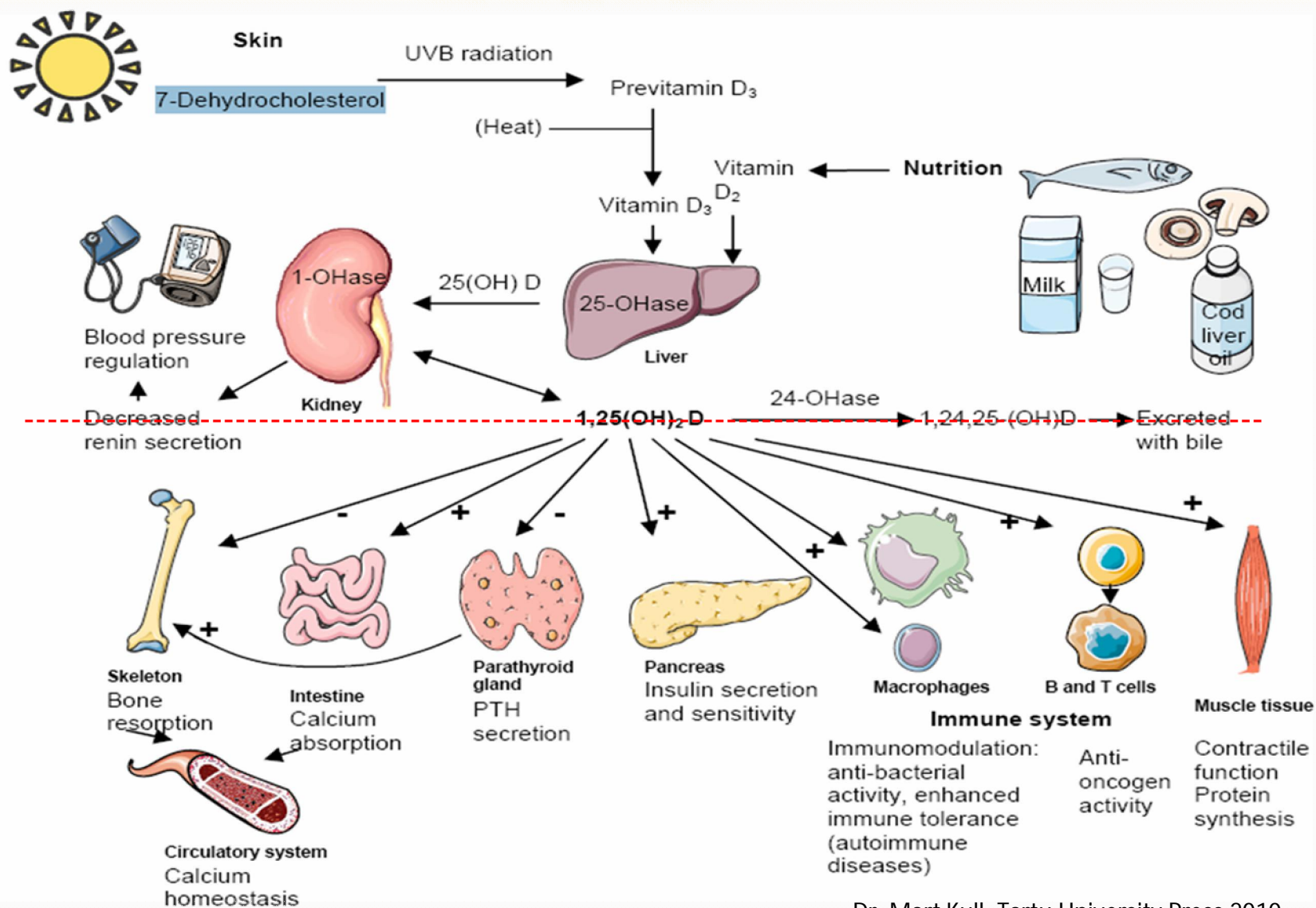


Causes And Consequences Of Vitamin D Deficiency

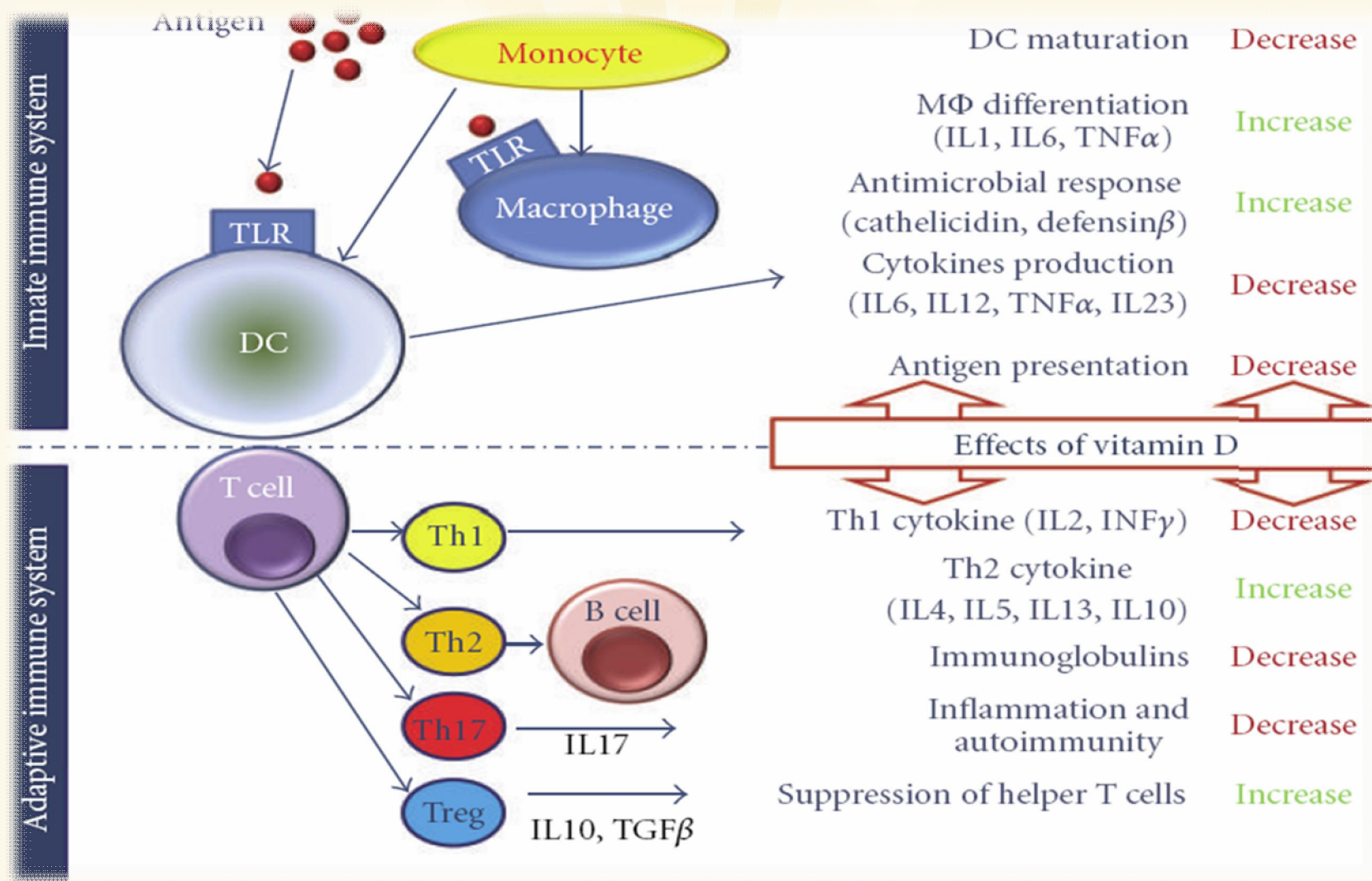


Holick MF, Nature Rev Endocrinol 7: 73-75 (2011)

