ILSI Workshop New Delhi

A Global Assessment of Vitamin D Status in Healthy Populations

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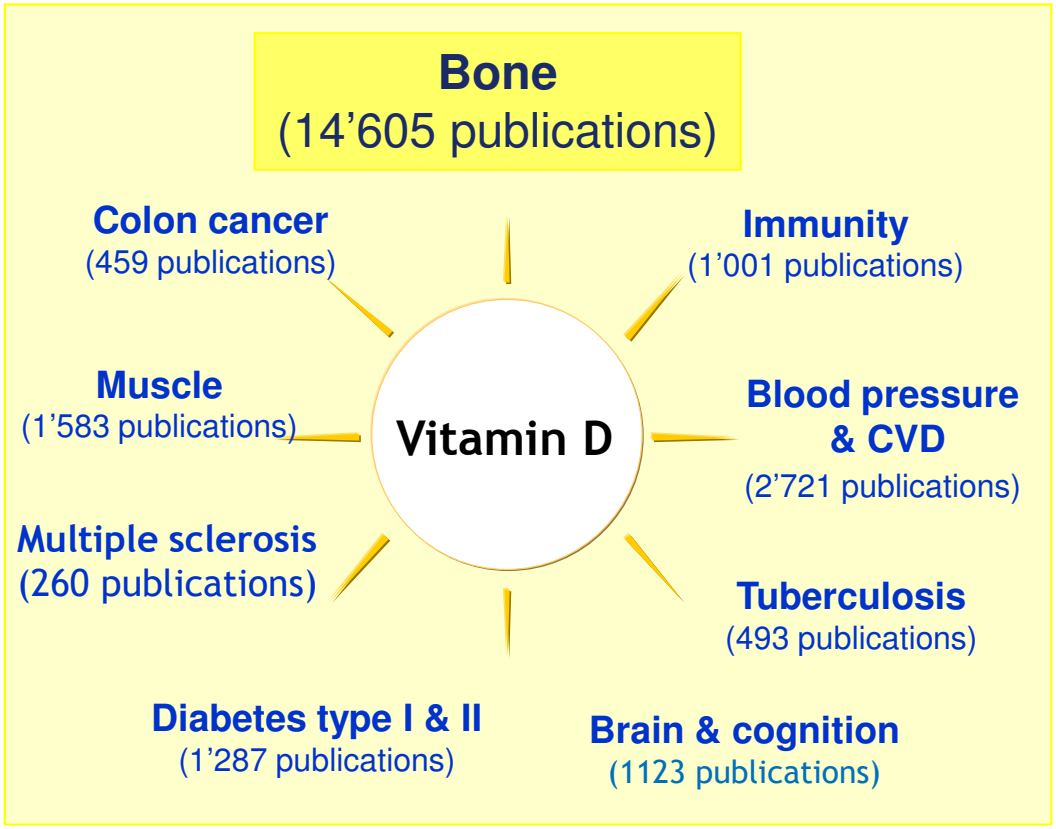
DSM Nutritional Products

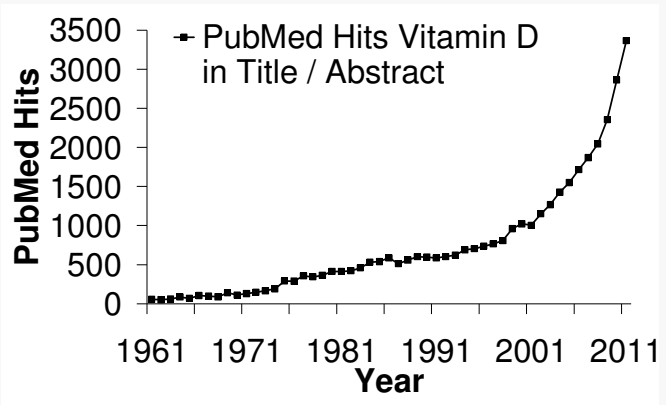
July 12, 2013

HEALTH · NUTRITION · MATERIALS

Scientific evidence supports vitamin D benefits in different segments



- ~3500 publications in 2011
- More than 250 human studies ongoing
- Indications well beyond bone health



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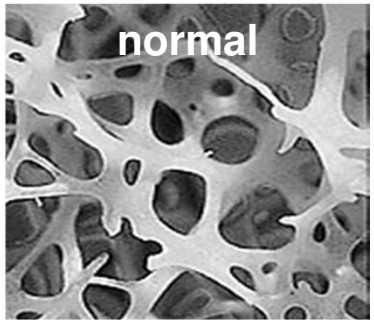
Vitamin D - the inadequate status impacts a number of body functions

Classical role of vitamin D: bone health

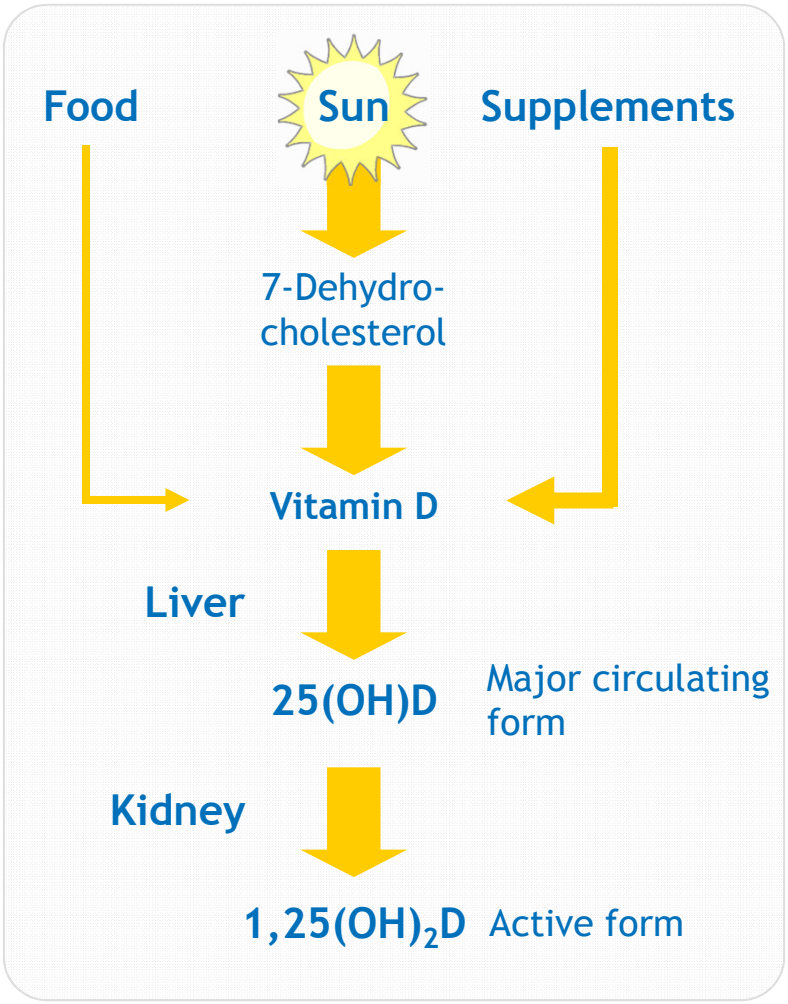
- Improves **bone mineral density** through calcium absorption and deposition
- Necessary to prevent rickets & osteomalacia



Emerging health benefits of vitamin D

- Muscle - Reduces risk of falling by improving muscle strength
- Immunity - Strengthens the immune system
  - Reduces risk of multiple sclerosis and diabetes type I and II
- Cardiovascular - Lowers blood pressure
- Cancer - Inhibits cell proliferation

Vitamin D comes from different sources



25(OH)D serum level is the relevant indicator of Vitamin D status (IOM 1997)

	< 25	25 - 50	50 - 75	> 75
nmol/L	*deficient*	*insufficient*	*(in)adequate*	*desirable*
ng/ml	< 10	10 - 20	20 - 30	> 30

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Traditionally living populations have a mean serum 25-OH D concentration of 115 nmol/l.

Br J Nutr. 2012 Jan 23:1-5.
Luxwolda MF, Kuipers RS, Kema IP, Janneke Dijck-Brouwer DA, Muskiet FA.
Laboratory Medicine, University Medical Center Groningen (UMCG), PO Box 30.001, 9700 RB, Groningen, NL

Cutaneous synthesis of vitamin D by exposure to UVB is the principal source of vitamin D in the human body. Our current clothing habits and reduced time spent outdoors put us at risk of many insufficiency-related diseases that are associated with calcaemic and non-calcaemic functions of vitamin D. Populations with traditional lifestyles having lifelong, year-round exposure to tropical sunlight might provide us with information on optimal vitamin D status from an evolutionary perspective.
We measured the sum of serum 25-hydroxyvitamin D2 and D3 (25(OH)D) concentrations of 35 pastoral Maasai (34 (sd 10) years, 43 % male) and 25 Hadzabe hunter-gatherers (35 (sd 12) years, 84 % male) living in Tanzania.
The mean serum 25(OH)D concentrations of Maasai and Hadzabe were 119 (range 58-167) and 109 (range 71-171) nmol/l, respectively. These concentrations were not related to age, sex or BMI.
People with traditional lifestyles, living in the cradle of mankind, have a mean circulating 25(OH)D concentration of 115 nmol/l.
Whether this concentration is optimal under the conditions of the current Western lifestyle is uncertain, and should as a possible target be investigated with concomitant appreciation of other important factors in Ca homeostasis that we have changed since the agricultural revolution.

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Why a global assessment on vitamin D?

- Provide a global overview on the vitamin D status in the **general population**
- Understand the situation by **regions**, **countries** and by **sub-groups**.
- Generate **awareness** for the role of vitamin D for health
- Advocate for actions to improve vitamin D levels in populations/groups at risk for low status

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Approach taken

- **Systematic review according to PRISMA**

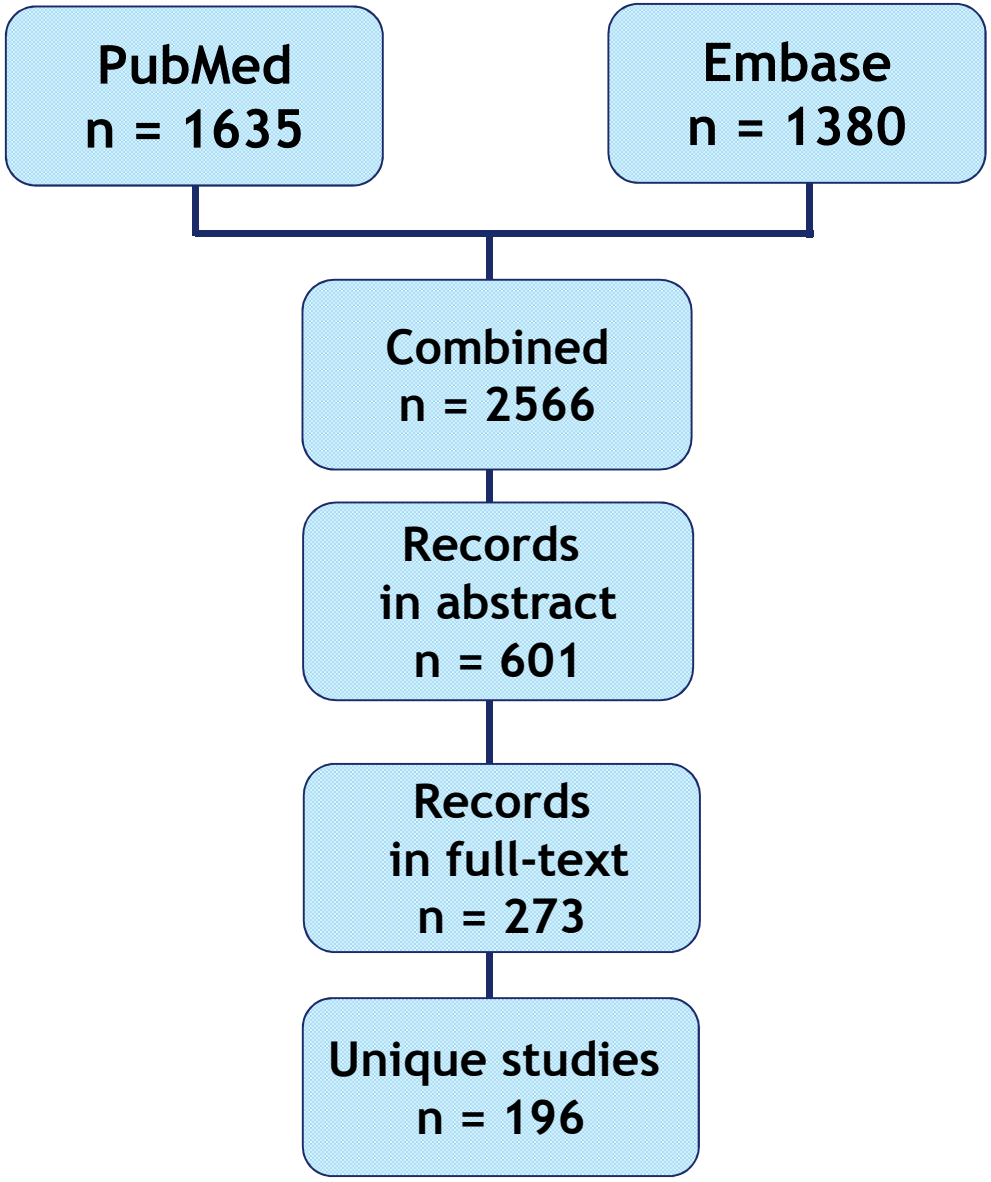
  (**P**referred **R**eporting **I**tems for **S**ystematic reviews and **M**eta-**A**nalyses)

