

Recent Research in Vitamin D

March 2, 2022

Susan J Whiting

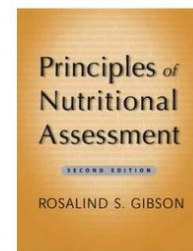
Distinguished Professor Emerita

University of Saskatchewan

BE WHAT THE WORLD NEEDS

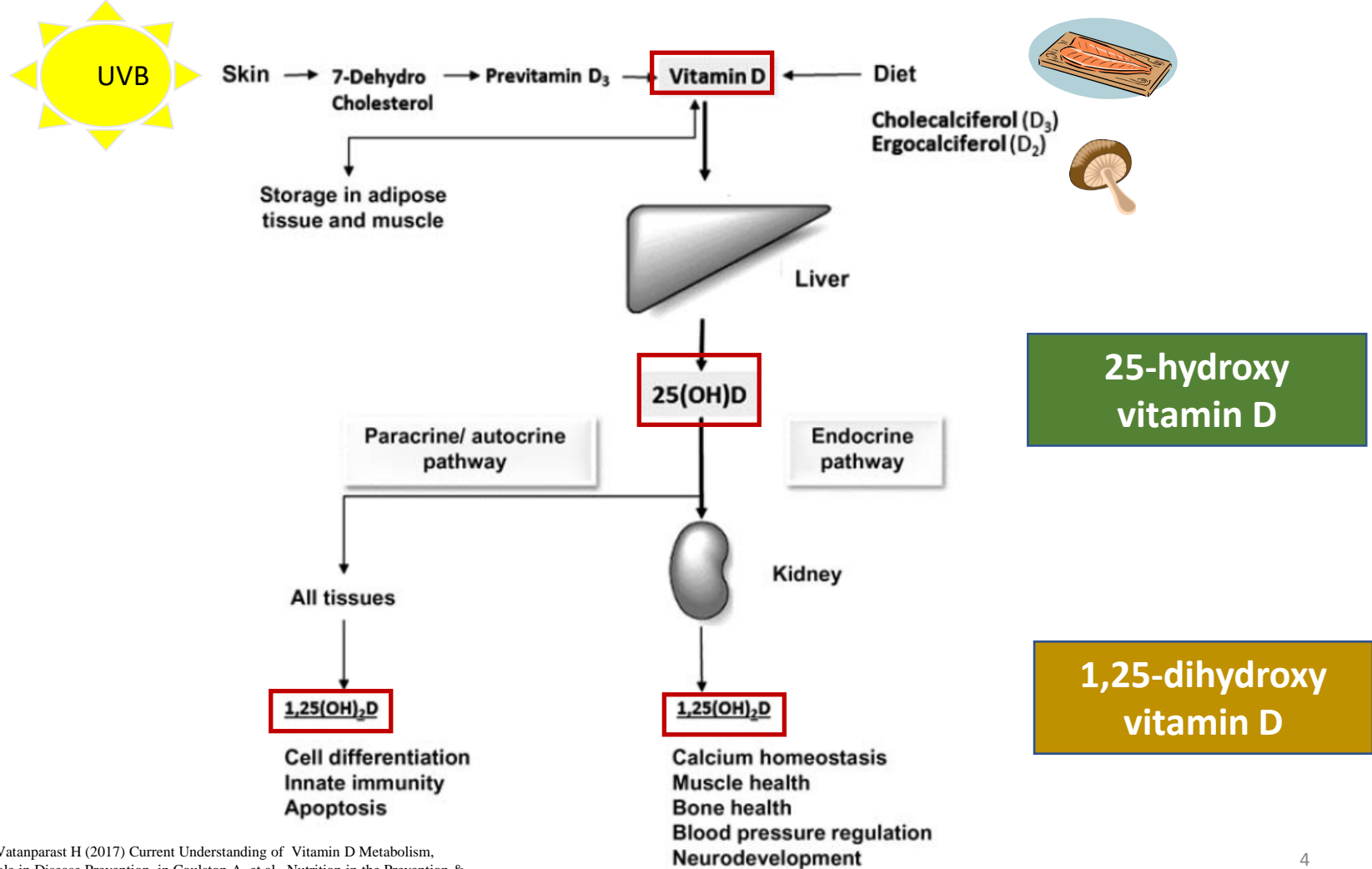
Disclosures

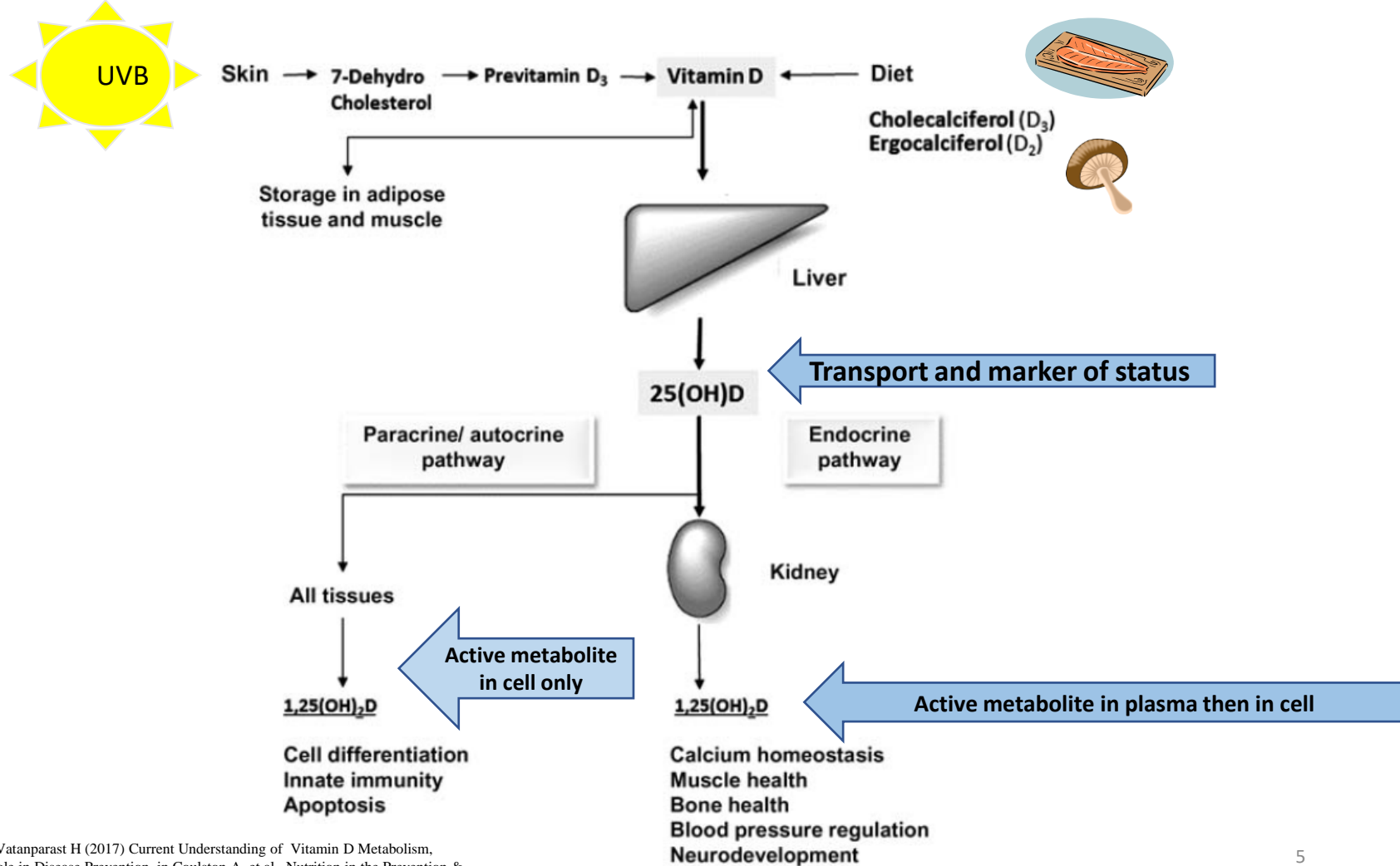
- No conflict of interest
- Volunteer member of the following groups but not speaking on behalf of any group:
 - Vitamin D Society; Vitamin D Workshop board
- Recent publications on vitamin D
 - <https://nutritionalassessment.org/>
 - Advances in Nutrition “Vitamin D in Brief”
 - BOTH ARE OPEN ACCESS



Outline

- 1. *Vitamin D sources, functions and recommendations***
 - *When is a “vitamin” not a vitamin?*
- 2. *A recent Randomized Controlled Trial (RCT) – VITAL***
 - *Getting the right interpretation*
- 3. *Balancing Safety and Effectiveness***
 - *Health Canada’s initiatives*






Recommendations for Vitamin D Intake

Organization/ Country	Serum 25(OH)D nmol/L	RDA or equivalent for adults <i>IU/d</i>	
		<i>Young Adult</i>	<i>Older adult</i>
<i>Public Health Focus</i>	Maintaining bone health		
IOM = CANADA (2011)	50	600	800
Nordic (2012)	50	400	800
DACH (2012)	50	800	800
Netherlands (2012)	30	400	800
Australia–NZ (2013)	50	600	800
UK (SACN 2016)	25	400	400
EFSA (2016)	50	600	600

Recommendations for Vitamin D Intake

Organization/ Country	Serum 25(OH)D nmol/L	RDA or equivalent for adults <i>IU/d</i>	
<i>Public Health Focus</i>	Maintaining bone health	<i>Young Adult</i>	<i>Older adult</i>
 IOM = CANADA (2011)	50	600	800
Nordic (2012)	50	400	800