Vitamin D Metabolism And Its Effect On Different Organ Systems

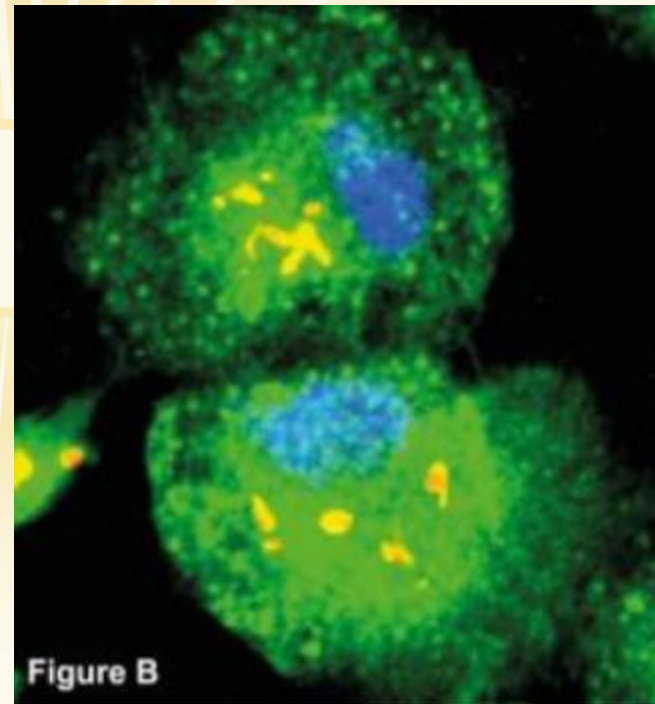
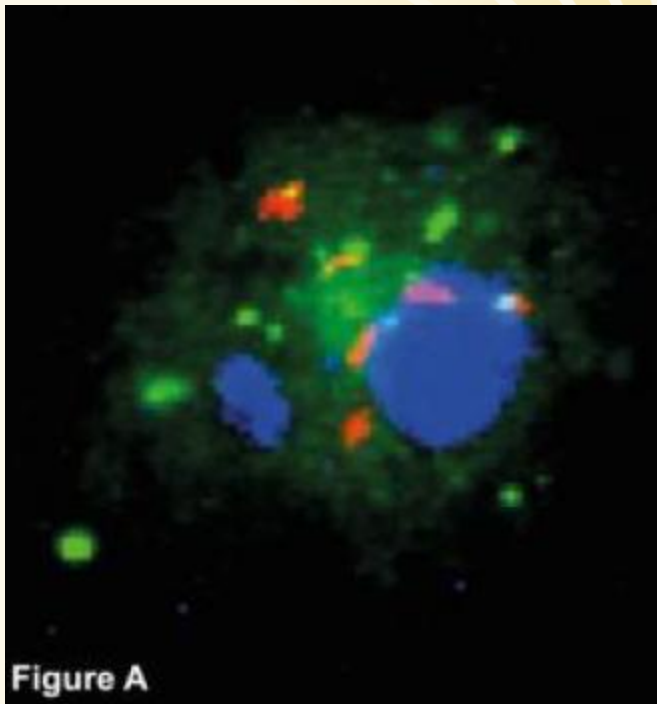


Effects of vitamin D: innate and adaptive immune responses to an antigenic challenge and the influence of vitamin D



Vitamin D Is Crucial In Human Immune Response To Tuberculosis

tuberculosis is estimated to cause 1.8 million deaths annually



<http://medicalxpress.com/news/2011-10-scientists-vitamin-d-crucial-human.html>

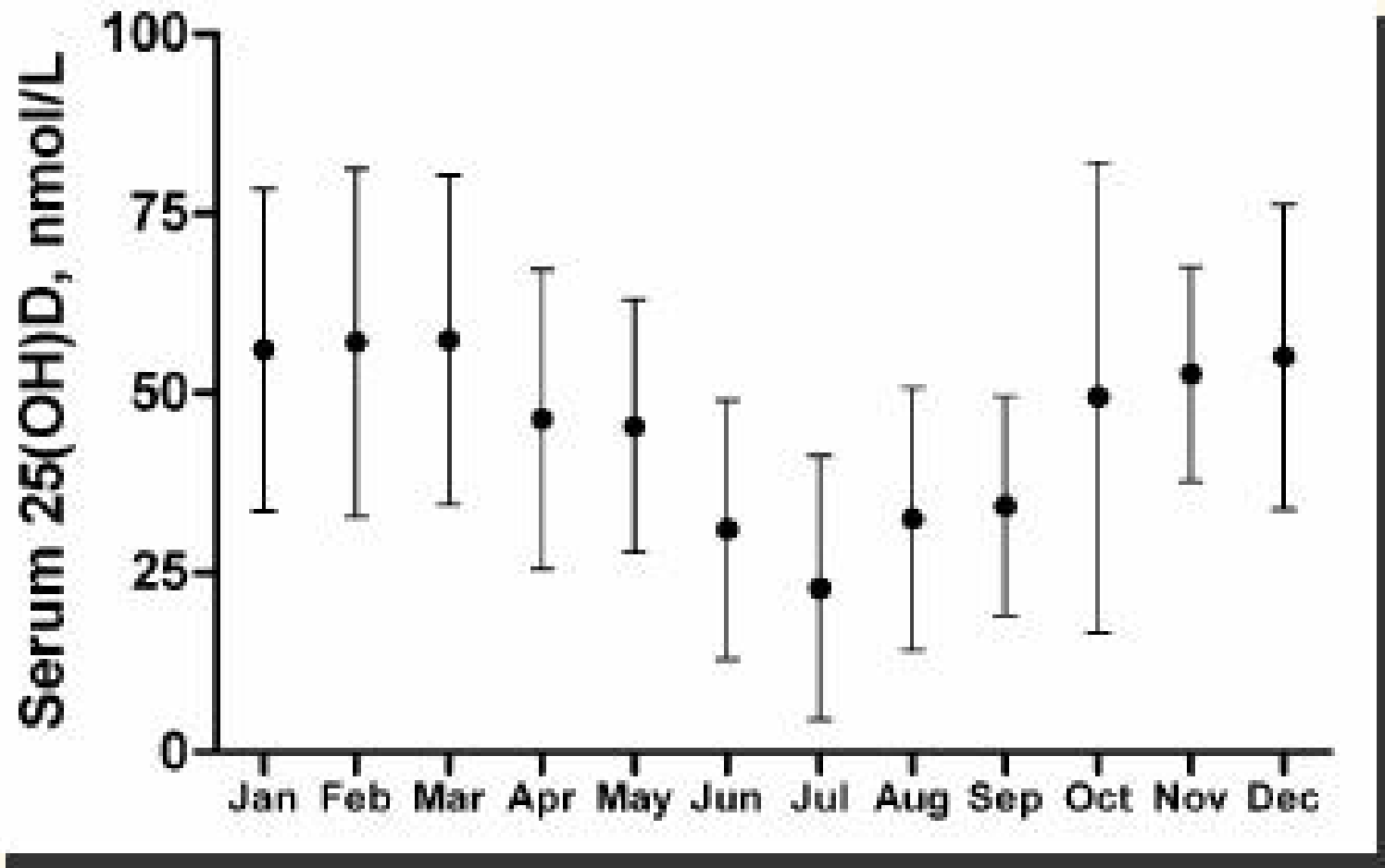
Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa

Martineau et al. *PNAS* November 22, 2011 vol. 108 no. 47 19013-19017

Populations Studied

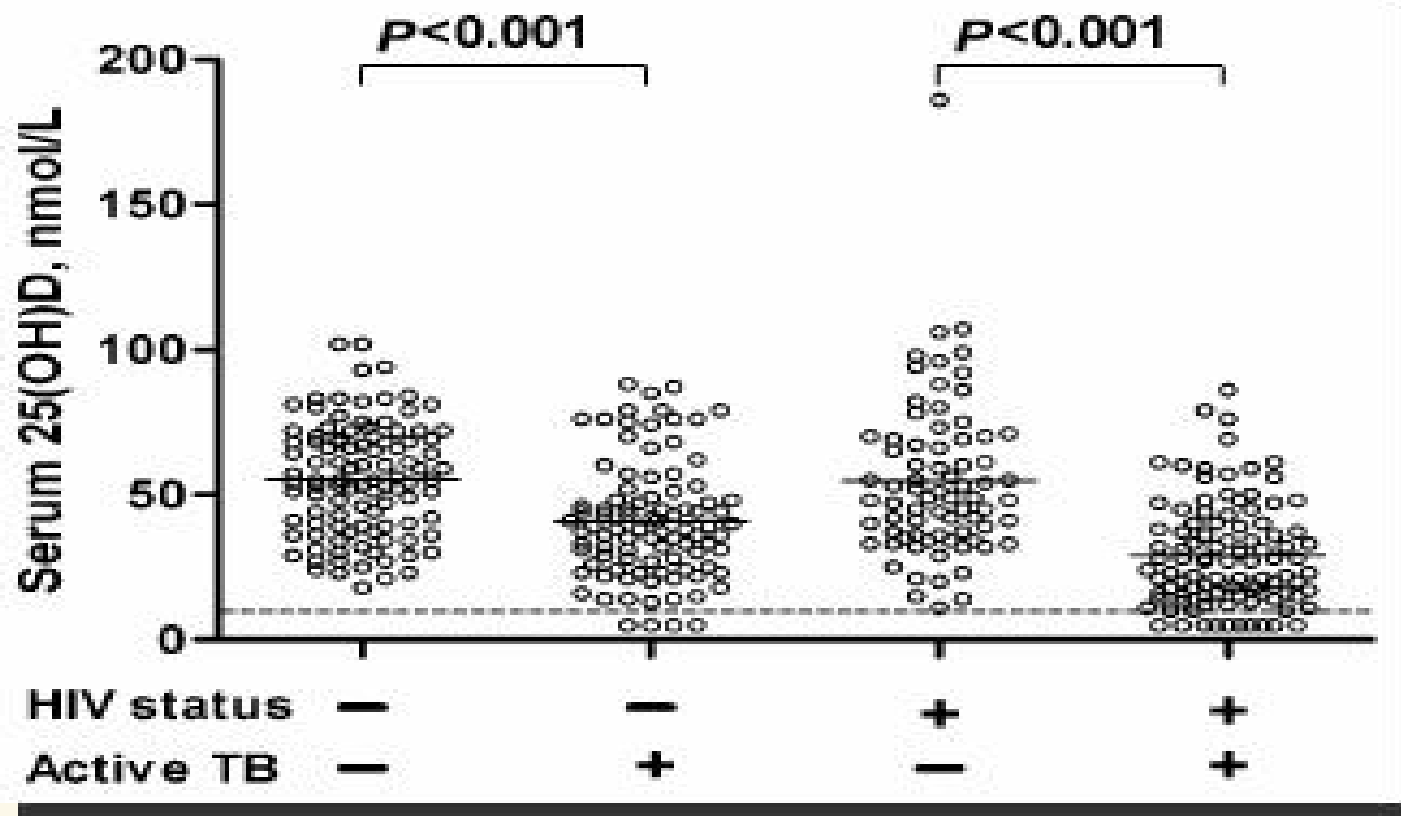
- ❖ 370 participants were recruited to the study between April 2005 and January 2010
- ❖ Of these, 103 were HIV-seronegative and had latent TB infection
- ❖ 93 were HIV-seronegative and had active TB
- ❖ 75 were HIV-seropositive and had latent TB infection
- ❖ 99 were HIV-seropositive and had active TB
- ❖ 4 of 174 HIV-seropositive participants were taking antiretroviral therapy at the time of recruitment to the study

Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa



Seasonal variation in mean serum 25(OH)D concentration, all study participants (n = 370). Error bars indicate SD. Martineau et al. *PNAS* November 22, 2011 vol. 108 no. 47 19013-19017

Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa



Serum 25(OH)D concentration by HIV and TB status. Bars represent means. Dashed line represents limit of detection (10 nmol/L)



Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa.

Martineau et al. *PNAS* November 22, 2011 vol. 108 no. 47 19013-19017

- ❖ Vitamin D deficiency is highly prevalent among black Africans in Cape Town (LC-MS/MS)
- ❖ D-deficiency is associated with susceptibility to active TB both in the presence and absence of HIV infection

Worsening severity of vitamin D deficiency is associated with increased length of stay, surgical intensive care unit cost, and mortality rate in surgical Intensive care patients

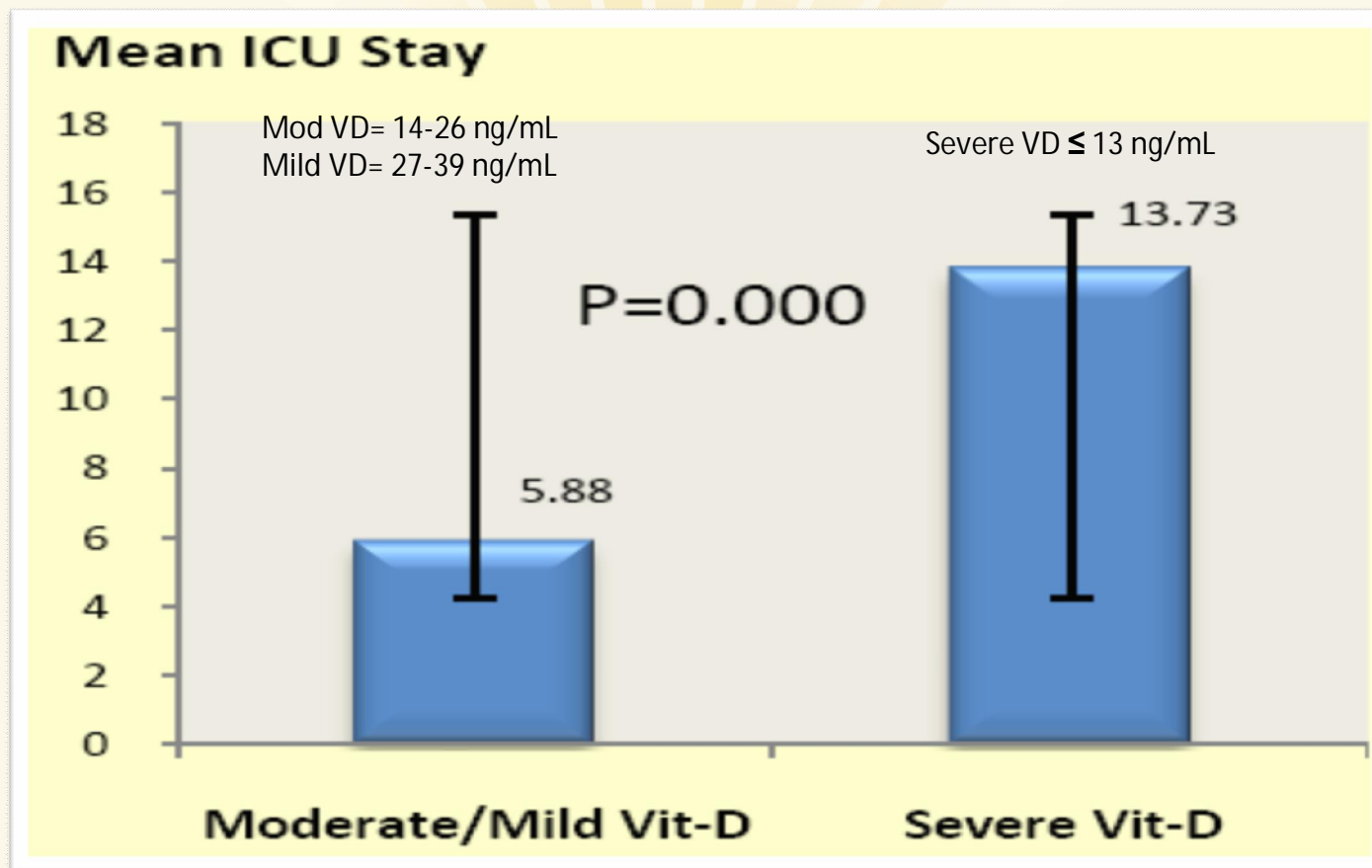
Table 2 Baseline population characteristics

Characteristics	Frequency, n	Percentage
Men	181	70.2
Women	77	29.8
African American	148	57.6
Non-African American	109	42.4
Severe vitamin D deficiency (≤ 13 ng/mL)	138	53.5
Moderate vitamin D deficiency (14–26 ng/mL)	96	37.2
Mild vitamin D deficiency (27–39 ng/mL)	18	7.0
Normal vitamin D level (≥ 40 ng/mL)	3	1.2
Trauma	206	79.8
Intubated	85	32.9
Pneumonia	52	20.2
Comorbidity	44	17.1
Mortality	28	10.9

Matthews LR et al. 2012; Amer J Surgery (in press)

Severe Vitamin D deficiency, length of stay and cost of surgical intensive care patients with ventilated-associated pneumonia

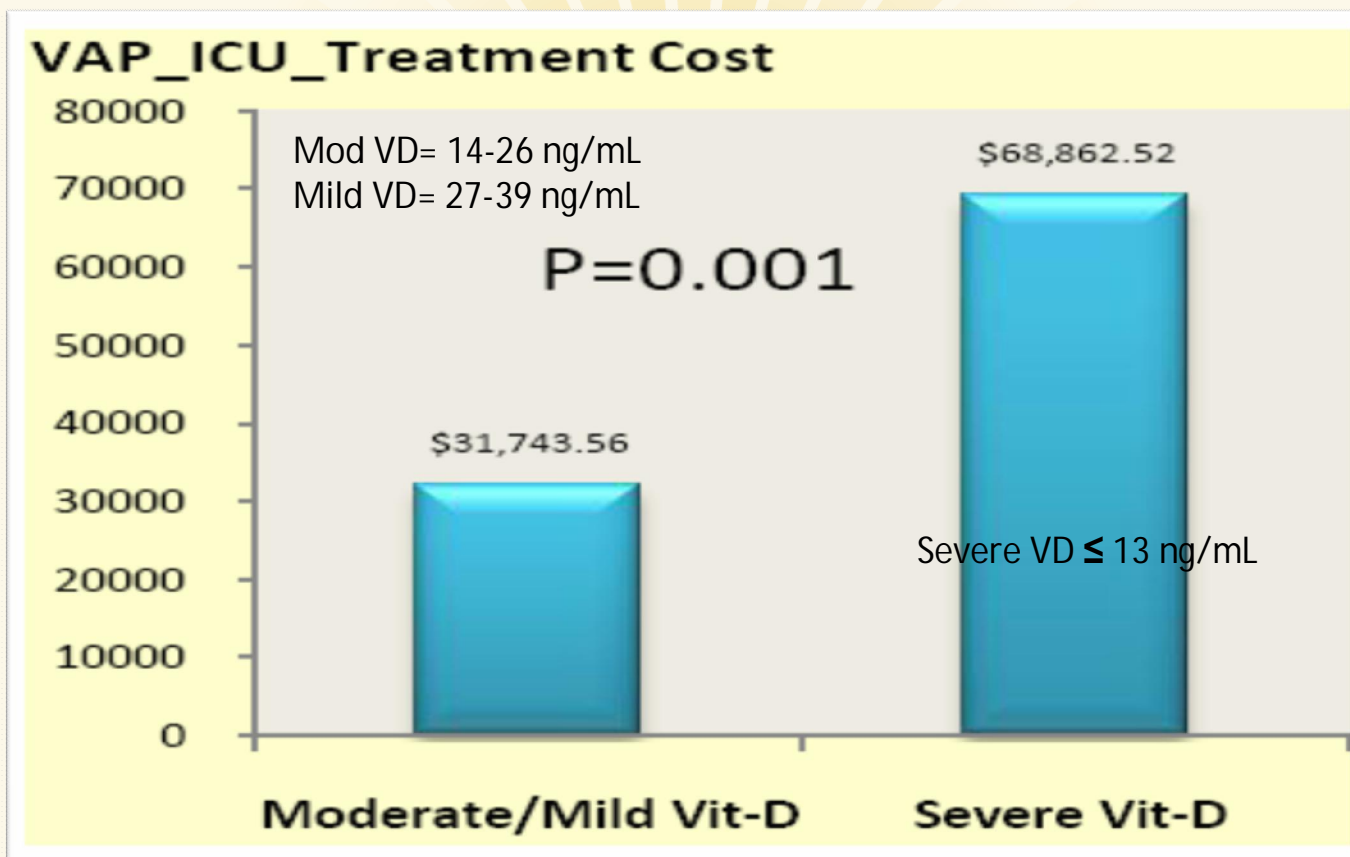
Matthews LR et al. 2012; Amer J Surgery (in press)