  - Collaboration with the Mannheim Institute of Public Health, Germany

- **Visualizing the outcome (Global Map)**

  - Co-created with the International Osteoporosis Foundation (IOF)

Approach taken for systematic review



Search for relevant studies in relevant data bases

Exclusion of not relevant publications

- No outcome measures vitamin D
- Patient populations
- Duplicates
- Reviews
- Others

Taken into account

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Studies fulfilling the following criteria were selected

- Randomly selected persons from the general population in countries worldwide
- Mean or median 25(OH)D serum levels reported
- Population-based cohorts
- Only English publications
- Published between Jan 1st 1990 to Feb 28th 2011

.... an update of the map is planned for 2014

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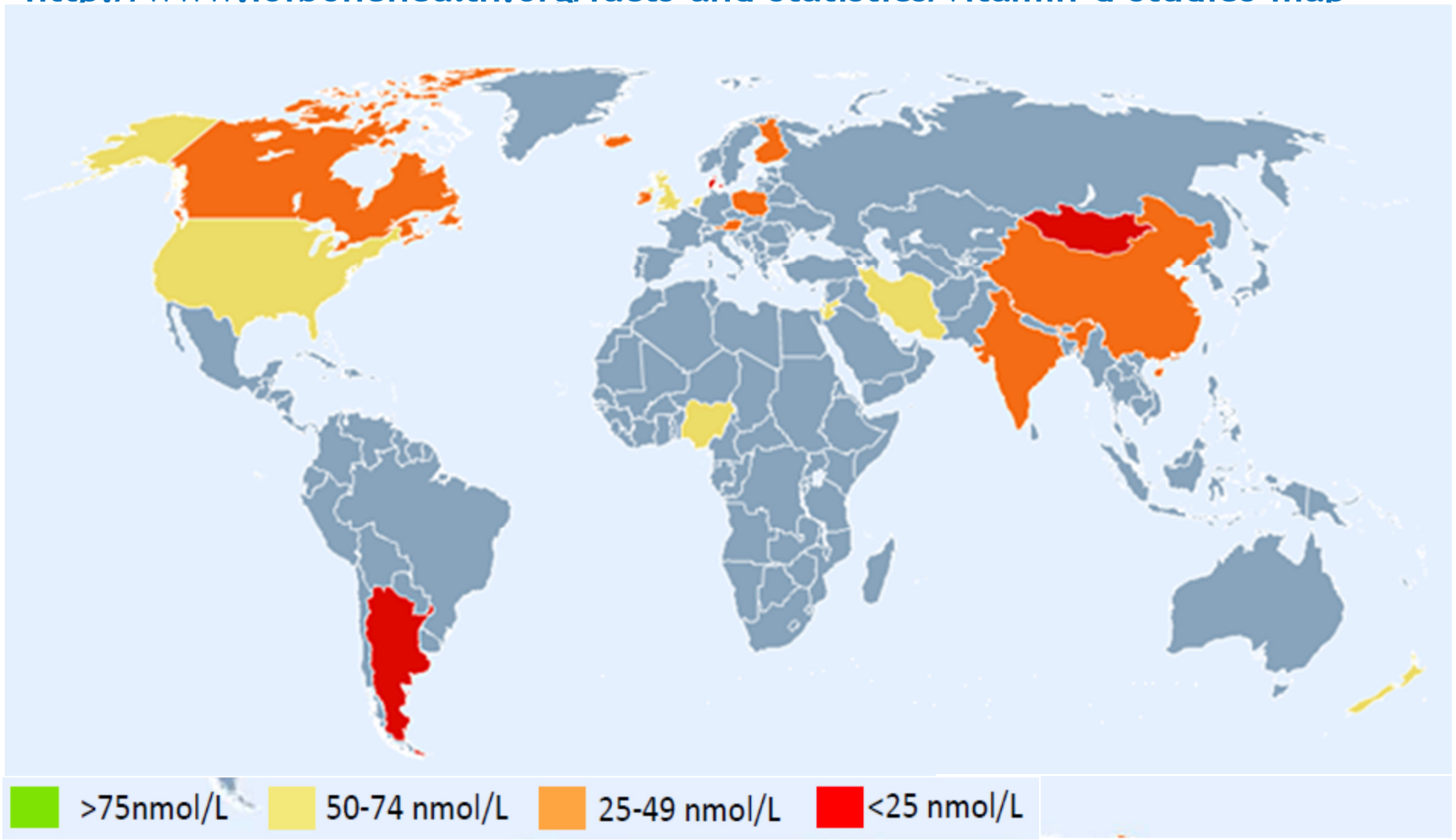
Global Vitamin D status in children & adolescents

http://www.iofbonehealth.org/facts-and-statistics/vitamin-d-studies-map



Ref: Wahl DA et al, Archives of Osteoporosis 2012

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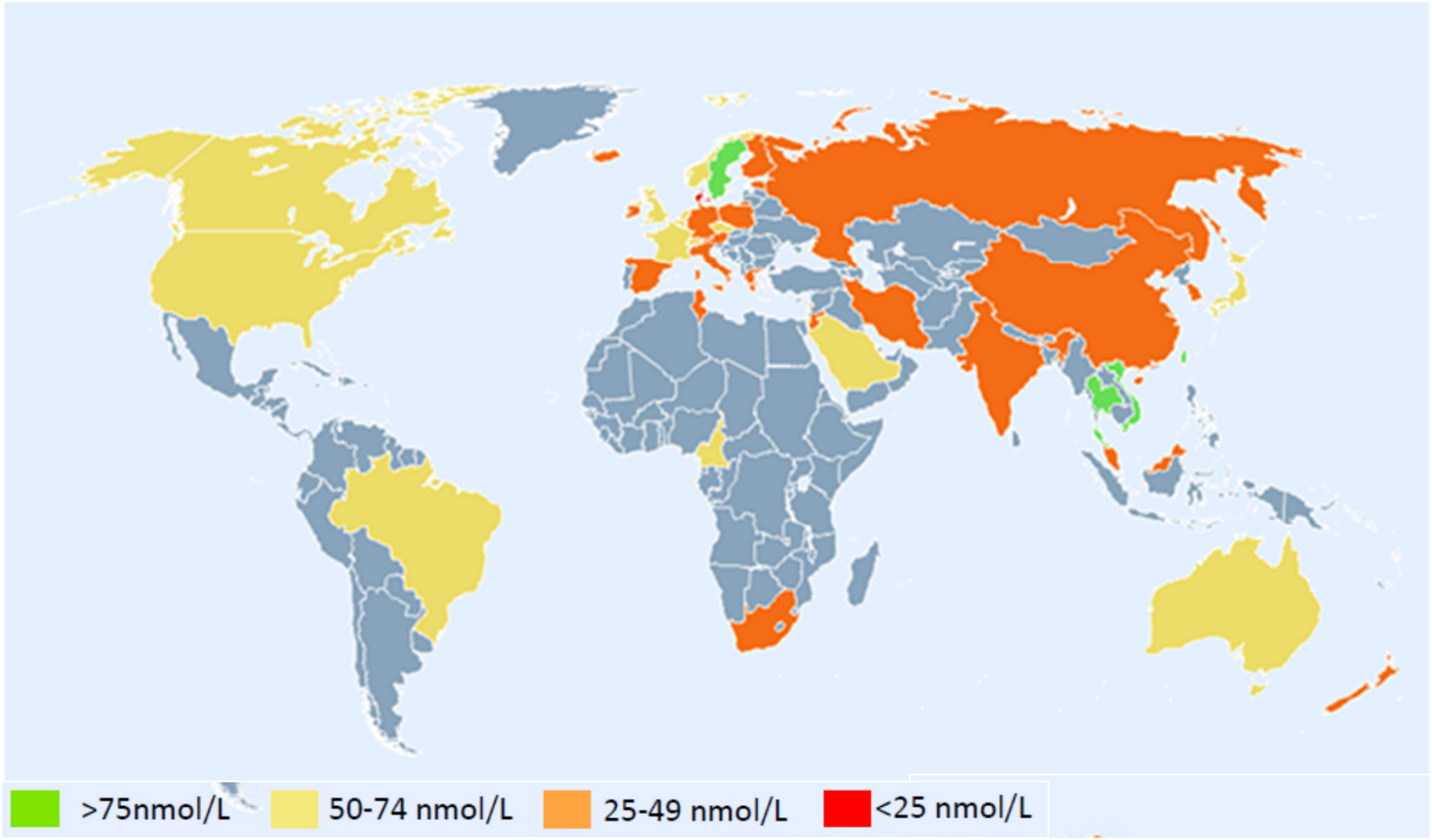
Global Vitamin D status in adults

http://www.iofbonehealth.org/facts-and-statistics/vitamin-d-studies-map



Ref: Wahl DA et al, Archives of Osteoporosis 2012

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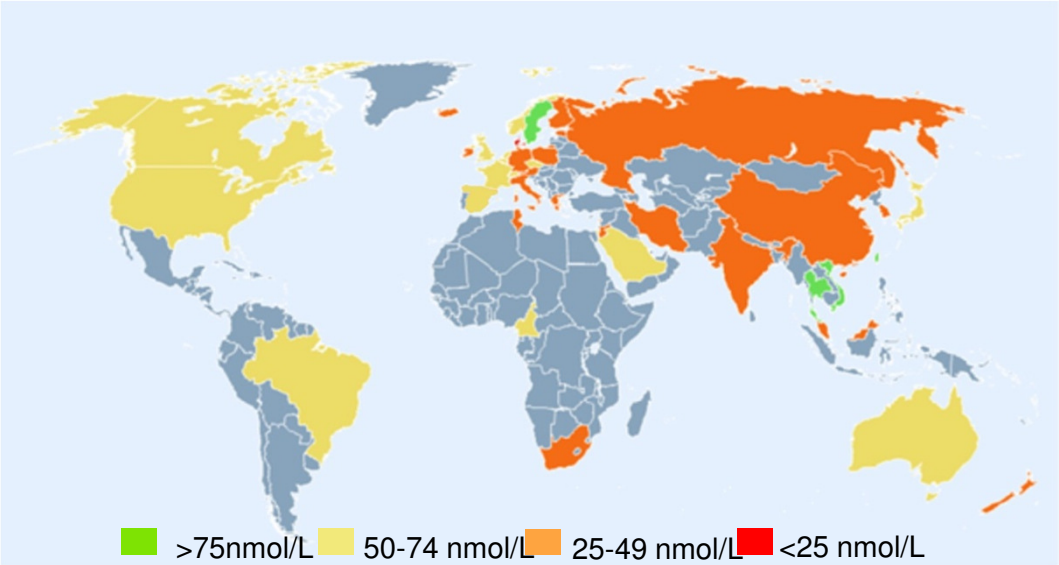
Main findings (1)

- Data coming mostly from Europe (48%), followed by North America (27%) and Asia Pacific region (16.5%)
- Insufficiencies affect both developing world and industrialized countries
- Women have lower status compared to men



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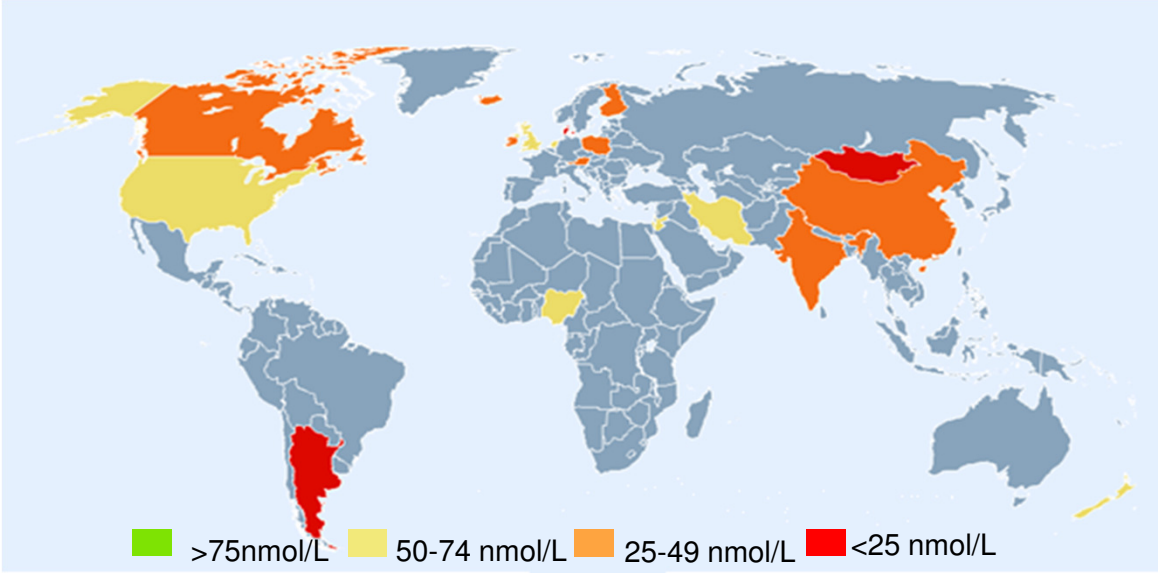
Main findings (2)