DACH (2012)	50	800	800
Netherlands (2012)	30	400	800
Australia–NZ (2013)	50	600	800
UK (SACN 2016)	25	400	400
EFSA (2016)	50	600	600
<i>Clinical Health Focus</i>	Optimizing health for those at-risk	<i>Healthy</i>	<i>At-Risk</i>
OSTEO CANADA (2010)	75	400-1000	800-2000
IOF (2010)	75	800	2000
Endocrine Soc (2011)	75	n.a.	1500-2000

Clinical
 “At-risk” can include pre-existing disease of the gut, the liver and the kidney, and/or medication use

Causes of Secondary vitamin D Deficiency	
Pathology	Diseases
Malabsorption of fat reduces absorption of dietary vitamin D	Cystic fibrosis Celiac disease, Whipple’s disease, Crohn’s disease, Bypass surgery.
Liver failure prevents production of 25(OH)D	Cirrhosis Hepatitis
Inability to produce 1,25(OH)2D in kidney	Chronic kidney disease
Medications	
Drugs reducing Vitamin D absorption	Cholesterol-lowering agents: cholestyramine Weight loss drug orlistat and food additive olestra
Drugs reducing 25(OH)D levels due to increased catabolism	Anticonvulsant medications such as carbamazepine, phenobarbital, and phenytoin, gabapentin Antiretrovirals agents such as ritonavir and efavirenz, valproic acid (AIDS treatment) Histamine H2 receptor antagonist cimetidine
Drugs Impairing vitamin D metabolism	Oral corticosteroids such as glucocorticoids

Sources of Vitamin D

Sun exposure on skin

- At Latitude 42° and above we lack UVB between November and April
- Melanin (skin colour), clothing, glass windows, sunscreen, clouds, tall buildings (shade) reduce ability for synthesis
- Age: 13% decline per decade after age 20y