Vitamin-D status on 191 patients admitted to the SICU between August 2009 and August 2010

Severe Vitamin D deficiency , length of stay and cost of surgical intensive care patients with ventilated-associated pneumonia

Matthews LR et al. 2012; Amer J Surgery (in press)

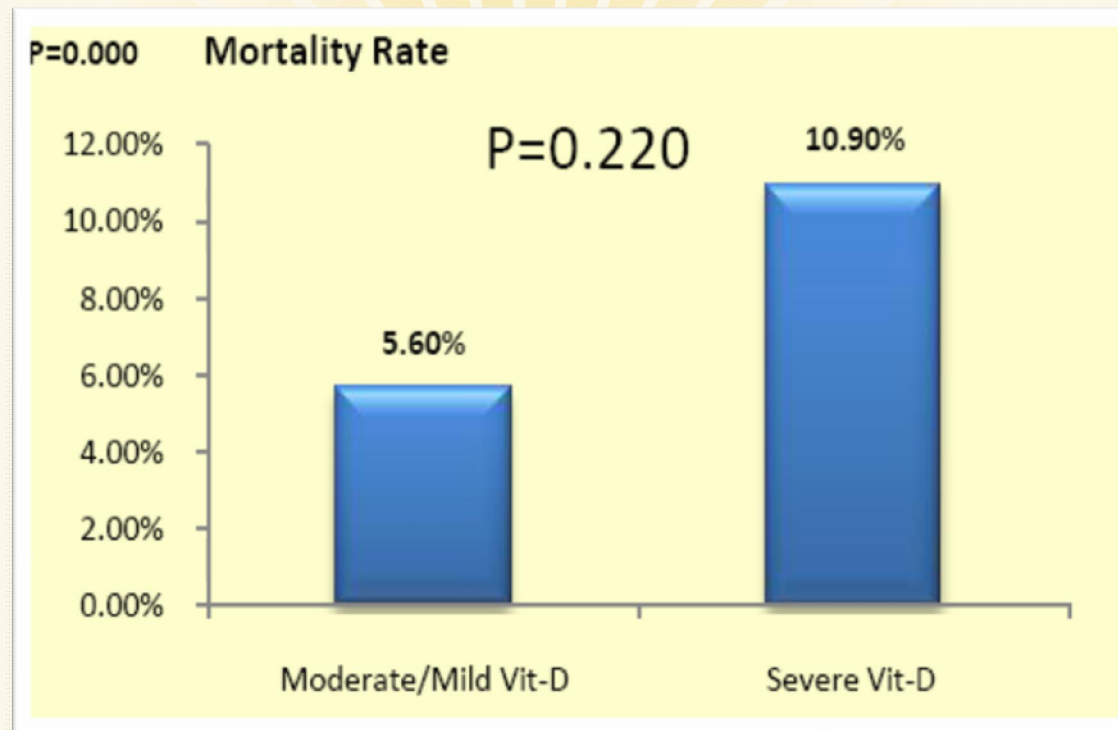


December 2010, Supplemental Critical Care Medicine Journal
American Journal of Surgery 2012



Severe Vitamin D deficiency , length of stay and cost of surgical intensive care patients with ventilated-associated pneumonia

Matthews LR et al. 2012; Amer J Surgery (in press)



December 2010, Supplemental Critical Care Medicine Journal
American Journal of Surgery 2012



Matthews LR et al.2012; Amer J Surgery (in press)

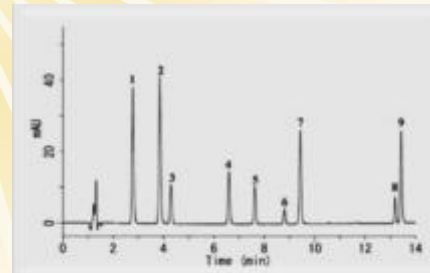
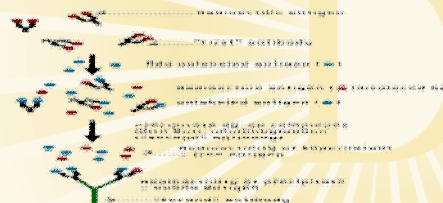
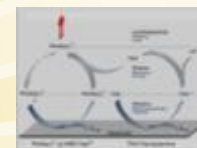
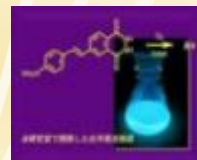
- ❖ Severe vitamin-D deficiency increases VAP-incidence, LOS, and total hospital costs in SICU patients
- ❖ Therefore, Vitamin D deficiency should be corrected in critically-ill SICU patients expeditiously

The following is a list of illnesses and diseases that either occur more frequently in people who are vitamin D deficient, or that occur less frequently in people on a vitamin D3 supplement regimen

- 
- ❖ Breast Cancer
 - ❖ Skin Cancer
 - ❖ Prostate Cancer
 - ❖ ADHD
 - ❖ Alzheimer's
 - ❖ Autism
 - ❖ Multiple Sclerosis
 - ❖ Allergies
 - ❖ Parkinson's Disease
 - ❖ Depression
 - ❖ AIDS
 - ❖ Fibromyalgia
 - ❖ Rickets
 - ❖ Influenza
 - ❖ H1N1 Flu
 - ❖ Various Autoimmune Disorders
 - ❖ Osteoporosis
 - ❖ Lung Transplant Rejection
 - ❖ Asthma
 - ❖ Childhood Obesity
 - ❖ Chronic Pain
 - ❖ Tooth Loss
 - ❖ Gingivitis
 - ❖ Type 1 & Type 2 Diabetes
 - ❖ Arterial Stiffness
 - ❖ Metabolic Syndrome
 - ❖ Heart Disease
 - ❖ High Blood Pressure (Hypertension)
 - ❖ Chronic Fatigue Syndrome
 - ❖ Lupus
 - ❖ Psoriatic Arthritis

Methodologies

- ❖ Chemiluminescence
- ❖ Electrochemiluminescence
- ❖ RIA
- ❖ HPLC
- ❖ LC-MS/MS
- ❖ ELISA



Vitamin D Reference Ranges

25(OH)D (nmol/L)	Vitamin D status
< 50	Deficiency
50- 74*	Insufficiency
75 – 200	Sufficiency
> 250	Toxicity

25(OH)D or 125(OH)2D

- ❖ 25 (OH)D is the main storage form in the human body
- ❖ 25 (OH)D is the main Vitamin D metabolite circulating in the serum/plasma
- ❖ 25(OH)D is approximately 1000 fold greater than the circulating 1,25 (OH)2D
- ❖ 25 (OH)D half life is 2-3 weeks while 1,25 (OH)2D half life is only 4-6 hours



Frequency of 25(OH)D Testing

- ❖ At least once a year if patient is on supplement, monitor 25(OH)D levels approximate every three months until results in the optimal range
- ❖ If the patient is on high doses (10,000 IU/day then Ca, PO₄, and PTH levels must be checked every 3 months



Vitamin D Deficiency Testing

ICD-9 Codes that Support Medical Necessity for D-deficiency
ICD-9 codes must be coded to the highest level of specificity