In children and adolescents, predominant colour is orange (25-49 nmol/L), which means that levels are in the insufficient range



Gaps in data:
Central America, much of South America, most of Africa,much of Europe, in Australia

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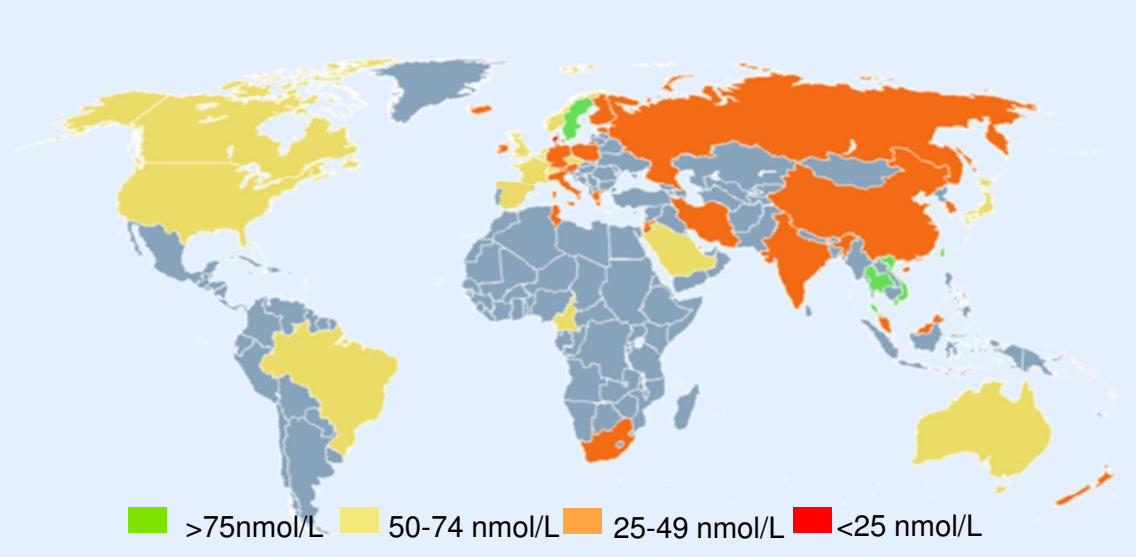
Main findings (3)

In adults, predominant colour code is orange (25-49 nmol/L) **and yellow** (50-74 nmol/L)



Gaps in data:
Central America, South America (with the exception of Brazil), much of Africa

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Inadequate vitamin D status is a global issue

.... if we extrapolate the data, it means globally are

88.1 %	**below 75 nmo/l**	**= est. 6.2 bio**
37.3 %	**below 50 nmol/l**	**= est. 2.6 bio**
6.7 %	**below 25 nmol/l**	**= est. 500 mio**

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Limitations of the Map

- Variability in the measurement of vitamin D
- Seasonality of vitamin D levels
- Adequate information not always available, e.g:
  - small study in a limited region of a country and a too narrow age range
  - small regions within large countries with diverse latitudes
- Information on clothing habits and skin pigmentation not always available

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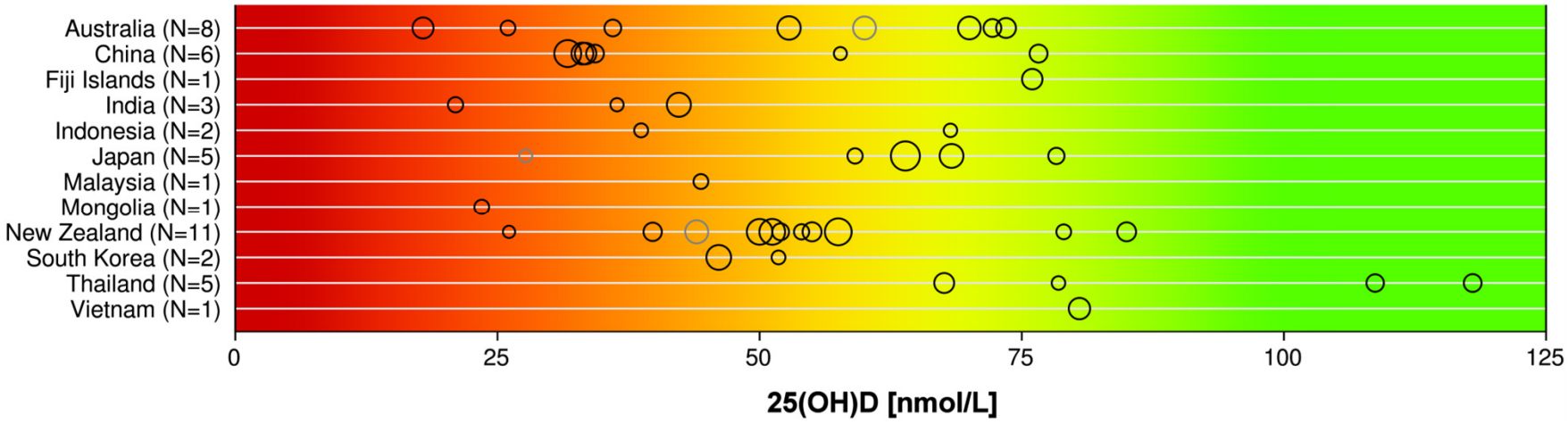
Even in ‘sunny’ countries vitamin D status is frequently low!

Vitamin D serum levels from n=46 studies in ASIA



< 25	25 - 50	50 - 75	> 75	nmol/L
deficient	*insufficient*	*inadequate*	*desirable*	

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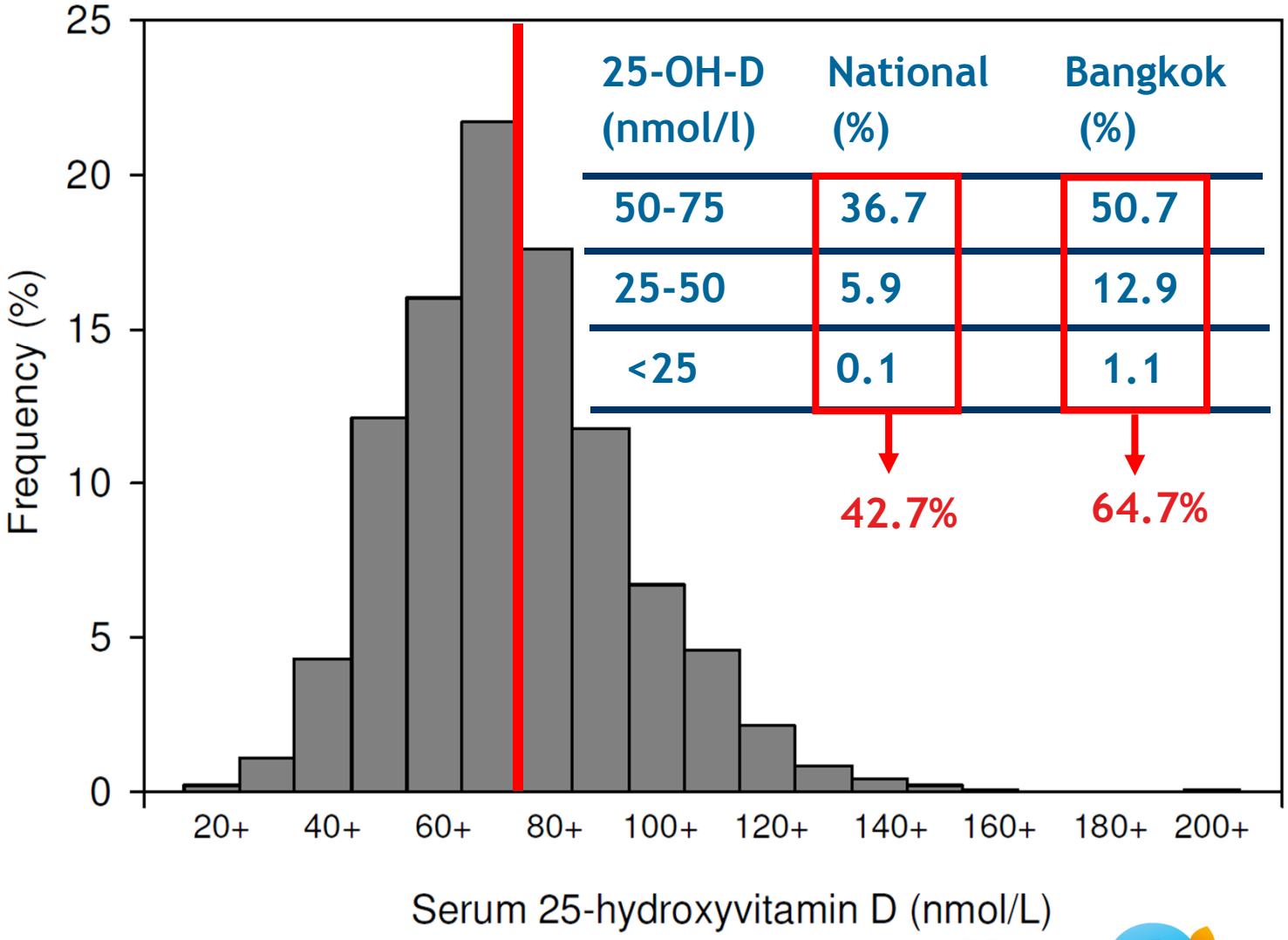
Vitamin D Insufficiency is prevalent in the general adult population in Thailand



25-OH-D (nmol/l)	National (%)	Bangkok (%)
50-75	36.7	50.7
25-50	5.9	12.9
<25	0.1	1.1

42.7%

64.7%

Source: Chailurkit et al, BMJ Public Health 2011,11:853.

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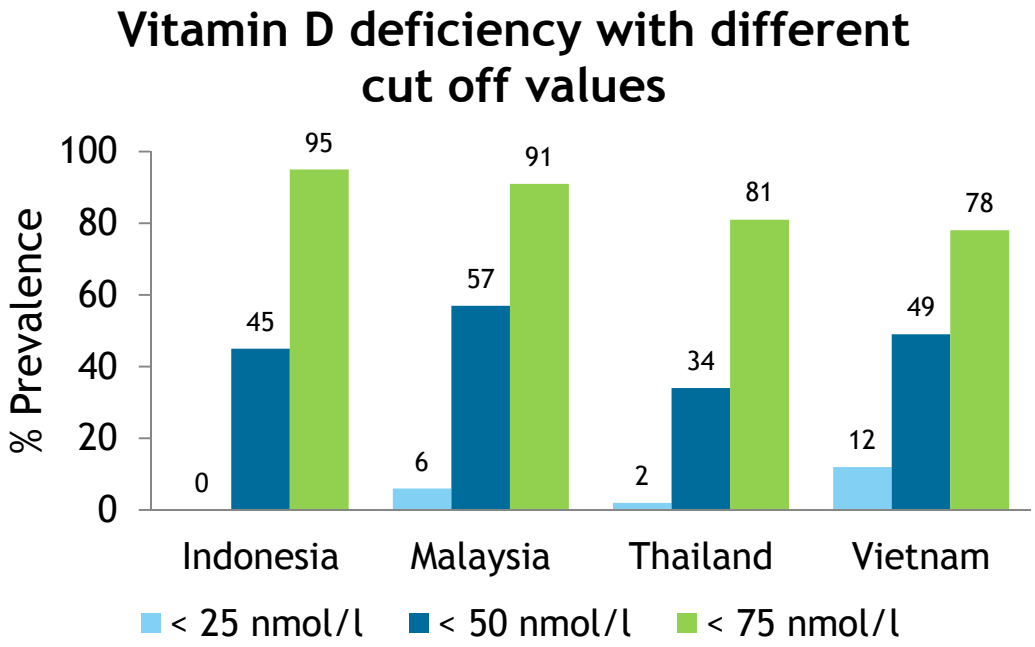
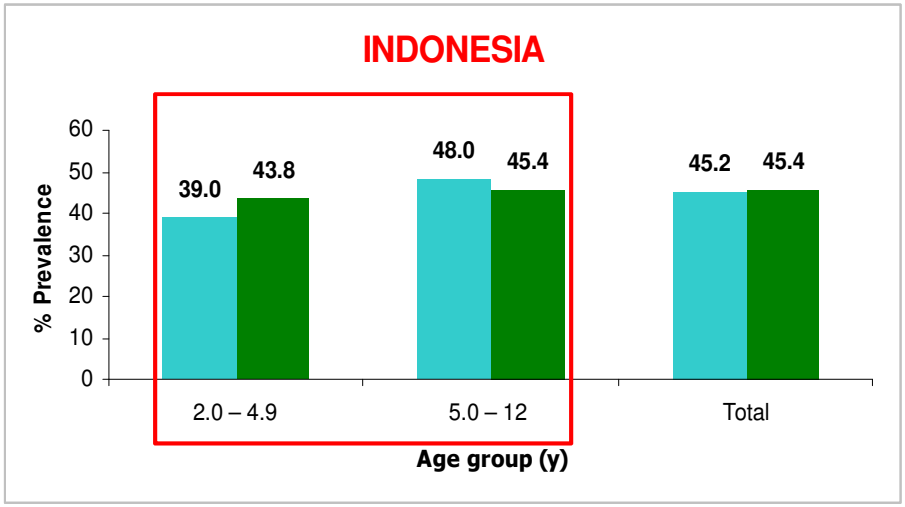
Vitamin D: striking deficiency in SEA