Dietary intake

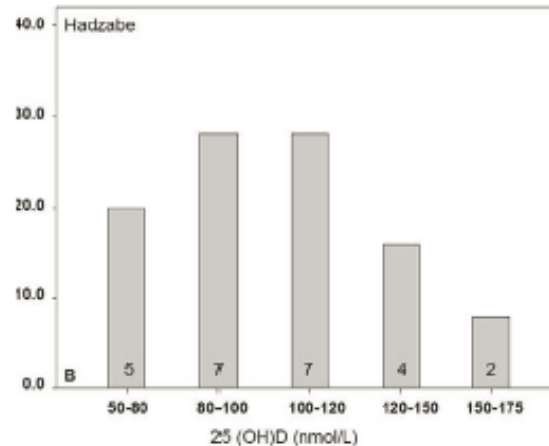
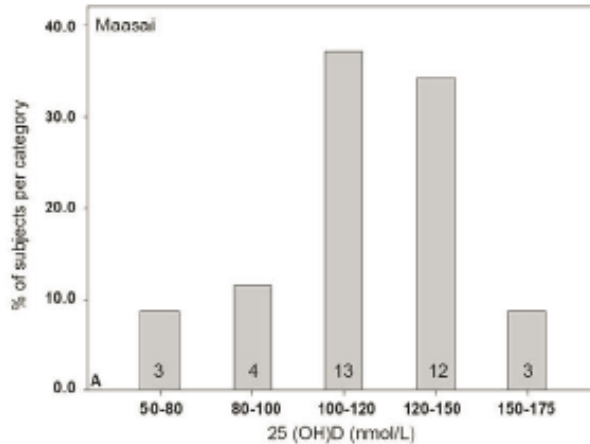
- Natural food sources are limited to animal sources: oily fish, fish liver, eggs, meat; fungi with D₂
- Fortification of milk and margarine is mandatory
- Other foods may be fortified e.g., some breakfast cereals, juice, plant “milks”

Getting all vitamin D from sun: People living and working outside in Equatorial East Africa

No one < 50 nmol/L

Maasai (n = 35)

Hadzabe (n = 25)



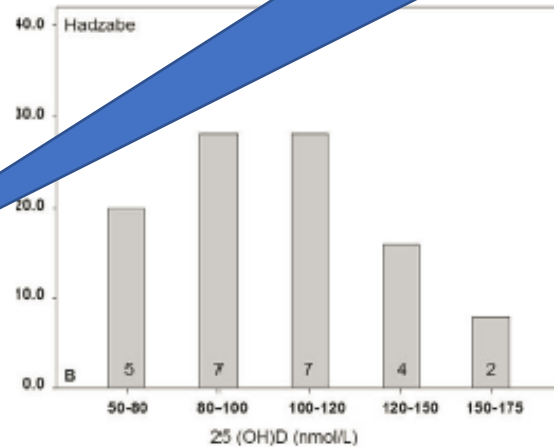
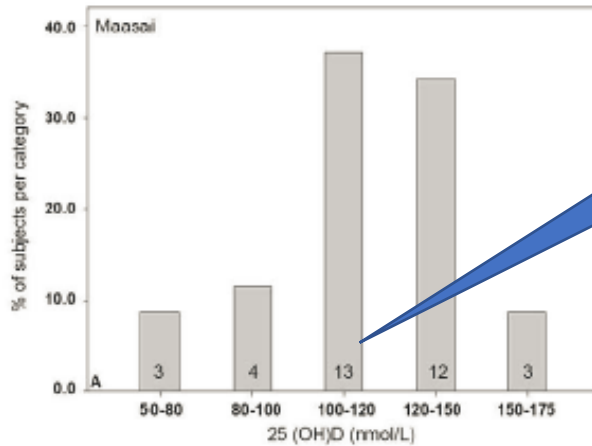
Getting all vitamin D from sun: People living and working outside in Equatorial East Africa

No one < 50 nmol/L

Because “in nature” 25OHD averages 100 nmol/L, many use this as the optimal

Maasai (n = 35)

Hadzabe (n = 20)



Time to make 1000 IU with full arms and legs exposed to sun

Factors for sun (UVB) exposure:

Skin colour
(Fitzpatrick skin type) and length of exposure are other important factors

Skin Type	Time (minutes) at noon June 21 At 42.5 °N
I - White burns easily	4
II - White – mostly burns	6
III - White - mostly tans	8
IV - Mediterranean	12
V - East Asian	15
VI - African	18

Webb & Engelsen 2006: cloudless day

Sources of Vitamin D

Sun exposure on skin

- At Latitude 42° and above we lack UVB between November and April
- Melanin (skin colour), clothing, glass windows, sunscreen, clouds, tall buildings (shade) reduce ability for synthesis
- Age: 13% decline per decade after age 20y

Dietary intake

- Natural food sources are limited to animal sources: oily fish, fish liver, eggs, meat; fungi with D₂
- Fortification of milk and margarine is mandatory
- Other foods may be fortified e.g., some breakfast cereals, juice, plant “milks”