585.3	CHRONIC KIDNEY DISEASE, STAGE III (MODERATE)
585.4	CHRONIC KIDNEY DISEASE, STAGE IV (SEVERE)
268.9	UNSPECIFIED VITAMIN D DEFICIENCY
268.0	RICKETS , ACTIVE
268.2	OSTEOMALACIA UNSPECIFIED
585.5	CHRONIC KIDNEY DISEASE, STAGE V
585.6	END STAGE RENAL DISEASE
588.81	SECONDARY HYPERPARATHYROIDISM (OF RENAL ORIGIN)
756.51	OSTEOGENESIS IMPERFECTA
756.52	OSTEOPETROSIS
V45.86	BARIATRIC SURGERY STATUS

All the above recommended codes are billable medical codes that can be used to specify a diagnosis on a reimbursement claim

Recently Sales Of Vitamin D In The U.S. Have Risen Dramatically



25(OH)D Status In The Middle East

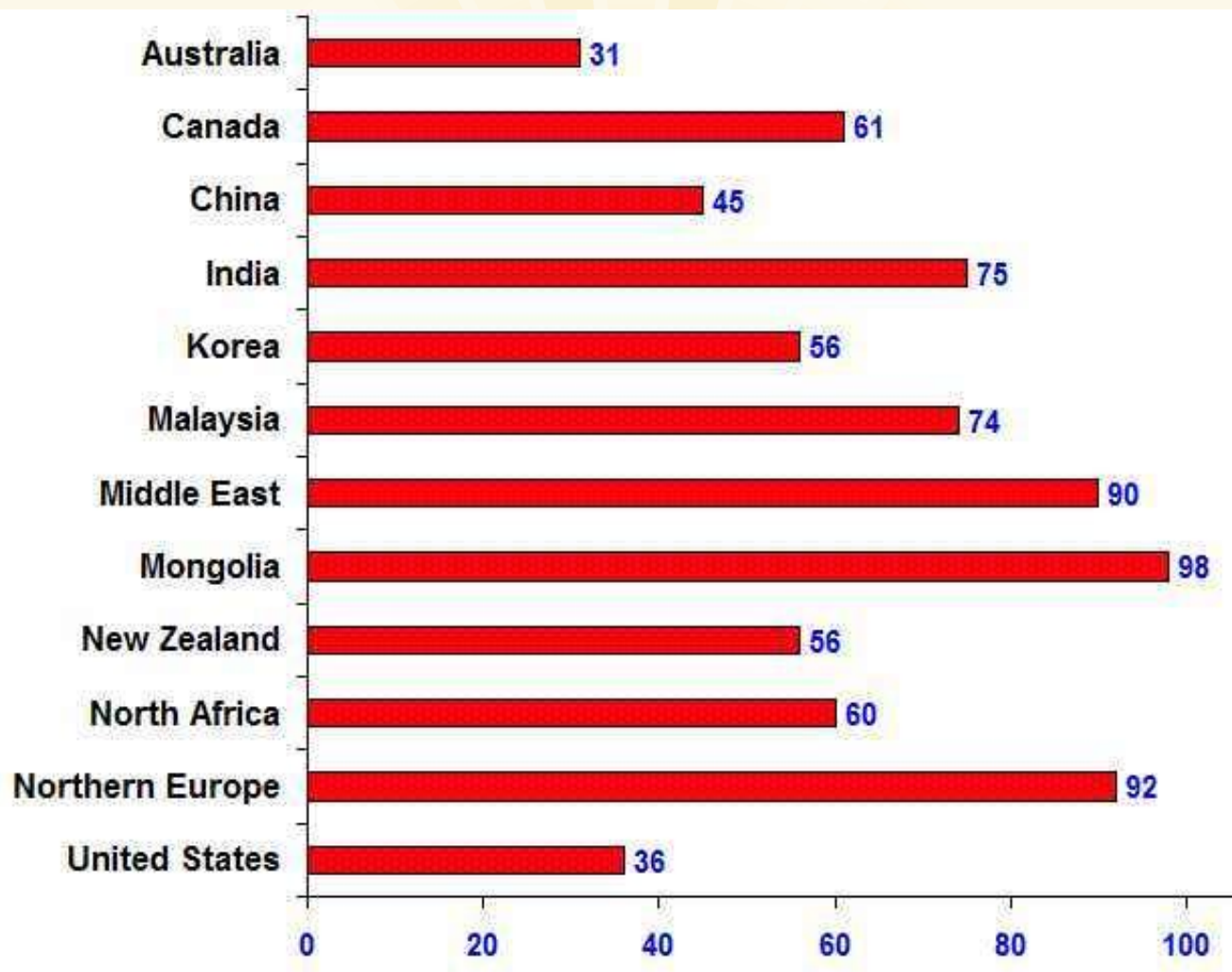
- ❖ 80% of adolescent girls in Saudi Arabia had 25 (OH) D levels <7 ng/ml. [Bahijri \(2011\) Saudi Med.J 22:973-79](#)
- ❖ 81% of Middle East post menopausal women tested for osteoporosis have inadequate vitamin D levels. [Arabi et al. \(2006\) Bone 39:268-75](#)
- ❖ 82% of UAE infants were found with <25 nmol/L of Vitamin D. [Dawodu A et al. \(2006\) Emirates Med J 2429-35.35](#)
- ❖ 90% of UAE population tested Vitamin D deficient when recorded on the 1st visit. [Haq, A., J. Rajah and L.O. Abdel-Wareth, 2009. Middle East Lab., 12: 6-10](#)
- ❖ >90% of UAE students at Abu Dhabi were found D-deficient . [Al Anouti F ; Thomas J, Abdel-Wareth L, Rajah, J, Grant W and Haq A \(2011\) Dermato-Endocrinology 3:3, 1-5](#)
- ❖ 68% Qatari children were deficient in Vitamin D (≤ 20 ng/mL). [Bener A et al. Int Arch Allergy Immunol 2012; 157:1 68-175](#)