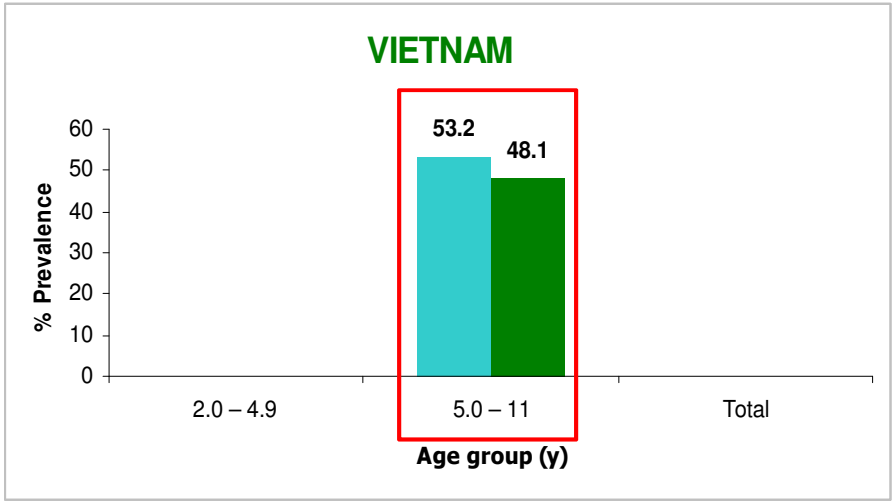


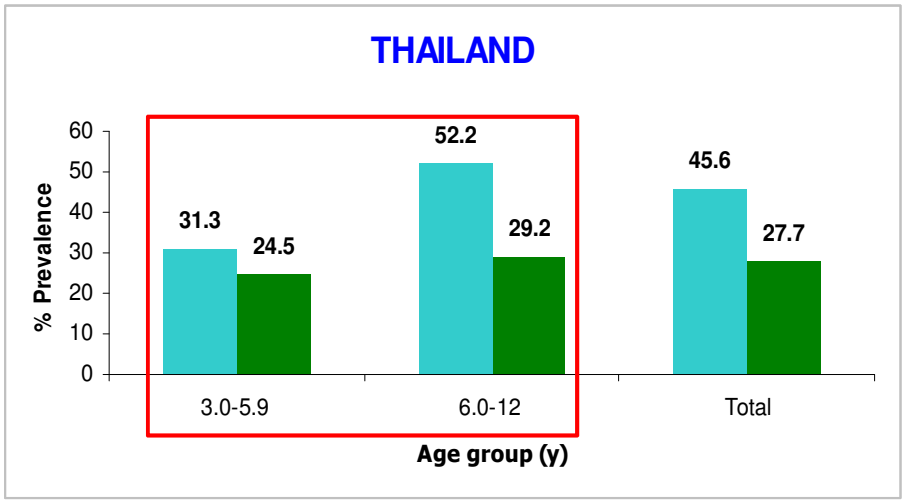
Serious problem!

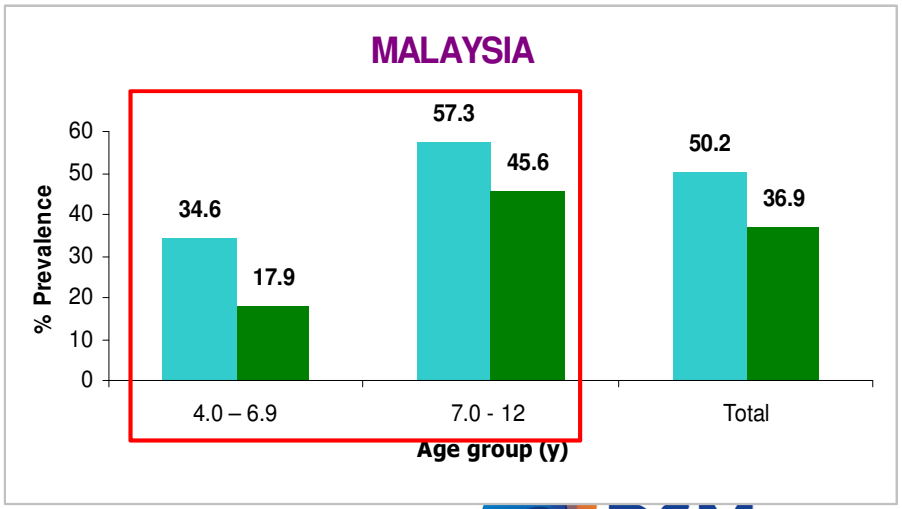
British Journal of Nutrition (in press), 2013

Vitamin D insufficiency









Urban

Rural

Vitamin D deficiency based on 25 (OH) D < 50 nmol/l

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Vitamin status in Chinese children

< 25	25 - 50	50 - 75	> 75
deficient	insufficient	(in)adequate	desirable

Publication	Age	Number	Site	Latitude (north)	Season	D Use	25-OH-D nmol/L	Prevalence <12.5	<25	<50	<75	<80
World J Pediatr 2010	Newborn	77 (MF)	Chengdu	30	Sept	Unknown	40.98±18.9					96.1
Public Health Nutr 2012	Newborn	58 (MF)	Beijing	40	Apr-May	No	27.9±1.6		46.6	93.2	100	
BMC Public Health 2012	6-11 yrs	1440 (MF)	Hangzhou	30	All	Unknown	56.1±19.9		2.0	40.3	88.3	
	12-16 yrs	183 (MF)	Hangzhou	30	All	Unknown	52.1±17.0		3.3	46.4	89.6	
J Orthop Surg 2002	12.2 yrs	16 (MF)	Beijing	40	Dec	No	34.3±12.0					
Am J Clin Nutr 2001	12.7 yrs	108 (F)	Beijing	40	Jan	Unknown	13.9±9.6	42.5				
					Sept-Oct	Unknown	30.2±11.9	5.1				
	13.0 yrs	57 (F)	Beijing	40	Jan	Unknown	12.7±5.9	49.6				
					Sept-Oct	Unknown	24.7±10.6	6.6				
	13.2 yrs	64 (F)	Beijing	40	Jan	Unknown	12.8±6.7	45.1				
					Sept-Oct	Unknown	23.8±8.7	9.2				
Osteoporos Int 2009 & J Nutr 2009	15.0 yrs	301(F)	Beijing	40	Mar-Apr	No	34.0		32.8	89.2		
J Clin Endocrinol Metab 2009	16.4 yrs	226 (FM)	Anqing	33.5	All	Unknown	45.0±23.5					90.3

Vitamin D status was poorer in the north
Vitamin D status was poorer in winter-spring
Vitamin D levels were largely below 50 nmol/l

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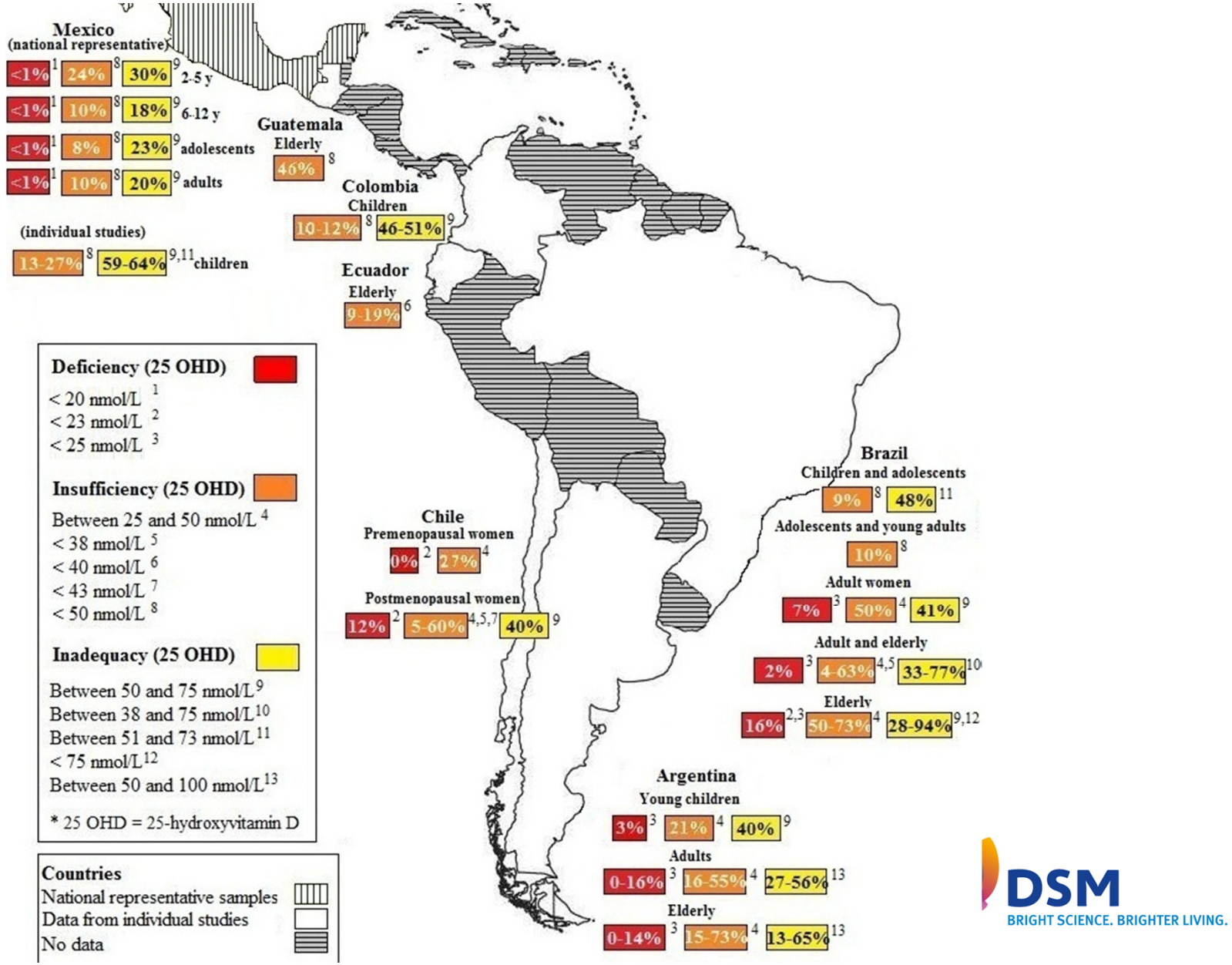
Vitamin status in Chinese adults

< 25 | 25 - 50 | 50 - 75 | > 75

Publication	Age (yrs)	Number	Site	Latitude (north)	Season	D Use	25-OH-D nmol/L	Prevalence <25	Prevalence <50	Prevalence <75
Bri J Nutr 2008	26.9	220 (F)	Beijing	40	Feb-May	No	29	40*	94 *	
	27.9	*221 (F)*	*Hong Kong*	*22*	*Feb-May*	*No*	*34*	*18**	*92 **	
World J Pediatr 2010	End-pregancy	77 (F)	Chengdu	30	Sept	Unknown	36.0±18.9			
Acta Paediatr 2012	27.4	78 (F)	Nanjing	32	Winter	No	22.6±12.7		96.1	
	27.4	78 (F)	Nanjing	32	Summer	No	31.8±9.2		94.7	
J Matern Fetal Neonatal Med 2012	28.1	1695 (F)	Shanghai	31	All	No	43.9±28.6		69.0	91.0
Int J Androl 2012	29.4	41 (M)	Xian	34	All	Unknown	52.5±15.9			
Public Health Nutr 2012	29.9	70 (F)	Beijing	40	Apr-May	No	28.6±1.4	54.3	90.2	100
Int J Androl. 2012	30.3	314 (M)	Xian	34	All	Unknown	53.3±14.5			
	30.5	195 (M)	Xian	34	All	Unknown	54.1±14.3			
Eur J Clin Nutr 2000	30.9	48 (F)	Shenyang	42	Apr-May	No	40.7±14.1	13.0		
	31.1	48 (M)	Shenyang	42	Mar-May	No	31.4±10.4	29.0		
Plos One 2012	43 .0	2588(M+F)	Shanghai	31	All	No	52.2			