The Canadian Diet is Inadequate in Vitamin D

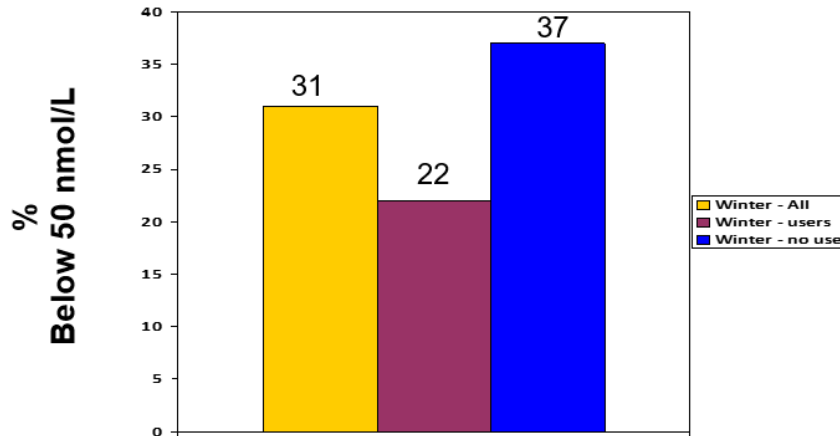
2004			2015		
<i>Food</i>		<i>% Inadequate</i>	<i>Food</i>		<i>% Inadequate</i>
200 IU		92%	160 IU		96%

Vitamin D Intake from Supplemental Sources but Not from Food Sources Has Increased in the Canadian Population Over Time

Hassan Vatanparast,^{1,2} Rashmi Prakash Patil,² Naorin Islam,² Mojtaba Shafiee,² and Susan J Whiting²

The Canadian Diet is Inadequate in Vitamin D

2004			2015		
Food		% Inadequate	Food		% Inadequate
200 IU		92%	160 IU		96%



Whiting et al., Am J Clin Nutr 2011

Vitamin D Intake from Supplemental Sources but Not from Food Sources Has Increased in the Canadian Population Over Time

Hassan Vatanparast,^{1,2} Rashmi Prakash Patil,² Naorin Islam,² Mojtaba Shafice,² and Susan J Whiting²

Relying Exclusively on Diet

People living in Arctic areas

no one < 50 nmol/L eating traditional foods

SEA MAMMALS

IU

Hooded seal blubber (100 g) 640

Harp seal blubber (100 g) 120

FISH

Halibut, Greenland, raw (100 g) 1100

Autumn mackerel (100 g) 500

Sockeye salmon (100 g) 670

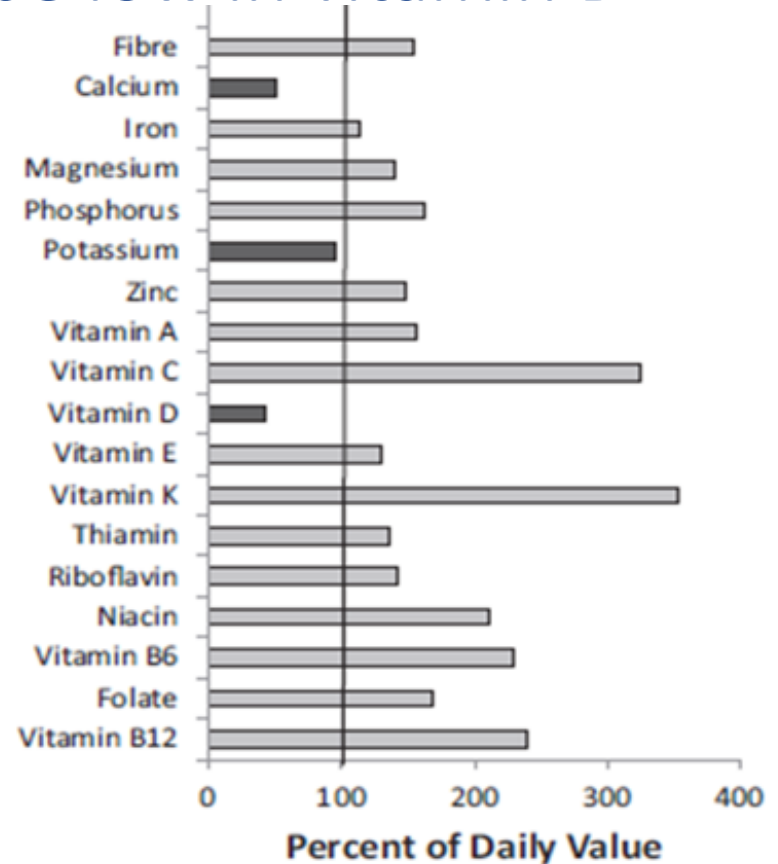
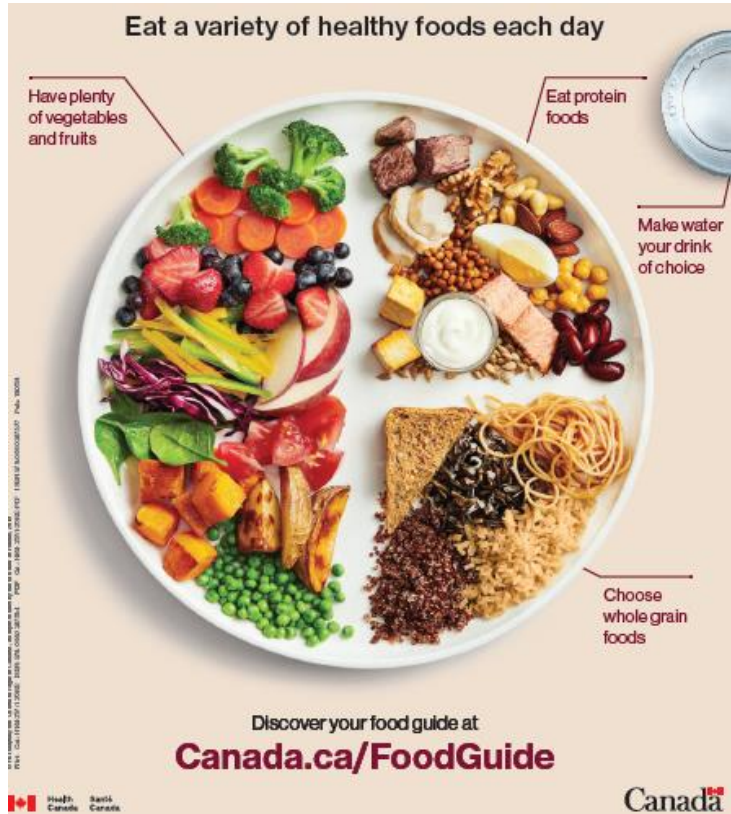
Salmon, canned (85 g) 400 – 650