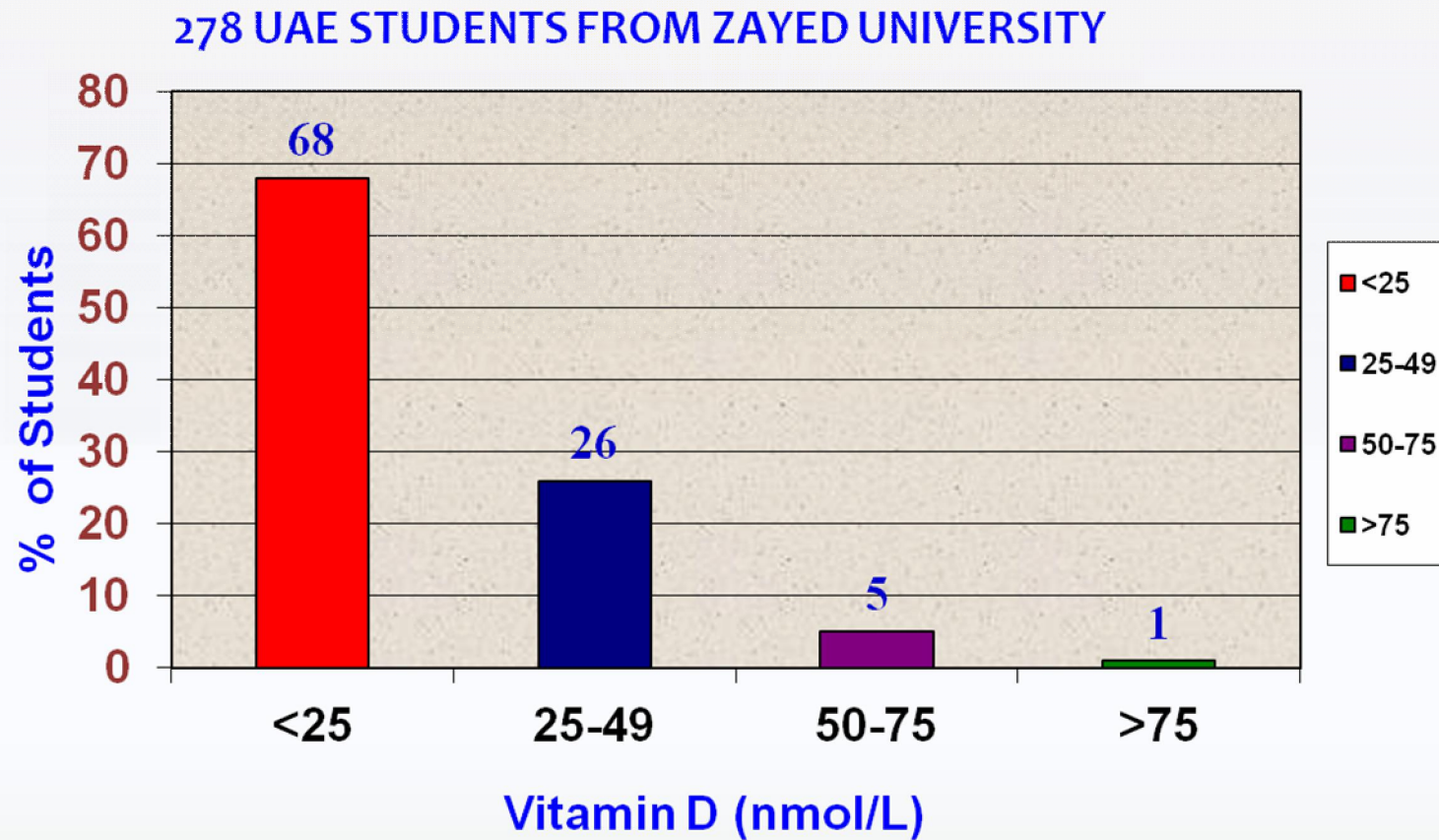
Reasons for Vitamin D Deficiency

- ❖ Air conditioning - to avoid the hot sun ME
 - ❖ Increased use of multi-media indoors
 - ❖ More indoor jobs - more office workers, fewer farmers ME
 - ❖ Living in cities more ME
 - ❖ Want whiter skin - especially women ME
 - ❖ Fear skin cancer
 - ❖ Cholesterol reduced
 - ❖ More Obesity
 - ❖ No vitamin D fortification policy is in place of food and drinks ME
 - ❖ Meat from factory farms
 - ❖ Some drugs consume or block vitamin D
 - ❖ increased use of polyunsaturated fats
 - ❖ More glass windows which appear to destroy vitamin D
- Other than sun
- ❖ More Seniors
 - ❖ Excessive clothing (burka) ME
- Note: Women in ME have much less vitamin D than men
- ❖ Have a condition which Prevents Adsorption in the gut
 - ❖ Have a condition which Prevents Conversion to active form
 - ❖ Have a condition which requires more vitamin D
 - ❖ Lactose Intolerance or Vegan
 - ❖ Health reasons to avoid sun
 - ❖ Work long hours or night shift
 - ❖ Live far from equator NOT ME
 - ❖ DDT in bodies reduce the vitamin D
 - ❖ Myths about vitamin D
 - ❖ Dark Skin ME
 - ❖ Use [vitamin D2](#) so as to avoid both Vitamin D3 made from wool and gelatin-caps
 - ❖ which is typically made from animals ME Note: D2 has been known to have less benefit than D3

Global Vitamin D Status



Vitamin D Status In The UAE



Baseline Characteristics Of Female Students In summer And Winter

Al Anouti et al. Dermato-Endocrinology (2011) 3:3, 1-5

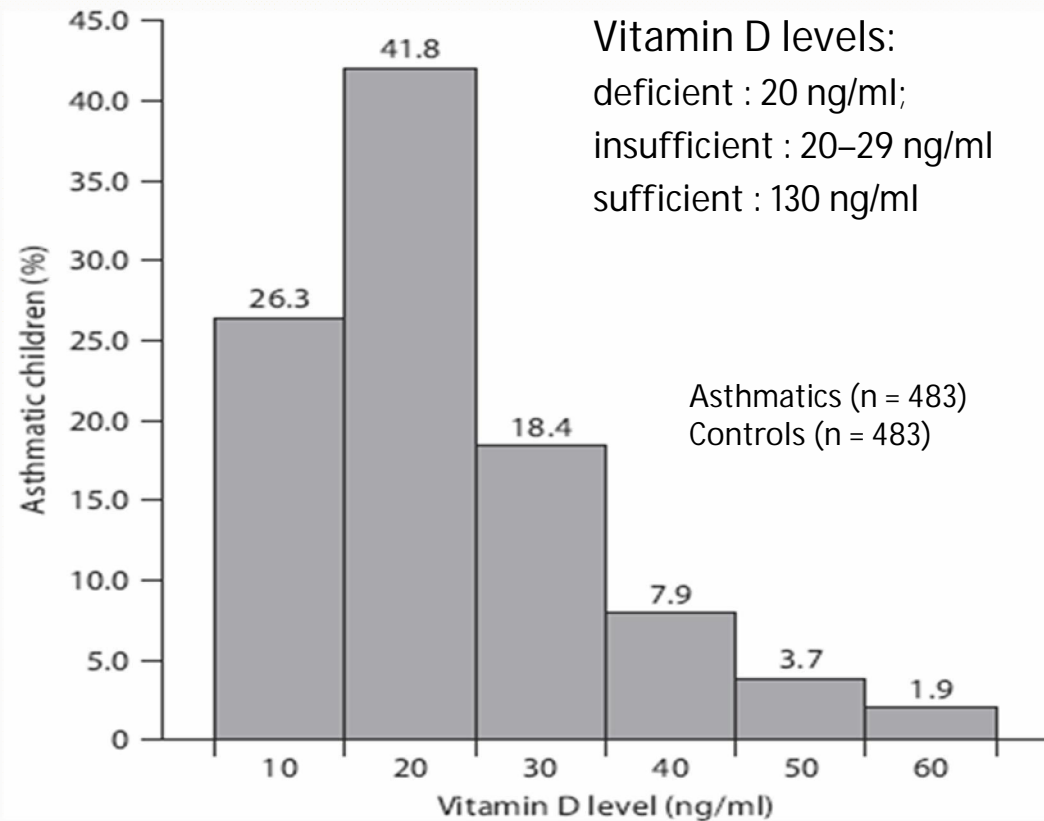
Characteristics	Females (summer) (n = 138)	Females (winter) (n = 70)	t-test 95% Confidence Interval of the Difference
Age (years)	21.1 ± 4.6	20.3 ± 1.9	0.106
BMI (kg/m ²)	22.6 ± 4.6	24.4 ± 5.6	0.30
25(OH)D(nmol/L)	20.9 ± 14.9	31.3 ± 12.3	0.0005*
SAI score	41.4 ± 7.4	35.1 ± 5.4	0.000*
FFQ score	13.2 ± 5.4	11.0 ± 3.2	0.06

* Differences are significant; p<0.05. All values are shown as mean ± SD., BMI, body mass index; SAI, sun avoidance inventory; FFQ, food frequency questionnaire.

Vitamin D Deficiency As A Strong Predictor Of Asthma In Children

Bener A et al. Int Arch Allergy Immunol 2012;157:168–175

The prevalence of asthma in Saudi Arabia (26.5%), Kuwait (16.8%) and in the UAE (13.6%) appears to be similar to that of industrialized or Western countries



Distribution of serum vitamin D in Qatari children with asthma

Al-Jabir, 20/10/2011

Baseline serum laboratory parameters among the studied asthmatic and control children

Laboratory parameter	Asthmatics (n = 483)	Controls (n = 483)	t test	p
Serum vitamin D, ng/ml	17.2 ± 11.0	26.8 ± 9.9	-8.719	<0.001
Calcium, mmol/l	2.4 ± 0.15	2.4 ± 0.14	0.9089	0.364
Phosphorus, mmol/l	1.56 ± 0.3	1.65 ± 0.3	-4.572	<0.001
Alkaline phosphatase, U/l	258.8 ± 38.4	229.3 ± 34.7	3.511	<0.001
Magnesium, mmol/l	0.77 ± 0.13	0.82 ± 0.11	-3.440	0.001
Creatinine, μmol/l	46.7 ± 13.4	48.2 ± 2.1	-0.658	0.511
Parathyroid hormone, mmol/l	44.4 ± 5.1	46.6 ± 4.1	-0.345	0.733
Log ₁₀ IgE	2.0 ± 0.7	1.7 ± 0.6	5.369	<0.001

Results are expressed as means ± SD.