Vitamin D status in Latin America and Caribbean



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Ways of Increasing Vitamin D Intake

1. Increase exposure to limited daily sunlight

2. Improving nutrition: consume foods that are high in vitamin D (fatty fish, eggs, fortified products)

3. Supplementation should be considered for people who are vitamin D insufficient or at risk

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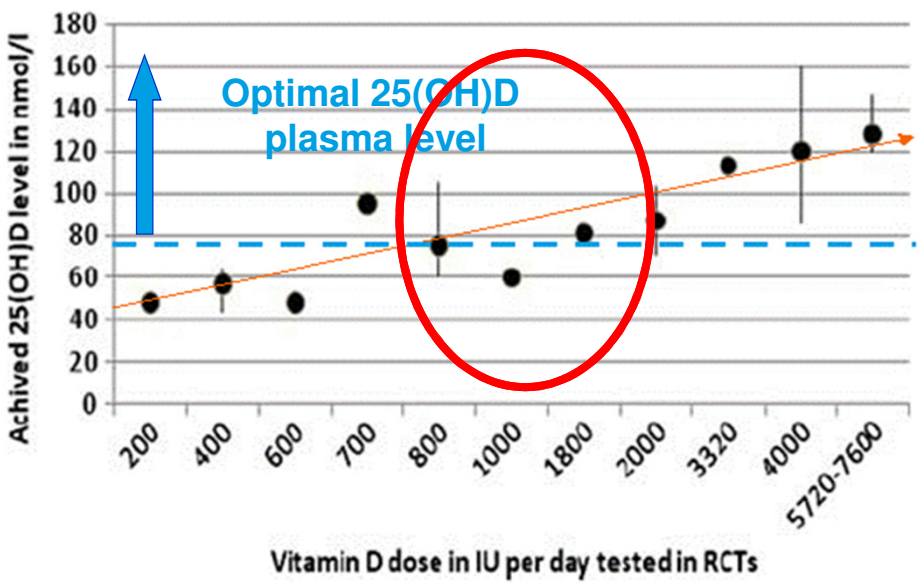
How to achieve adequate Vitamin D level

Randomized Clinical Trials with vitamin D less than 10‘000 IU per day and duration of at least 4 weeks



Conclusion

- Optimal 25(OH)D range between 75 - 110nmol/L
- These levels can be obtained with oral doses in the range of 800 IU – 2000 IU
- **Benefit is clearly dose dependent**

Bischoff-Ferrari, 2009 Osteoporos Int

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Who is most at risk of vitamin D deficiency?

- People over 65 years of age
- People who avoid sun exposure such as institutionalized or housebound or who cover their skin for cultural reasons
- Pregnant and breastfeeding women and their newborns
- Obese individuals
- People with darker skin, because they are not able to produce much vitamin D in their skin, especially if they immigrate to Northern countries
- In some regions, such as South Asia and Middle East vitamin D deficiency is very common in all age groups, from infants to the elderly (despite ample sunshine)

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New recommendations for higher vitamin D intake

As a concern to the widespread vitamin D deficiency and the beneficial effect of vitamin D on bone health

government documents, ***position statements*** and ***clinical practical guidelines***

have recently been published with higher recommendations for daily vitamin D intake.

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Experts in the U.S. double recommended daily vitamin D intake for children to 400 IU in 2008

The American Academy of Pediatrics (AAP) has *doubled the recommended intake of vitamin D to 400 IU per day* for *infants, children and adolescents!*

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

AAP doubles vitamin D recommendation for children

The American Academy of Pediatrics has doubled its recommended dose of vitamin D for children, to 400 international units a day. The group says the dose should begin in the first few days of life and continue through adolescence to ward off rickets and other bone problems.

http://pediatrics.aappublications.org/content/122/5/1142.full.html

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The U.S. raised Vitamin D recommendation

IOM tripled the DRIs for vitamin D3 on 1 Dec 2010

US Dietary Reference Intakes (DRIs)

Age (y)	RDA IU (µg)	*Pregnancy*	*Lactation*
0 – 1	400 (10) **AI**		
1 – 13	600 (15)		
14 – 50	600 (15)	600 (15)	600 (15)
>51–70	600 (15)		
71+	800 (20)		

- The IOM has reviewed the latest data on **bone health**
- This review has resulted in new Dietary reference intakes (DRIs) in the US:

  tripled to 600 IU/day for general population age 1 -70 years

  and

  to 800 IU/day for elderly > age 70 years

.... and many other countries followed

http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx

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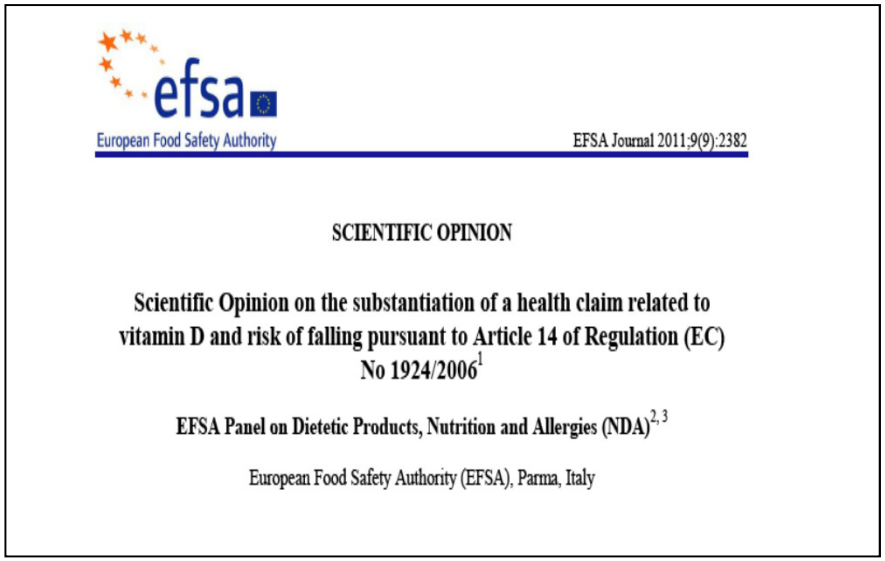
EFSA confirms DSM Health Claim Article 14 in 2011

Health claim
Vitamin D may reduce the risk of falling.
Falling is a risk factor for bone fractures


efsa
European Food Safety Authority
EFSA Journal 2011;9(9):2382

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to vitamin D and risk of falling pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

The Conditions of use:
In order to obtain the claimed effect, 800 I.U. (20 μg) of vitamin D from all sources should be consumed daily. The target population is men and women 60 years of age and older.

http://www.efsa.europa.eu/en/efsajournal/pub/2382.htm

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Conclusion

- Vitamin D deficiency is a global issue affecting developing and developed countries
- Specific groups like pregnant women, infants, elderly can be even more at risk
- Especially, in the Middle East, Asia and Southern Europe vitamin D deficiency is widespread
- Vitamin D deficiency and inadequacy has detrimental health effect
- Ensuring desirable Vitamin D levels is a cost effective approach for a healthy and productive life

The scientific evidence calls for action by a joint approach of the key stakeholders

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Back up

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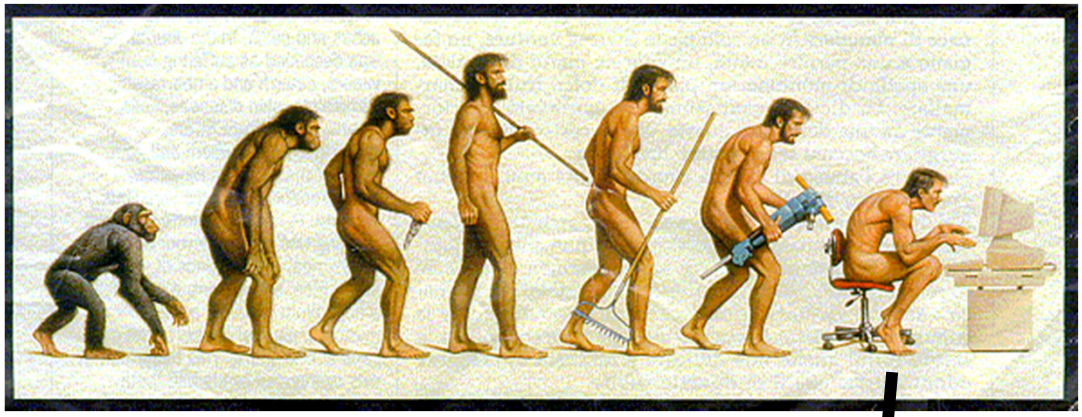
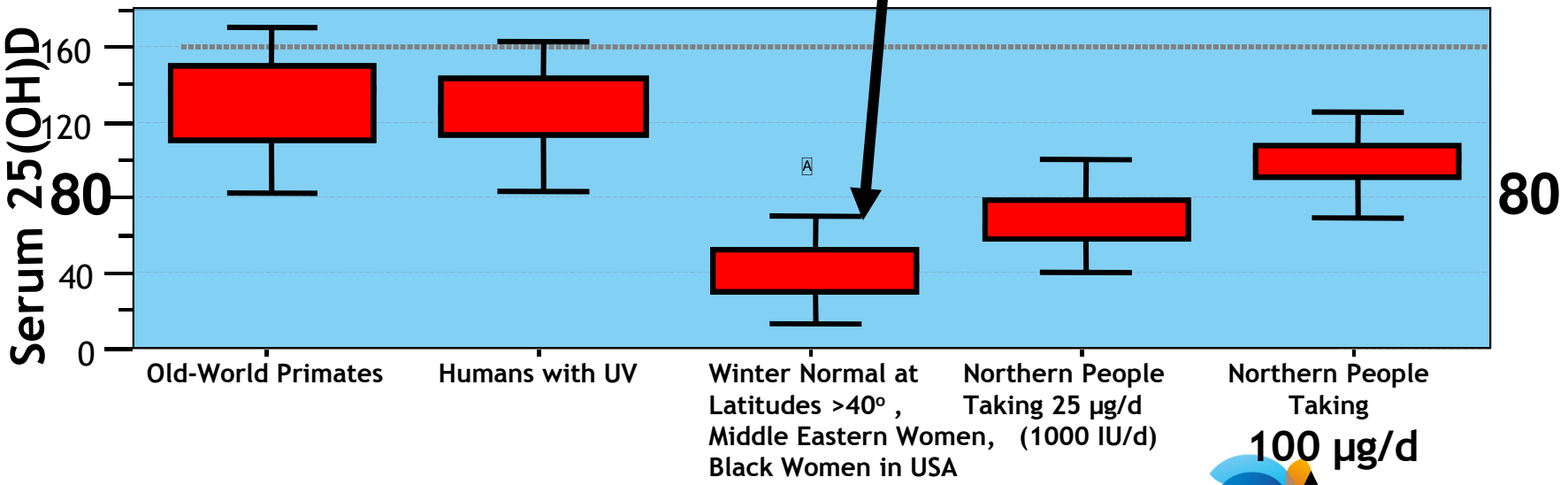
Vitamin D nutritional status through the ages





Sources, include Cosman, Osteoporosis Int 2000; Fuleihan NEJM 1999; Scharla Osteoporosis Int 1998; Vieth AJCN 1999, 2000

Vitamin D added to calcium osteoporosis health claim

Food and Drug Administration (FDA) on January 5, 2007

FDA Updates Health Claim for Calcium and Osteoporosis
Proposal Would Give Consumers More Information to Make Healthy Food Choices

Amendments in the published final rule include:

- Add a claim for calcium and **vitamin D** together and a reduced risk of osteoporosis.