Decrease in Vitamin D Status in the Greenlandic Adult Population from 1987–2010

Nina O. Nielsen^{1*}, Marit E. Jørgensen², Henrik Friis³, Mads Melbye⁴, Bolette Soborg⁵, Charlotte Jeppesen⁶, Marika Lundqvist⁶, Arieh Cohen⁶, David M. Hougaard⁶, Peter Bjerregaard^{1,7}

If you eat like this ... you will be low in vitamin D



Barr, Susan I. "Is the 2019 Canada's Food Guide Snapshot nutritionally adequate?." *Applied physiology, nutrition, and metabolism*. 44,12 (2019): 1387-1390.

Converting Units of Vitamin D Intake: 40 IU ⇔ 1 micrograms [μg, mcg]

Supplements as IU

- 2500 IU = 62.5 mcg on ingredient list



Food must be shown as mcg

Nutrition Facts	
Valeur Nutritive	
Per 1 cup (250 mL) par 1 tasse (250 mL)	
Calories 90	% Daily Value* % valeur quotidienne
Fat / Lipides 6 g	8%
Saturated / saturés 0.4 g + Trans / trans 0 g	2%
Carbohydrate / Glucides 2 g	
Fibre / Fibres 1 g	4%
Sugars / Sucres 0 g	0%
Protein / Protéines 8 g	
Cholesterol / Cholestérol 0 mg	
Sodium 160 mg	7%
Potassium 250 mg	5%
Calcium 300 mg	23%
Iron / Fer 2 mg	11%
Vitamin A / Vitamine A 100 mcg	14%
Vitamin D / Vitamine D 2 mcg	10%
Riboflavin / Riboflavine 0.4 mg	31%
Vitamin B12 / Vitamine B12 1 mcg	42%
Zinc 1 mg	9%

*5% or less is a little, 15% or more is a lot
*5% ou moins c'est peu, 15% ou plus c'est beaucoup

Because of low intake, Health Canada is doubling mandatory D in milk and margarine

Vitamin D fortification

Proposed FDR amendments

Food	Provisions	Current Vitamin D	Proposed Vitamin D
Milk	B.08.003-005	0.9 to 1.2 μg per 100 mL [300 to 400 IU per Reasonable Daily Intake]	2 μg per 100 mL or 5 μg per 250 mL (250 mL = reference amount or serving)
	B.08.007		
	B.08.010-014		
	B.08.016-020		
	B.08.023		
	B.08.026		
B.08.029			
Margarine	B.09.016	13.3 to 17.5 μg per 100 g [530 to 690 IU per 100 g]	26 μg per 100 g or 2.6 μg per 10 g (10 g = reference amount or serving)

Nutrition Facts Valeur Nutritive

Per 1 cup (250 mL)
par 1 tasse (250 mL)

	% Daily Value*
	% valeur quotidienne
Calories 90	
Fat / Lipides 6 g	8%
Saturated / saturés 0.4 g + Trans / trans 0 g	2%
Carbohydrate / Glucides 2 g	
Fibre / Fibres 1 g	4%
Sugars / Sucres 0 g	0%
Protein / Protéines 8 g	
Cholesterol / Cholestérol 0 mg	
Sodium 160 mg	7%
Potassium 250 mg	5%
Calcium 300 mg	23%
Iron / Fer 2 mg	11%
Vitamin A / Vitamine A 100 mcg	11%
Vitamin D / Vitamine D 2 mcg	10%
Riboflavin / Riboflavine 0.4 mg	31%
Vitamin B12 / Vitamine B12 1 mcg	42%
Zinc 1 mg	9%

*5% or less is a little, 15% or more is a lot

*5% ou moins c'est peu, 15% ou plus c'est beaucoup

Health Canada has a recommendation for vitamin D supplementation use (from 2007)

Vitamin D supplements

If you are over 50 years old, Health Canada recommends that you take a daily vitamin D supplement of 400 IU (equivalent to 10 µg).

Speak to your health care provider about taking a vitamin D supplement if you think you are not getting enough of it.

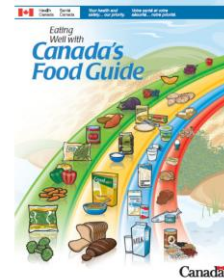
Screen shot
<https://www.canada.ca/en/health-canada/services/nutrients/vitamin-d.html#a2>

► Report a problem or mistake on this page

Share this page

Date modified: 2021-08-11

Origin of this recommendation is 2007 Food Guide when DRI for vitamin D was 400 IU for > 50y and 600 IU for > 70y.
Hence reason for “over 50y” as diet can only supply 200IU



Vitamin D Intake from Supplemental Sources but Not from Food Sources Has Increased in the Canadian Population Over Time

Hassan Vatanparast,^{1,2} Rashmi Prakash Patil,² Naorin Islam,² Mojtaba Shafiee,² and Susan J Whiting²

2004			2015		
<i>Food</i>	<i>Food + Supplement</i>	<i>% Inadequate</i>	<i>Food</i>	<i>Food + Supplement</i>	<i>% Inadequate</i>
200 IU	--	92%	160 IU	--	96%
200 IU	600 IU	21%	200 IU	2400 IU	14%

**Number of Supplement users has ↑
28 % in 2004 33% in 2015**

Keshavarz et al., APNM (2021)

- Less use in low income adults
- Greater use with education
- Food secure children use more supplements

Table 5. Factors associated with vitamin/mineral supplement use across age and gender groups of Canadians.