Vitamin D Deficiency As A Strong Predictor Of Asthma In Children

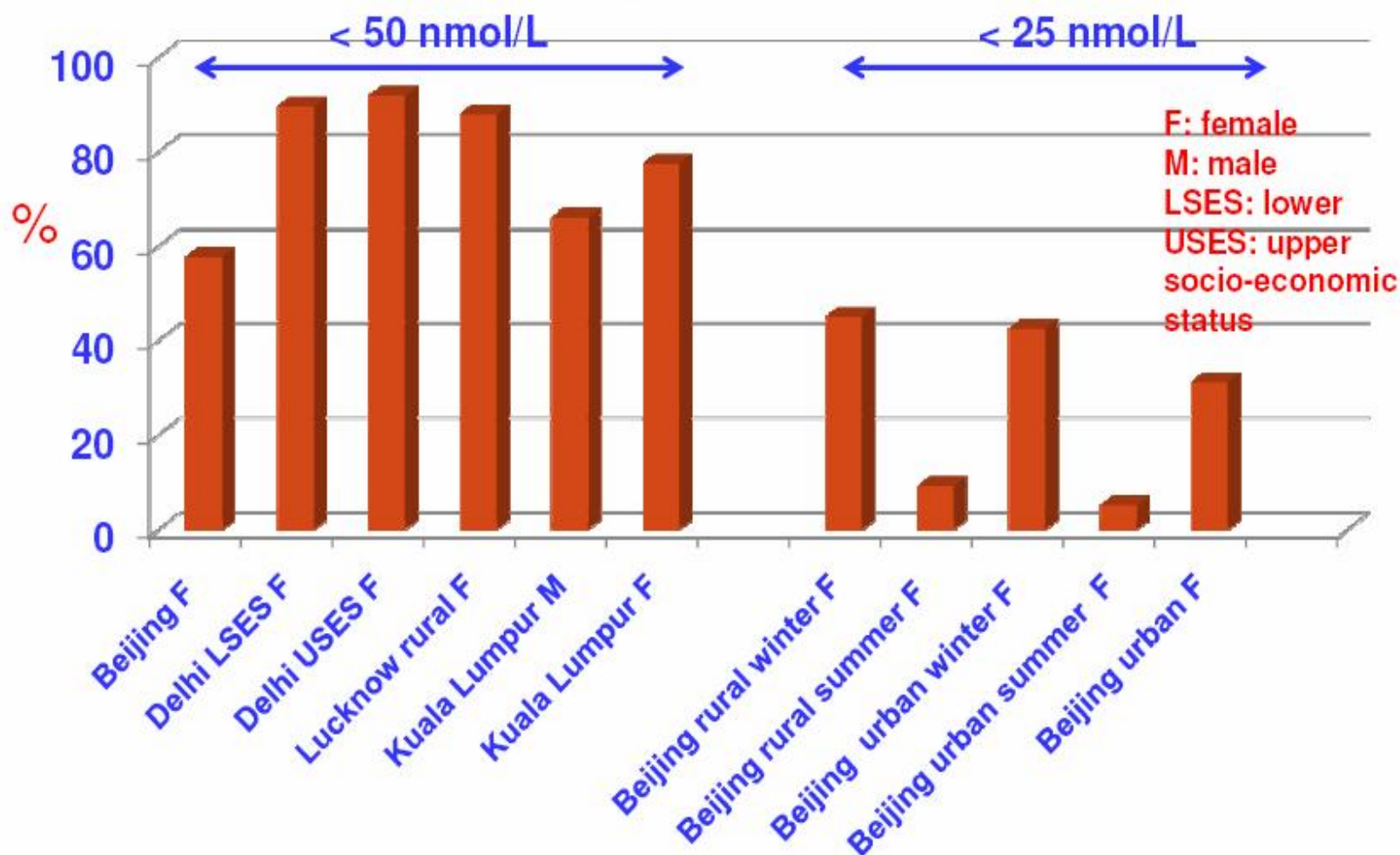
Bener A et al. Int Arch Allergy Immunol 2012;157:168–175

- ❖ The study revealed that a high proportion of Qatari children were deficient in vitamin D (26.3% = 10 ng/mL & 41.8% = 20 ng/mL)
- ❖ This deficiency was more frequent in children suffering from asthma compared to non-asthmatic controls (17.2 ng/mL Vs 26.8 nmol/mL)
- ❖ Vitamin D deficiency was the strongest predictor of asthma (stronger than familial history of asthma or serum IgE levels)

Why The Problem Is So High In The Middle East?

- ❖ Very hot climate
- ❖ Life style (decreased outdoor activities)
- ❖ Skin color
- ❖ Pollution
- ❖ Dress code (clothing-abaya/burqa)
- ❖ Lack of Authorities regulations for vitamin D fortification of food and drinks
- ❖ Prolonged breast feeding without Vitamin D supplementation
- ❖ Lack of population based studies

Prevalence of sub-optimal vitamin D status in children aged 10-18 years in Asia





Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/L

The Maasai

- ❖ Semi-nomadic lifestyle.
- ❖ They wear sparse clothes, which mainly cover their upper legs and upper body
- ❖ They eat mainly meat and milk from their cattles
- ❖ Their mean 25(OH)D level was (120 nmol/L)

The Hadzabe

- ❖ Traditional hunter-gatherers.
- ❖ Their diet consists of meat, occasional fish, honey and fruits.
- ❖ They wear fewer clothes than the Maasai i.e. nothing above the waist
- ❖ Their mean 25(OH)D was (110 nmol/L)

Thus, if mean natural levels are around (115 nmol/L) keeping your level around (125- 137 nmol/L)(keeps you within what both the Maasai and the Hadzabe are telling us)

Luxwolda et al. British Journal of Nutrition, 23 January, 2012

Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/L

Luxwolda et al. British Journal of Nutrition, 23 January, 2012

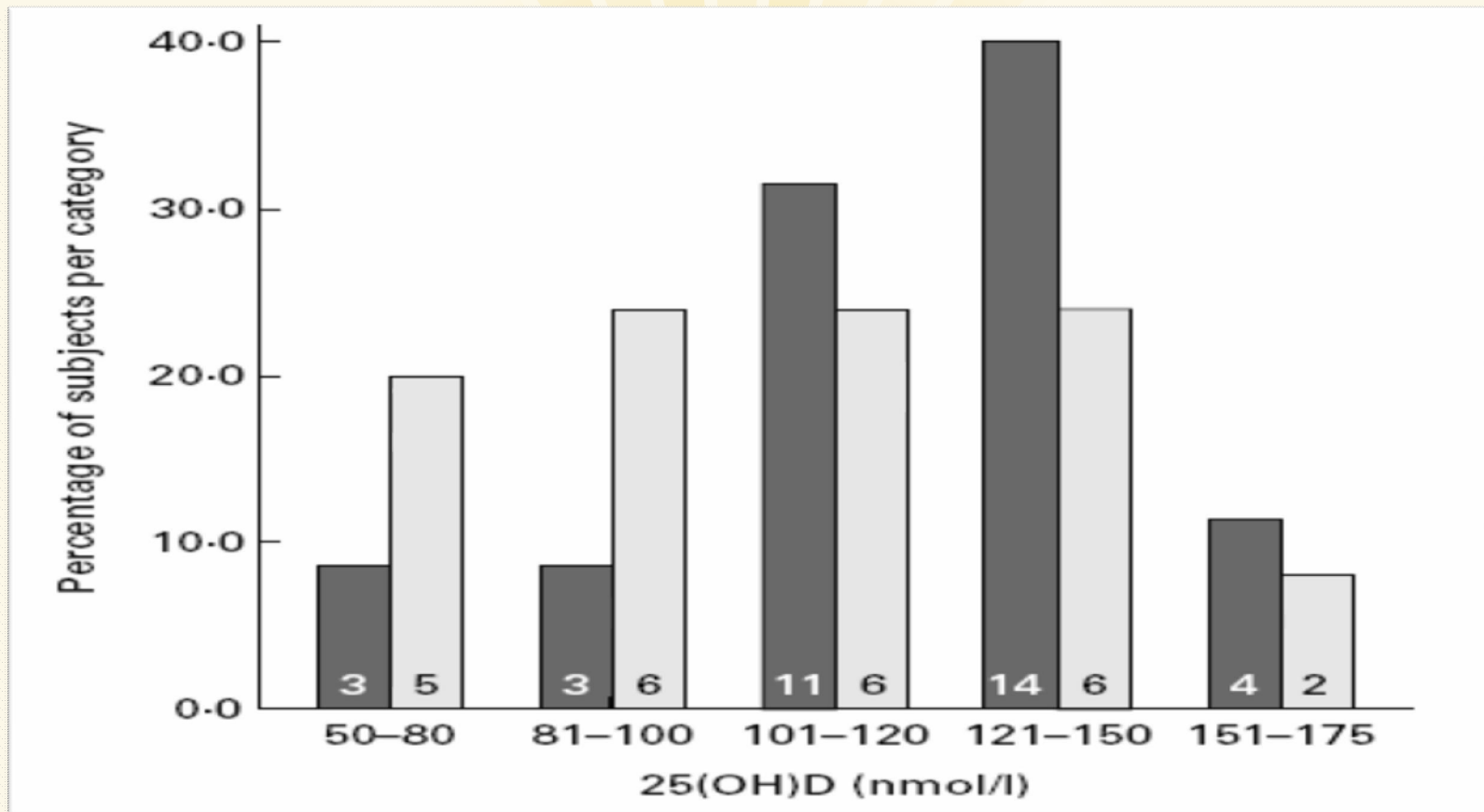


Fig. 1. Serum 25-hydroxyvitamin D (25(OH)D) frequency distributions for Maasai (■) and Hadzabe (□). The numbers in the bars refer to the absolute number of subjects.