Shorten the claim language by:

- Dropping the reference to sex, race, and age since the ***benefits apply to both sexes at all ages and race categories***.
- Dropping the need to identify the mechanism by which calcium reduces the risk of osteoporosis.
- Dropping the requirement that the claim state that there are limits to benefit of calcium intakes above 200% of the Daily Value.

www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108824.htm#.T0NmHNdLZHM.email

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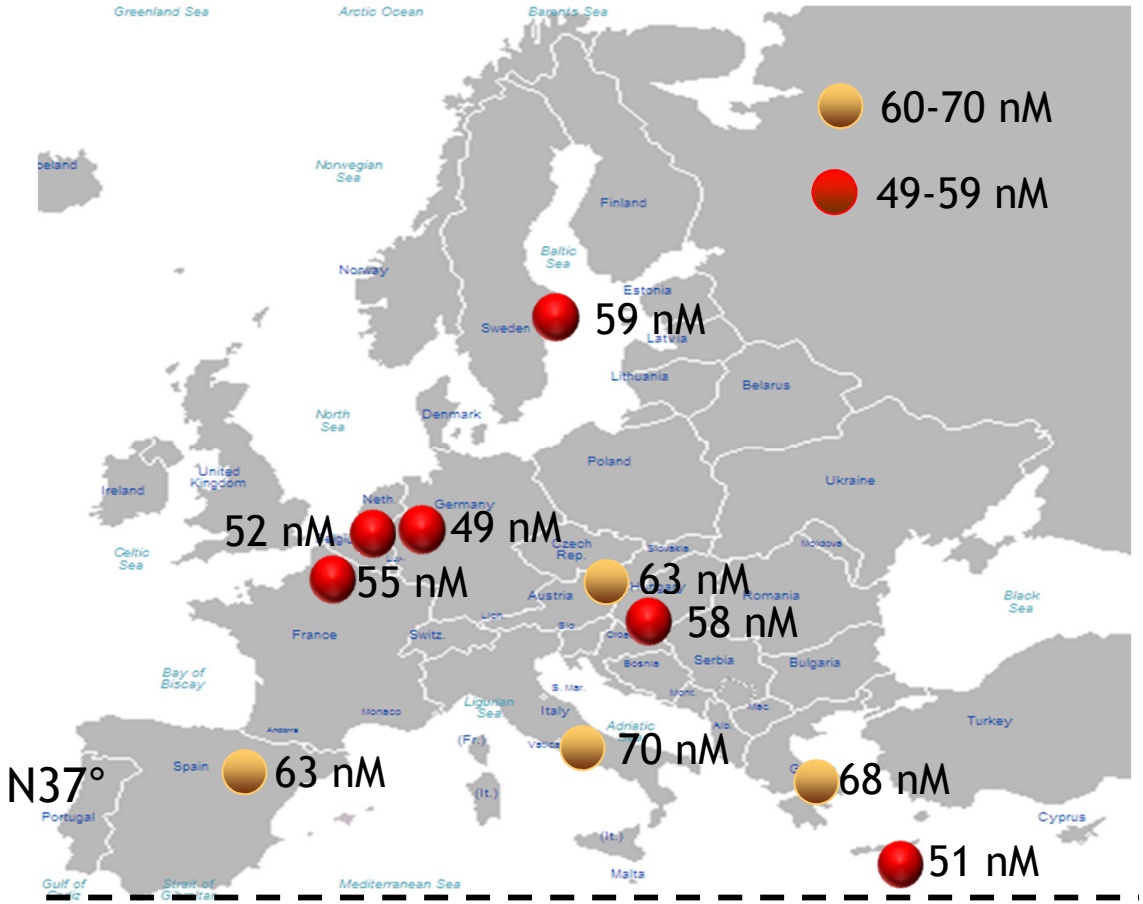
Europe: Vitamin D insufficiency in adolescents distribution according to geographic location

Vitamin D levels in 1006 adolescents: aged 12 to 17 years, from ten cities in nine European countries



- The highest levels of 25-OH-D were observed in Rome, Athens, Vienna and Zaragoza
- Lowest levels were obtained in Dortmund, Gent, Lille Heraklion.
- Average concentrations did not reach the 75 nmol/l cut-off in any of the cities.
- Deficiency/insufficiency influenced by age, sex, body weight, and geographical location.

González-Gross M et al, British Journal of Nutrition, 2012

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IOF interactive map

http://www.iofbonehealth.org/facts-and-statistics/vitamin-d-studies-map

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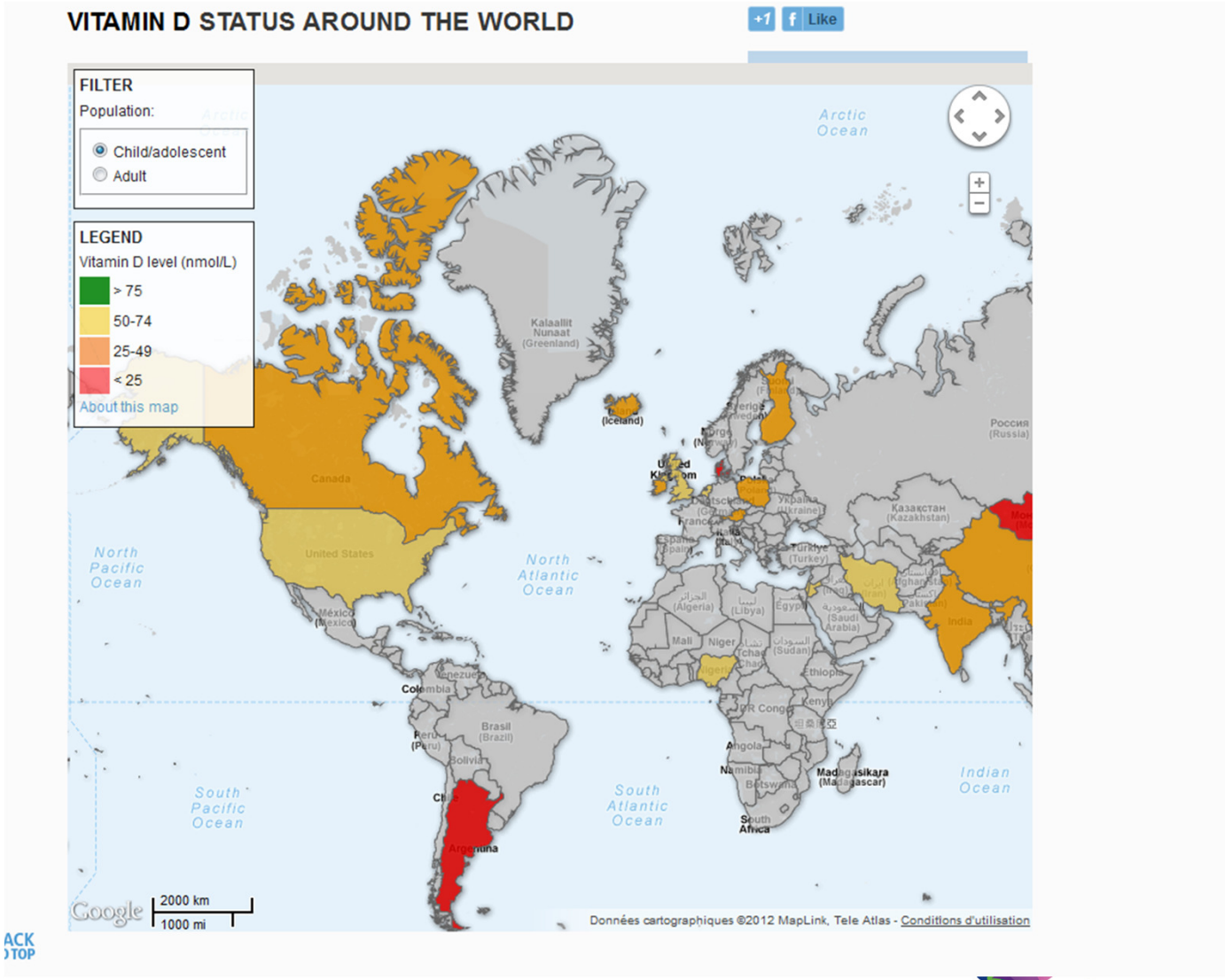
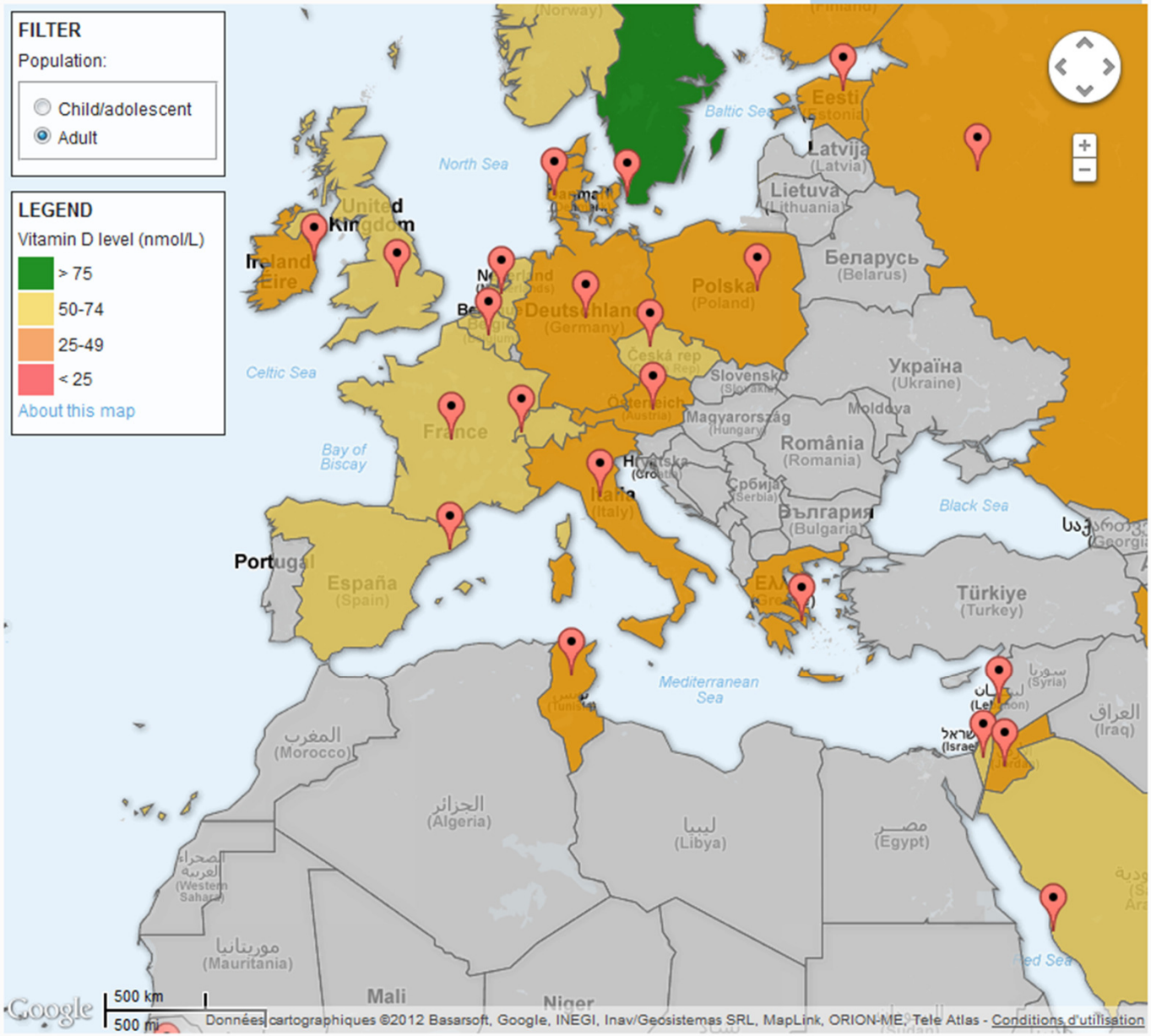
The Interactive Map

HTTP://WWW.IOFBONEHEALTH.ORG/FACTS-AND-STATISTICS/VITAMIN-D-STUDIES-MAP



VITAMIN D STATUS AROUND THE WORLD



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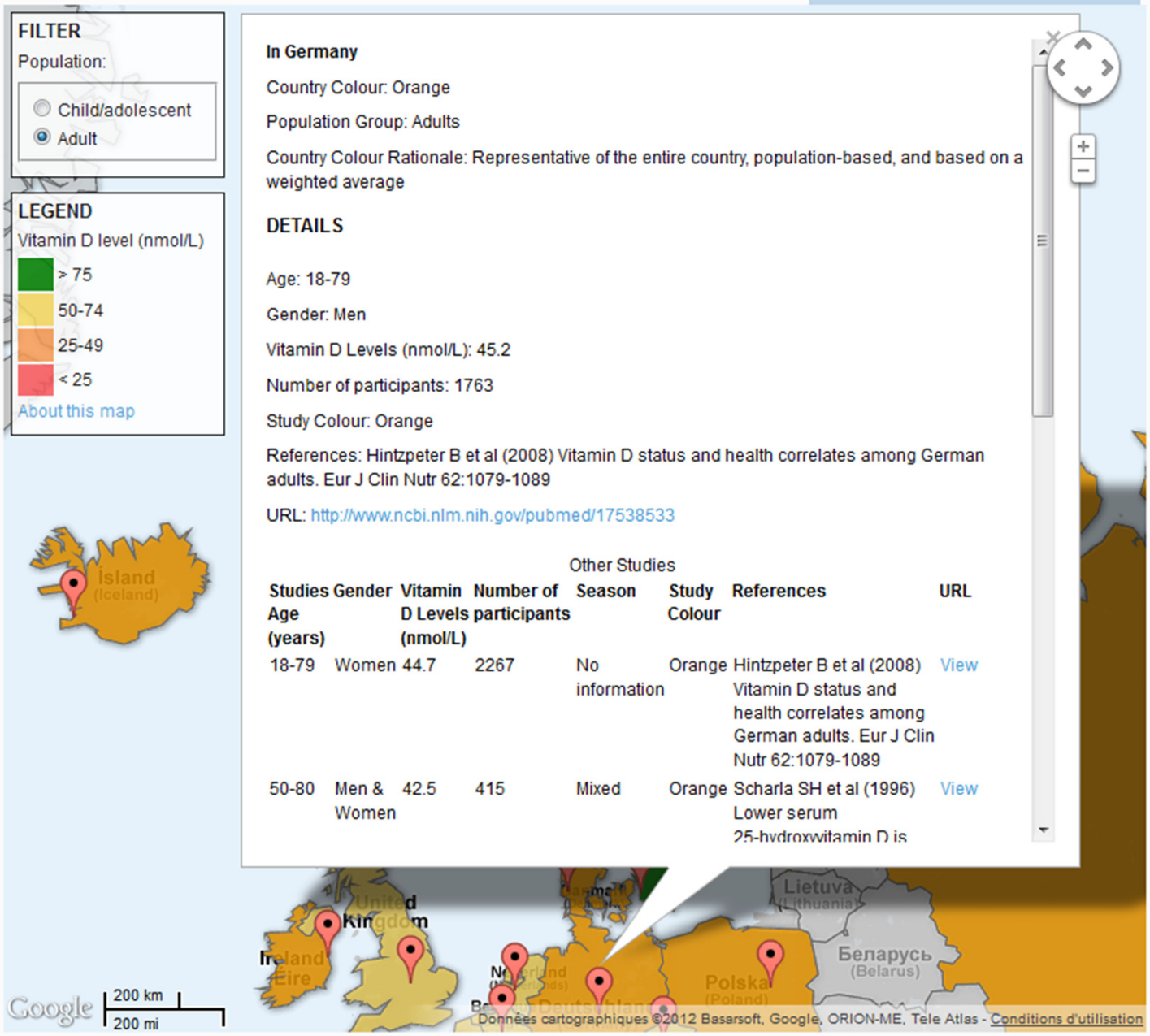