Variables	Adjusted OR (95% CI) ^a	
	Adults, ≥19 years	
Annual household income	<i>Odds ratio (OR):</i>	
\$80 000 or more	<i>Compared to highest income,</i>	1
\$60 000 to \$79 999	<i>lowest incomes</i>	0.85 (0.64–1.12)
\$40 000 to \$59 999	<i>are ~ 29 % less</i>	0.76 (0.58–1.00)
\$20 000 to \$39 999	<i>likely to use</i>	0.71 (0.54–0.94)
No income or <\$20 000		0.71 (0.50–0.99)
Education – household level	<i>University degree</i>	
No university degree	<i>-> 24 % more</i>	1
A university degree	<i>likely...</i>	1.24 (1.04–1.48) ←
Food security status		
Insecure	<i>Food secure -></i>	1
Secure	<i>27 % more likely</i>	1.27 (0.90–1.80) ←

Outline

1. *Vitamin D sources, functions and recommendations*
 - *When is a “vitamin” not a vitamin?*
2. **A recent RCT – VITAL**
 - *Getting the right interpretation*
3. *Balancing Safety and Effectiveness*

Principal Results of the VITamin D and OmegA-3 TriaL (VITAL) and Updated Meta-analyses of Relevant Vitamin D Trials

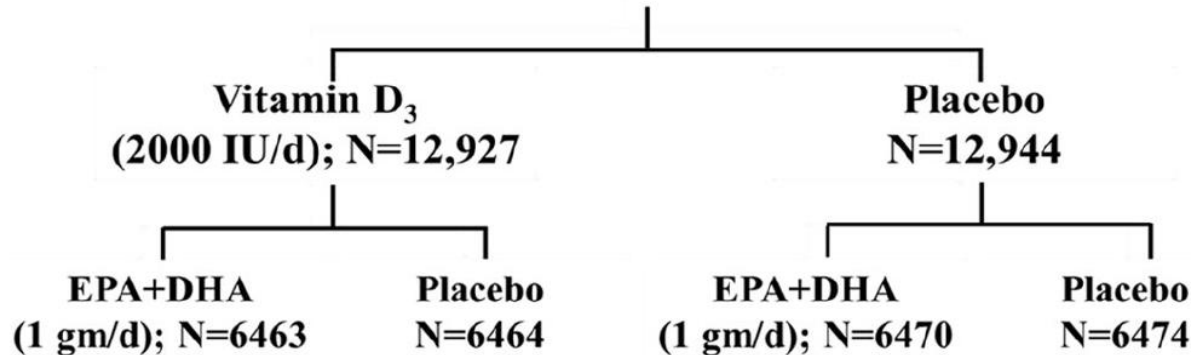
JoAnn E. Manson, MD, DrPH, Shari S. Bassuk, ScD, Julie E. Buring, ScD for the VITAL Research Group

Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Manson et al.

Page 18

**25,871 Initially Healthy Men and Women
(Men \geq 50 yrs; Women \geq 55 yrs)**



However, targeting those with known vitamin D deficiency for participation in a long-term trial with a 50% chance of randomization to placebo would not be ethical.

VITAL Trial

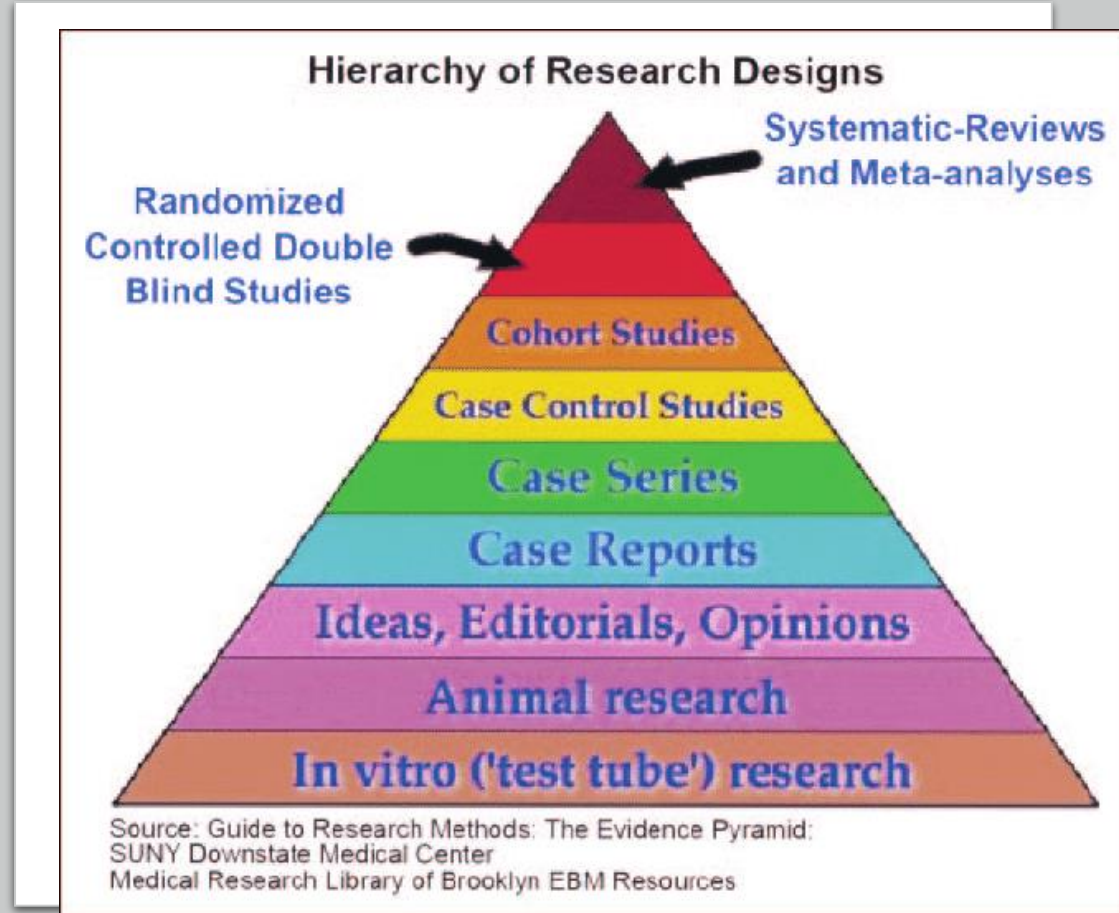
- Daily 2000 IU
- 5 years (median)
- 26,000 adults
- Mail-in
- Physician diagnosed
- Starting 25OHD was 75 nmol/L
- Everyone allowed to have up to 800IU
- Those in D treatment achieved 100 nmol/L
- 81 % adherence