Traditionally Living Populations In East Africa

The Masai tribe



Mean 25(OH)D = 120 nmol/L

The Hadzabe tribe



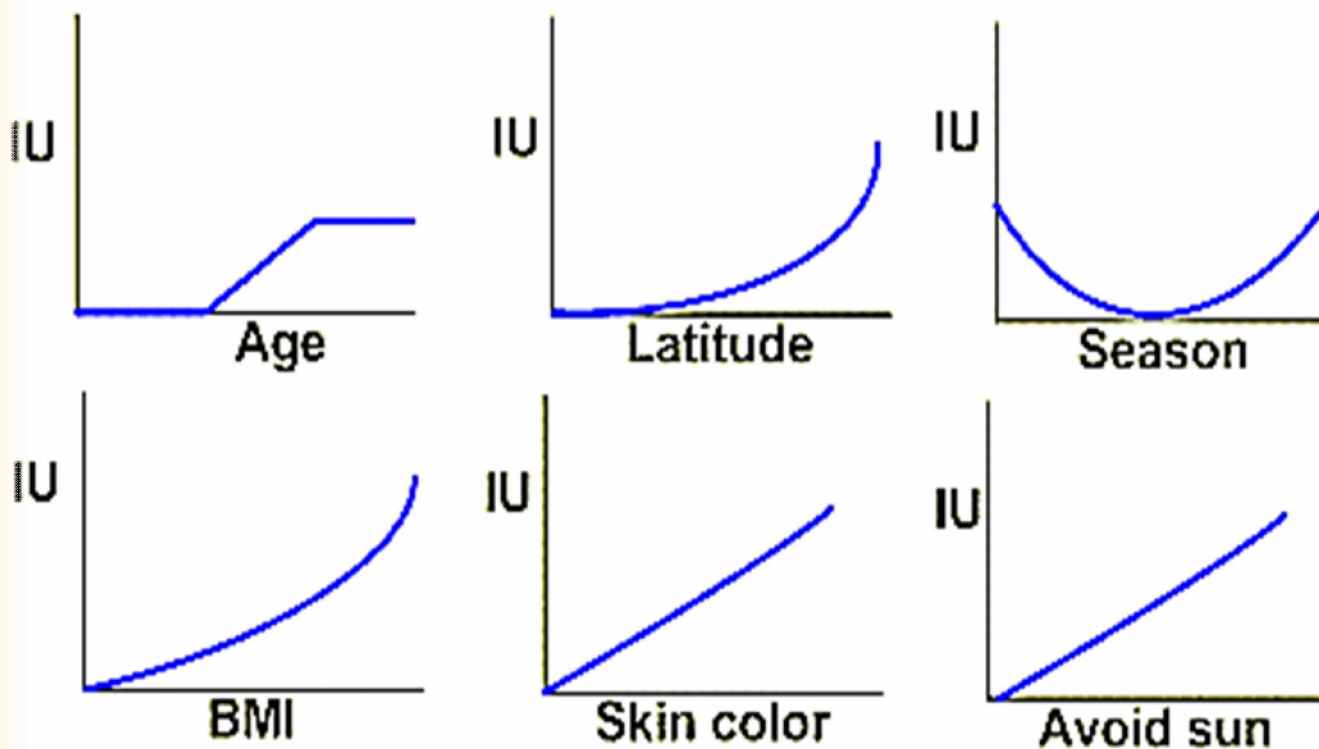
Mean 25(OH)D = 110 nmol/L

If the mean natural levels are around (115 nmol/L) keeping your level around (125- 137 nmol/L)
(keeps you within what both the Maasai and the Hadzabe are telling us)

Luxwolda et al. British Journal of Nutrition, 23 January, 2012

Need To Add Vitamin D For Each Of The Following Reasons:

Healthy People need to add vitamin D



Is Vitamin D Toxic. ?..

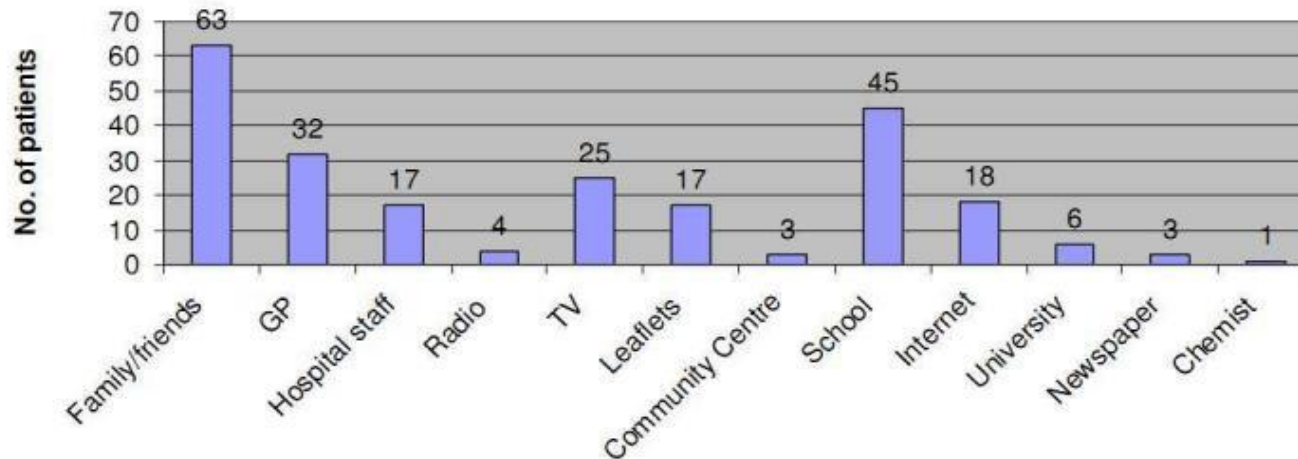
- ❖ Excessive exposure to sunlight does not lead to overproduction of vitamin D.
- ❖ Supplemental vitamin D in certain clinical settings may have toxicity.
- ❖ No case of hypercalcemia with doses < 10,000 IU daily.
- ❖ Symptoms are largely hypercalcaemia, high blood pressure, headache, fatigue, loss of appetite, excessive thirst and polyurea, severe itching, vomiting, diarrhoea, constipation, kidney damage, joints and muscle pain.

Groups @ Risk

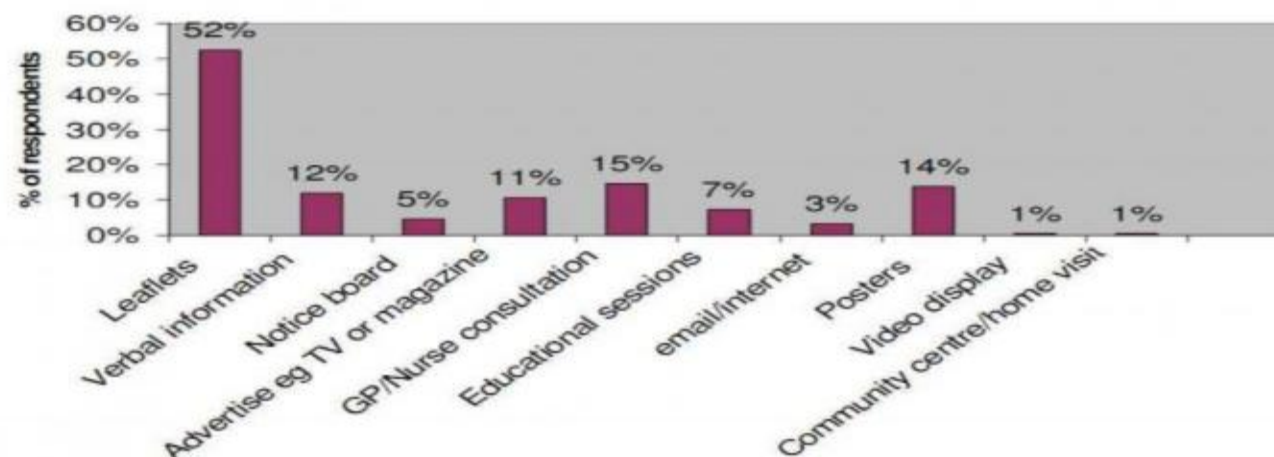
- ❖ **Infants**
- ❖ **Elderly**
- ❖ **Dark skinned (Africans)**
- ❖ **Covered women (Abaya/Burqa)**
- ❖ **Kidney failure patients**
- ❖ **Patients with chronic liver disease**
- ❖ **Fat malabsorption disorders**
- ❖ **Genetic types of rickets**
- ❖ **Patients on anticonvulsant drugs**

A program of targeted education of the at-risk population is recommended

Sources of information about vitamin D



Suggested ways of promoting awareness





Take Home Messages

- ❖ Since we are experiencing a global epidemic of vitamin D insufficiency, it is imperative that all individuals be encouraged to obtain vitamin D from either sunlight or supplementation or through fortification
- ❖ All age-groups require optimal levels of vitamin D to support physiologic functions that are dependent on circulating 25(OH)D
- ❖ Public education should be provided about the safety of vitamin D supplementation and the value of sensible sunlight exposure
- ❖ There is a growing consensus that the optimal range for 25(OH)D values lies above 30 to 32 ng/mL (75-80 nmol/L) for most populations
- ❖ Vitamin D is truly remarkable in that it plays a key role in a wide range of physiologic functions



Acknowledgements

- ❖ **Dr. Laila Abdel-Wareth**
- ❖ **Dr. Jaishen Rajah**
- ❖ **Dr. Fatme Al Anouti**
- ❖ **Prof. William Grant**
- ❖ **Mr. Nafiz Nimer**

THANK YOU