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Example Germany: Cost impact of low vitamin D status on fractures

Hip and vertebral fractures have the most „cost-intense“ medical implications

- Number osteoporosis patients: 8-10 mio (2010)*
- Number of hip and vertebral fractures p.a.: 150.000*

Optimized vitamin-D status reduces number of fractures by 20 %

- Reduction of 5.478 hip fractures and 18.420 less vertebral fractures (in osteoporosis-diagnosed population)

Net socio-economic benefit ranges from* : → **585 mio €**
Including medical and therapeutic costs for prevention, treatment and supplementation costs vitamin D

up to → **778 mio €**
Including societal perspective, e.g. family care, reha costs

Source: * Sproll 2011

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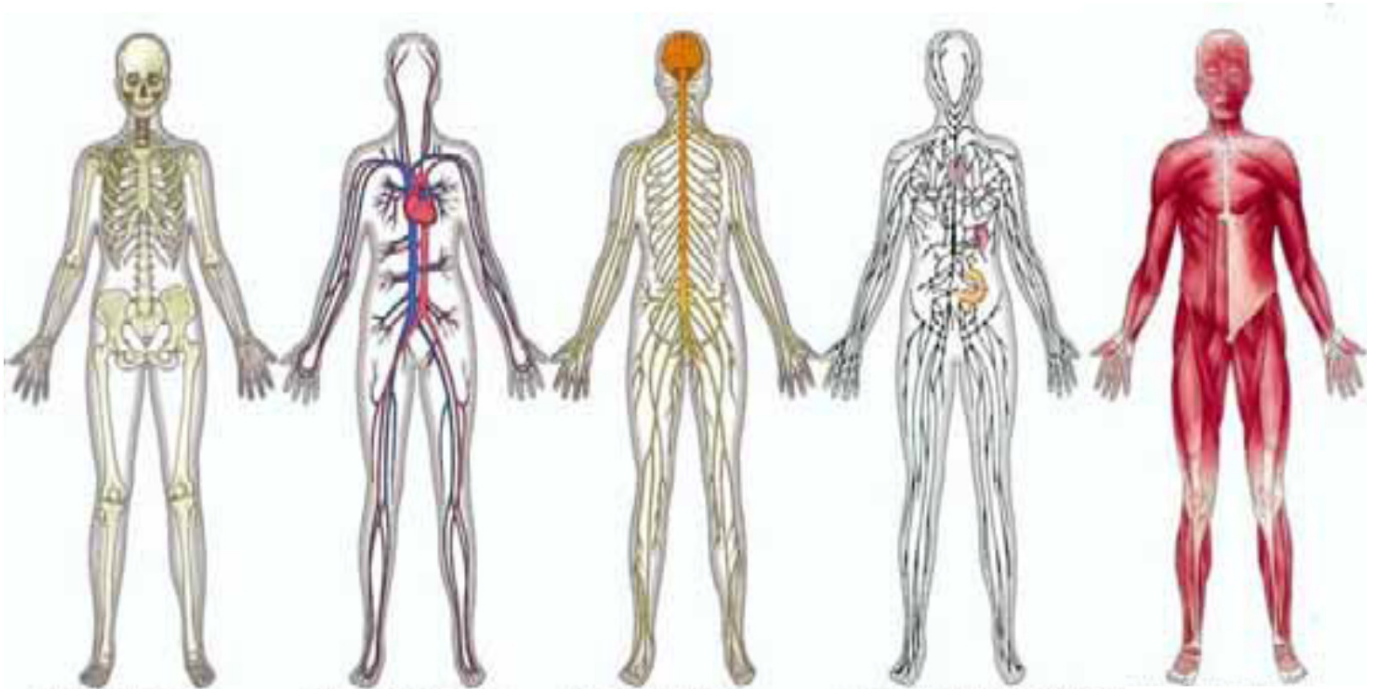
Magnitude of vitamin D considering additional health benefits



Risk reduction by optimal vitamin status:

Bone fractures	Cardio Vascular Diseases	Multiple Sclerosis	Diabetes	Cancer and others
20 %	20 %	50%	25%	25 %

Source: Grant et al 2009

Large health care cost savings could be achieved with adequate vitamin D status

Zittermann	2010	Germany: overall perspective,including direct and indirect costs and implications	€ 37,5 bio/y
Grant et al	2009	17 countries in Europe: direct and indirect cost savings (= 16,7 % of total health care costs)	€ 187 bio/y

Adequate levels can be achieved with voluntary food fortification and/or supplementation for risk groups with costs of only 20-30 EUR/person per year

Source: vitamin D and socioeconomic costs, T. Sproll

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A call to act on vitamin D deficiency

- 88 % of the healthy population is below the optimal vitamin D status of 75 nmol/l 25 (OH)D
- 37 % below 50 nmol/l
- Specific groups like pregnant women, infants, elderly can be even more at risk

Regulatory bodies act

- US RDA tripled
- Europe 4-fold increase proposed
- India evaluation ongoing
- China evaluation ongoing
- Thailand ?
- ...

Nutritional solutions required

- Communication
- Food fortification
- Supplementation

Scientists, International Osteoporosis Foundation, Endocrine Society and others engage to fight vitamin D deficiency

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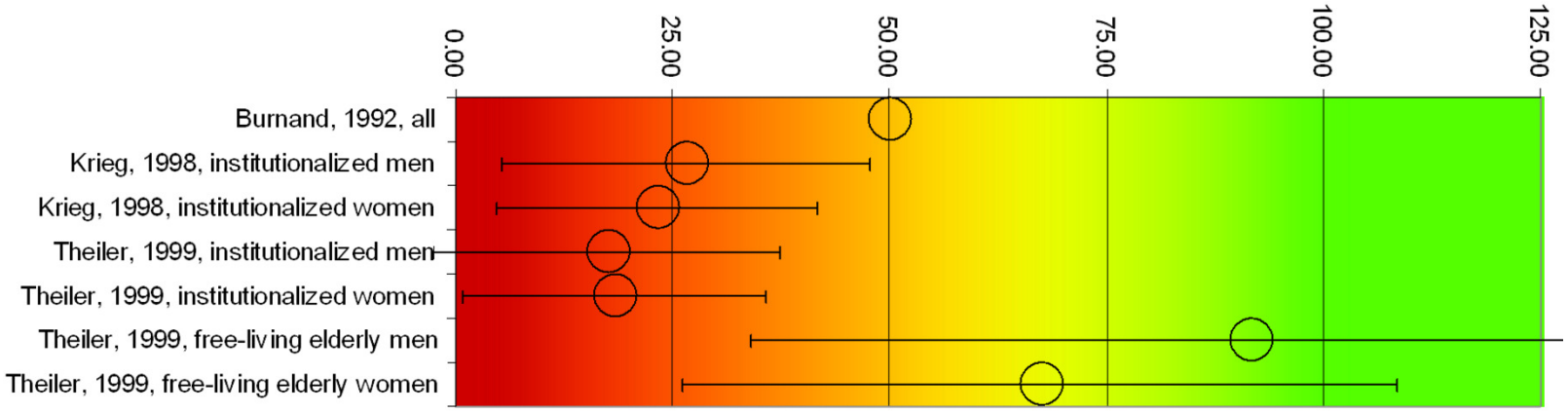
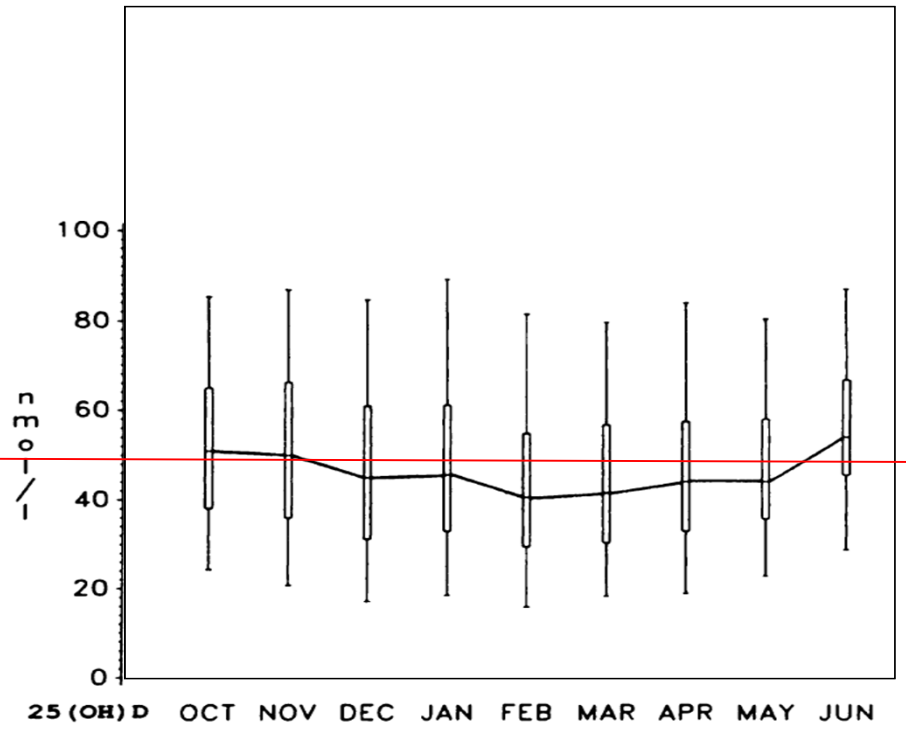
Broad variation of studies: example Vitamin D levels in Switzerland



Vitamin D levels are critical in institutionalized people compared to free-living elderly

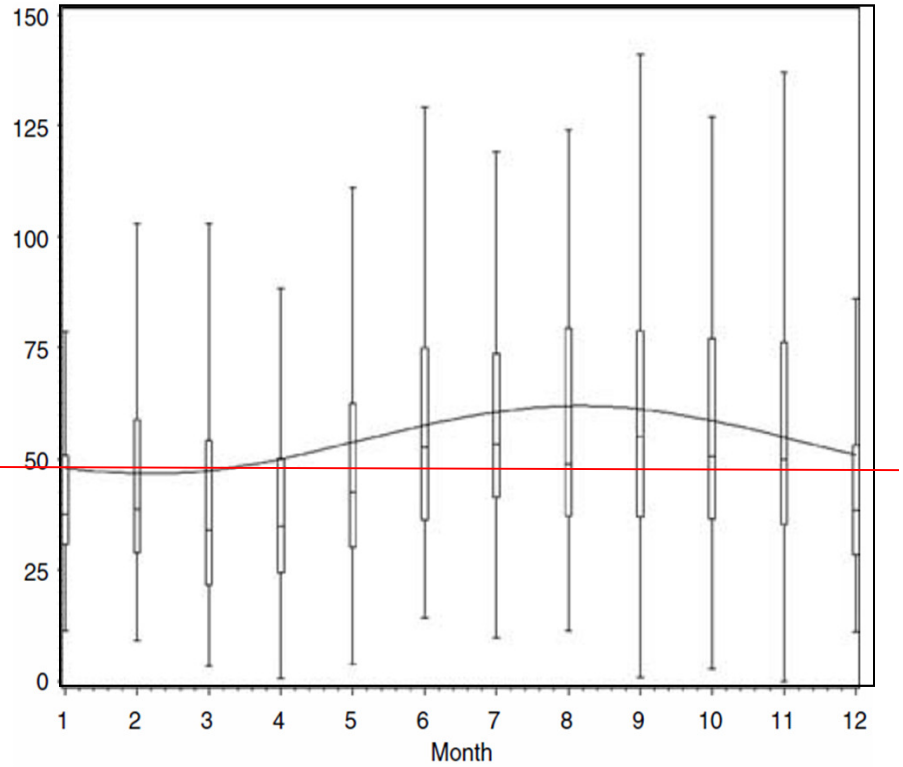
Seasonal variations in representative samples in Switzerland & Germany