Publications	Disease Outcome	Significant Findings of 2000 IU/day for 5 y
Manson et al., N Engl J Med. 2019;380:33–44	All invasive Cancer	Invasive cancer incidence (HR = 0.96 [CI 0.88-1.06]) Normal BMI: (HR=0.76 [0.63-0.90]) Total cancer mortality: (HR = 0.83 [0.67-1.02]), Excluding first year: (HR = 0.79 [0.63-0.99]) = 21% decrease Excluding first 2 years: (HR = 0.75 [0.59-0.96]) = 25% decrease
	Advanced colorectal	Greater benefit in those with starting levels below 75 nmol/L)
	CVD	No effects
LeBoff et al. JBMR 2020; 35:883-893.	Bone	Only when baseline FreeVD levels below the median, there was increase in spine aBMD (p = 0.043) and attenuation in loss of total hip aBMD (p = 0.044) with vitamin D3.
Kang et al, Sci Rep 2021	Cognitive decline (substudy of ~ 4000)	No effect over 2-3 y
Hahn et al., BMJ 2022 Jan 26;376:e066452	Autoimmune disease incidence over ~5 y	22% reduction in incident autoimmune diagnoses

What's Wrong with RCTs of VitD?

- They have been based on vitamin D dose rather than on baseline and achieved 25(OH)D concentrations
- They have involved participants with serum 25(OH)D above the population mean;
- They have given low vitamin D doses [in the past]
- They have permitted other sources of vitamin D.

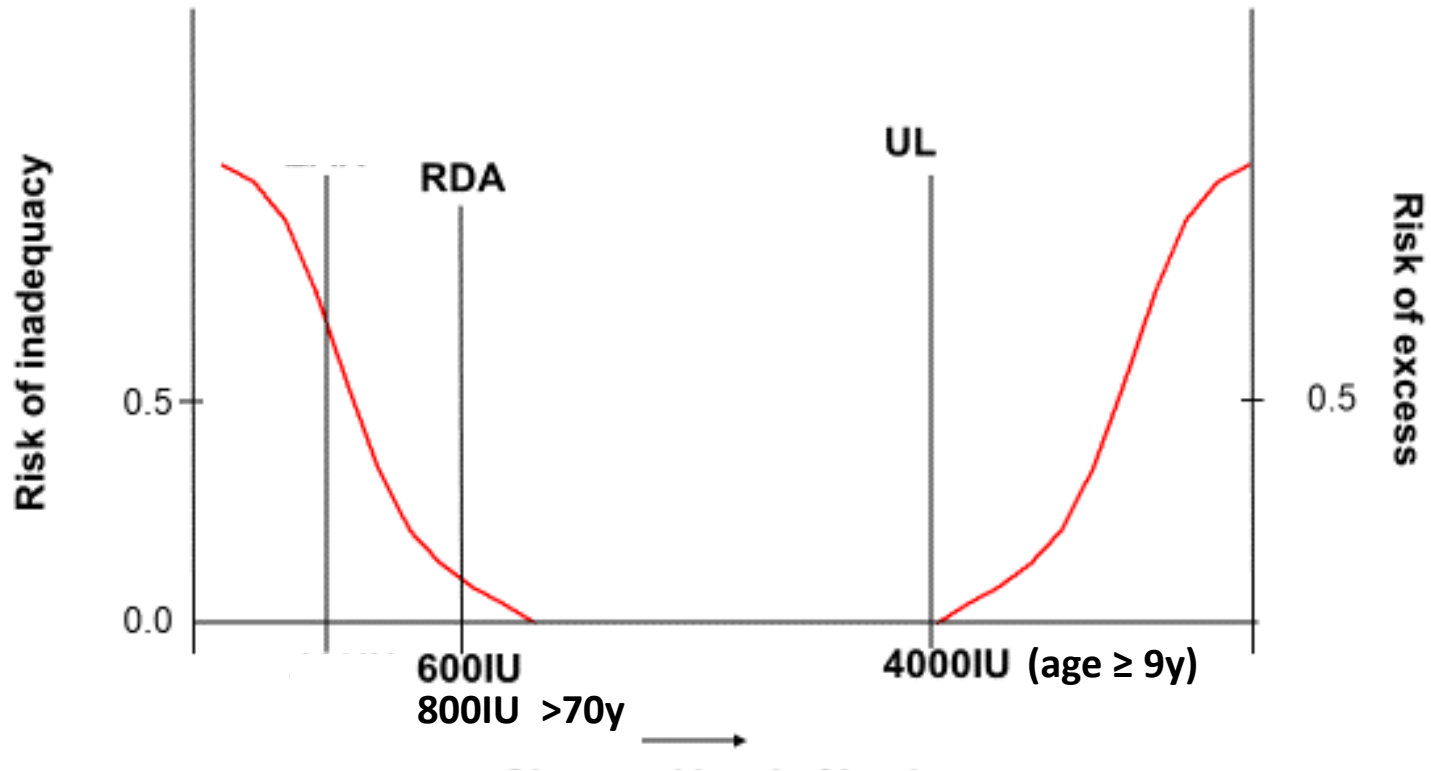
Grant et al., *Nutrients* **2022**, *14*, 639. <https://doi.org/10.3390/nu14030639>



Outline

1. *Vitamin D sources, functions and recommendations*
 - *When is a “vitamin” not a vitamin?*
2. *A recent RCT – VITAL*
 - *Getting the right interpretation*
3. ***Balancing Safety and Effectiveness***

In Nutrition the effect of intake is U-shaped

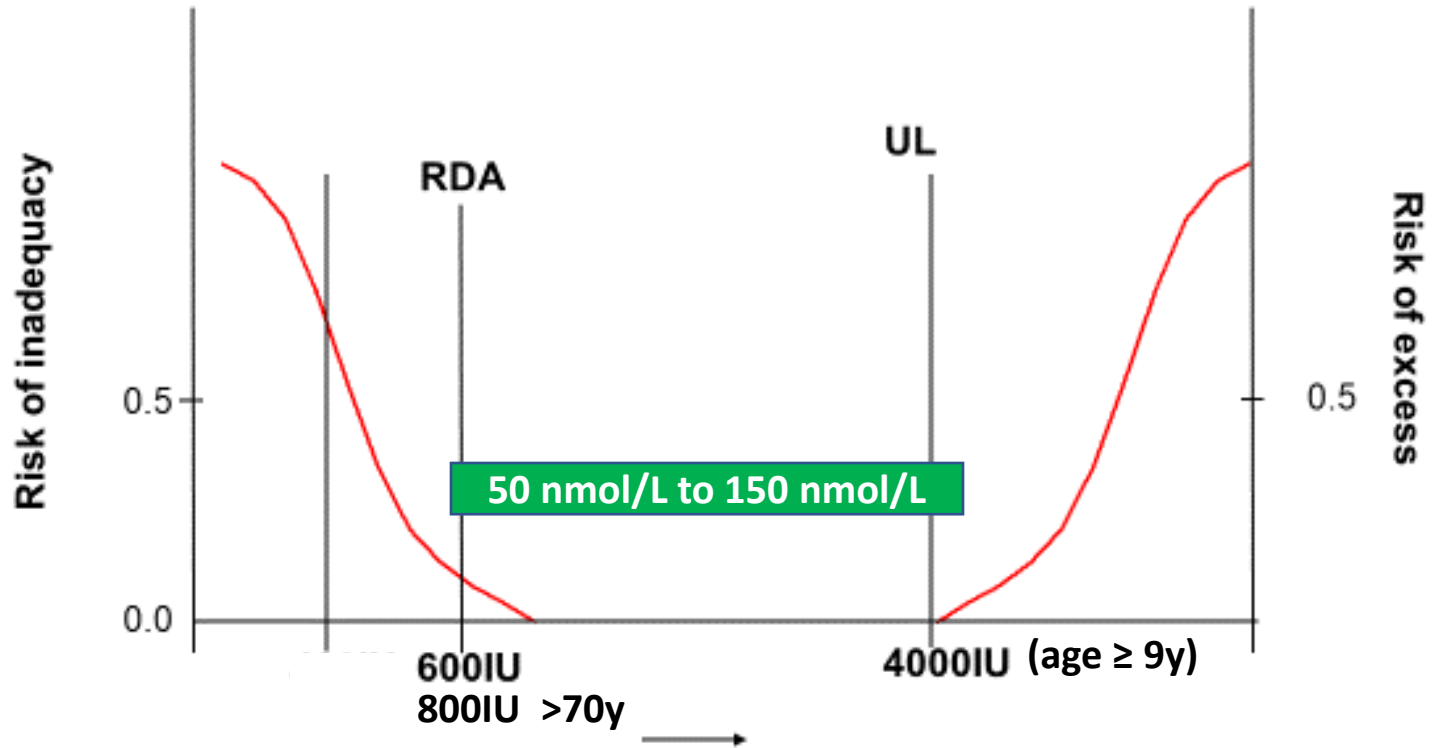


Health Canada now allows 2500 IU supplement that comes with a warning



Keep out of reach of children and pets. **15-20 mcg (600-800 IU) of vitamin D per day is adequate for most individuals.** Consult a health care practitioner to determine if you would benefit from additional vitamin D before taking this product. Do not use this product if you have **hypercalcemia** and/or hypercalciuria. Consult a health care practitioner prior to use if you: are pregnant or breastfeeding; have a kidney disorder; take other vitamin D supplements, multivitamin supplements containing vitamin D, or products containing vitamin D analogues; take any recommendation medications including antacids, anticonvulsants, digoxin, cholestyramine, colestipol, mineral oil, steroids, statins or thiazide diuretics. **Stop use** and consult a health care practitioner **if weakness, fatigue, drowsiness, headache, lack of appetite, dry mouth, metallic taste, nausea, vomiting, vertigo, ringing in the ears, lack of coordination and muscle weakness occur, which are early symptoms of hypercalcemia,** or if you have any other side effects.

Safety: stay below Upper Level unless under supervised treatment



SUMMARY

1. Vitamin D sources, functions and recommendations

- *Understanding history, anthropology, cell biology to reach an understanding of how much is enough*

2. A recent RCT – VITAL

- *RCTs in nutrition are costly and often show little effect*

3. Balancing Safety and Effectiveness

- *New 2500 IU tablets now available = dose in VITAL trial*