Switzerland



Burnand et al, 1992

Germany



Hintzpeter et al, 2008

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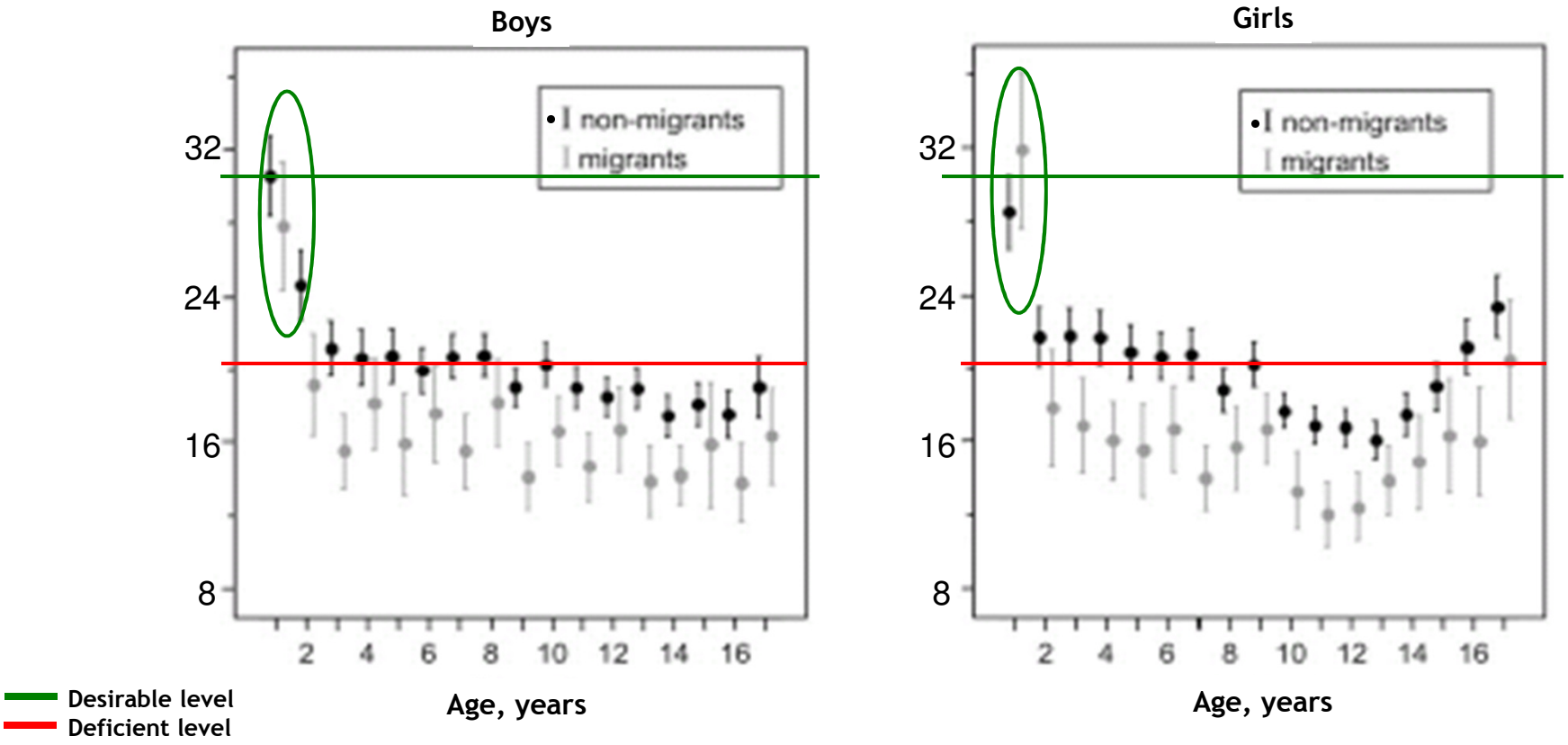
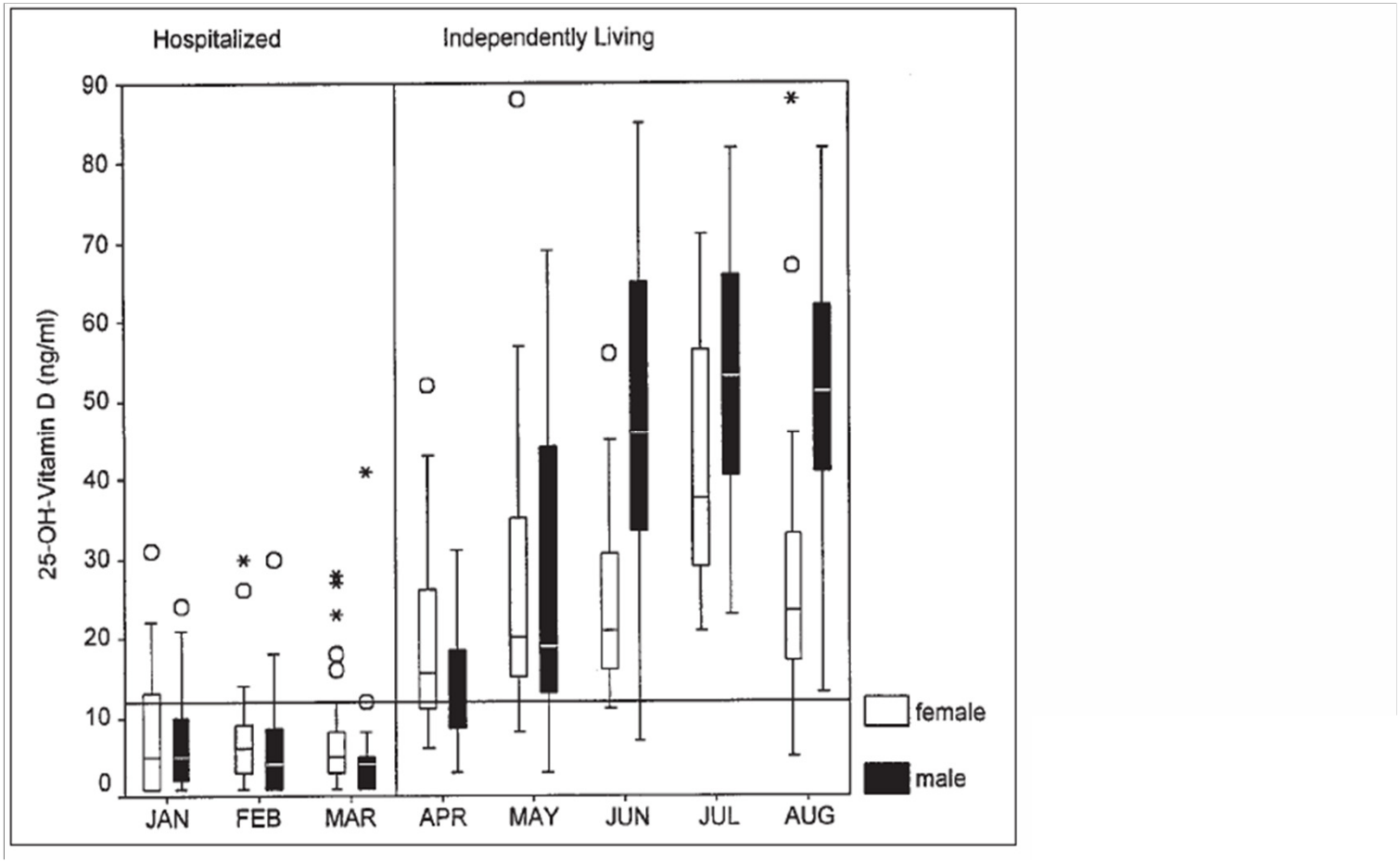
Vitamin D Status of migrants and non-migrants children and adolescent in Germany



Infants achieve a higher vitamin D status due to recommended supplemtation during the first year of life

Hintzpeter, 2009

Vitamin D status in hospitalized elderly is critical (Theiler et al, 1999)



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Building a map on global vitamin D status

- **The challenge:**

  Quality and quantity of data differs between the countries

- **Assigning a color code to a specific country was based on hierarchical selection criteria:**

  1. Representative of the entire country
  2. Representative of a region/city of the country
  3. Based on a weighted mean of multiple studies
  4. Based on a single study

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Vitamin status in Chinese elderly

< 25	25 - 50	50 - 75	> 75
deficient	insufficient	inadequate	desirable

Publication	Age	Number	Latitude (north)	Site	Season	25-OH-D nmol/L	D Use	Prevalence <25	<50	<75
Eur J Clin Nutr 2000	66.9 yrs	48 (F)	42	Shenyang	Apr-May	42.9±21.2	No	15.0		
	68.9 yrs	50 (M)	42	Shenyang	Mar-May	28.4±12.5	No	48.0		
Diabetes Care 2009	50-70 yrs	3262 (M+F)	31 40	Shanghai+ Beijing	Apr-Jun	40.4	Unknown		69.2	
Bri J Nutr 2012	61 yrs	1460 (M+F)	31	Shanghai	All	34.7	Unknown			96.1
Menopause 2011	64.1 yrs	1724 (F)	40	Beijing	Unknown	33.0±13.5	Unknown		89.7	99.4
Bone 2003	65.2 yrs	110 (F)	42	Shenyang	Feb-Apr	30.9±13.5	14.5%	39.1		
	67.9 yrs	108 (M)	42	Shenyang	Feb-Apr	27.1±11.5	9.3%	52.8		

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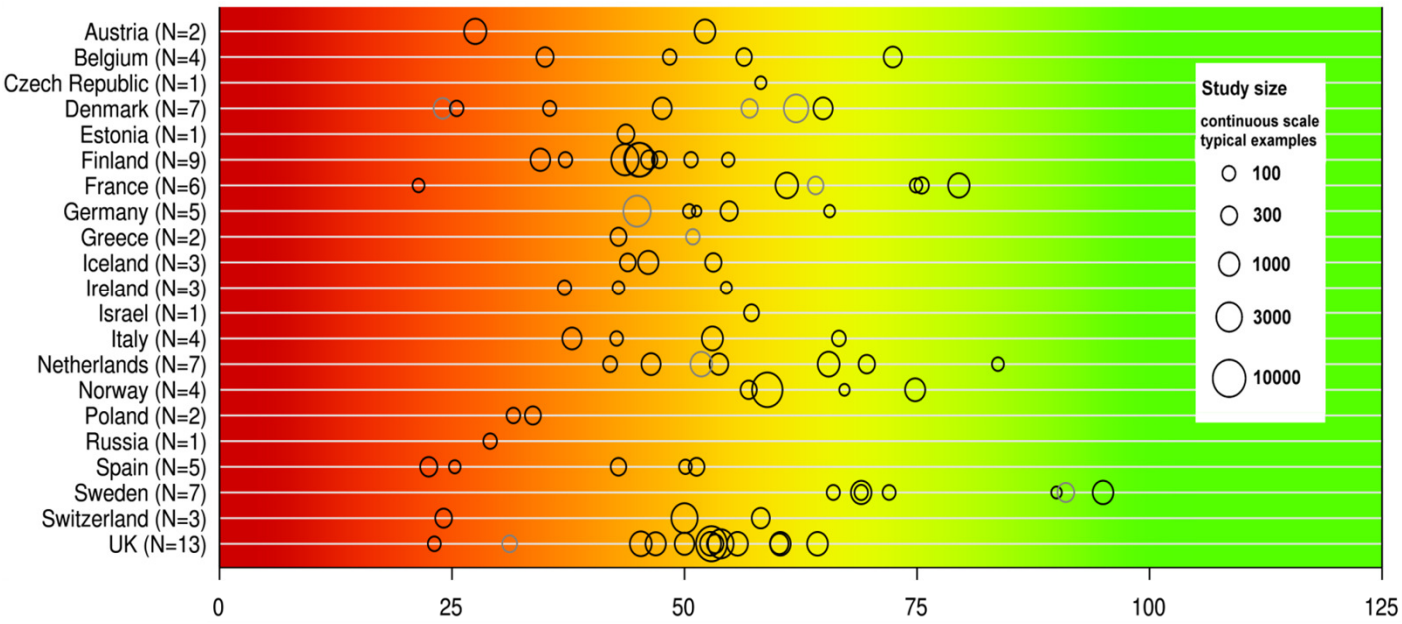
Vitamin D deficiency in China: present & widespread

East of Hu's line: <40 % land, >90 % population since 1930s

Ch_dem_alb
-200 - 0
1 - 50
51 - 100
101 - 200
201 - 300
301 - 400
401 - 500
501 - 600
601 - 700
701 - 800
801 - 900
901 - 1000
1001 - 1250
1251 - 1500
1501 - 2000
2000 - 3000
3001 - 4000
4001 - 5000
5001 - 6000
6001 - 10000
No Data

Image produced by ACASIAN, Griffith University

Broad variation of studies: example Vitamin D levels throughout Europe



High variations within one country and between countries