



# Vitamin D, Cognition and Dementia

## Summary Slides

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## Faculty/Presenter Disclosure

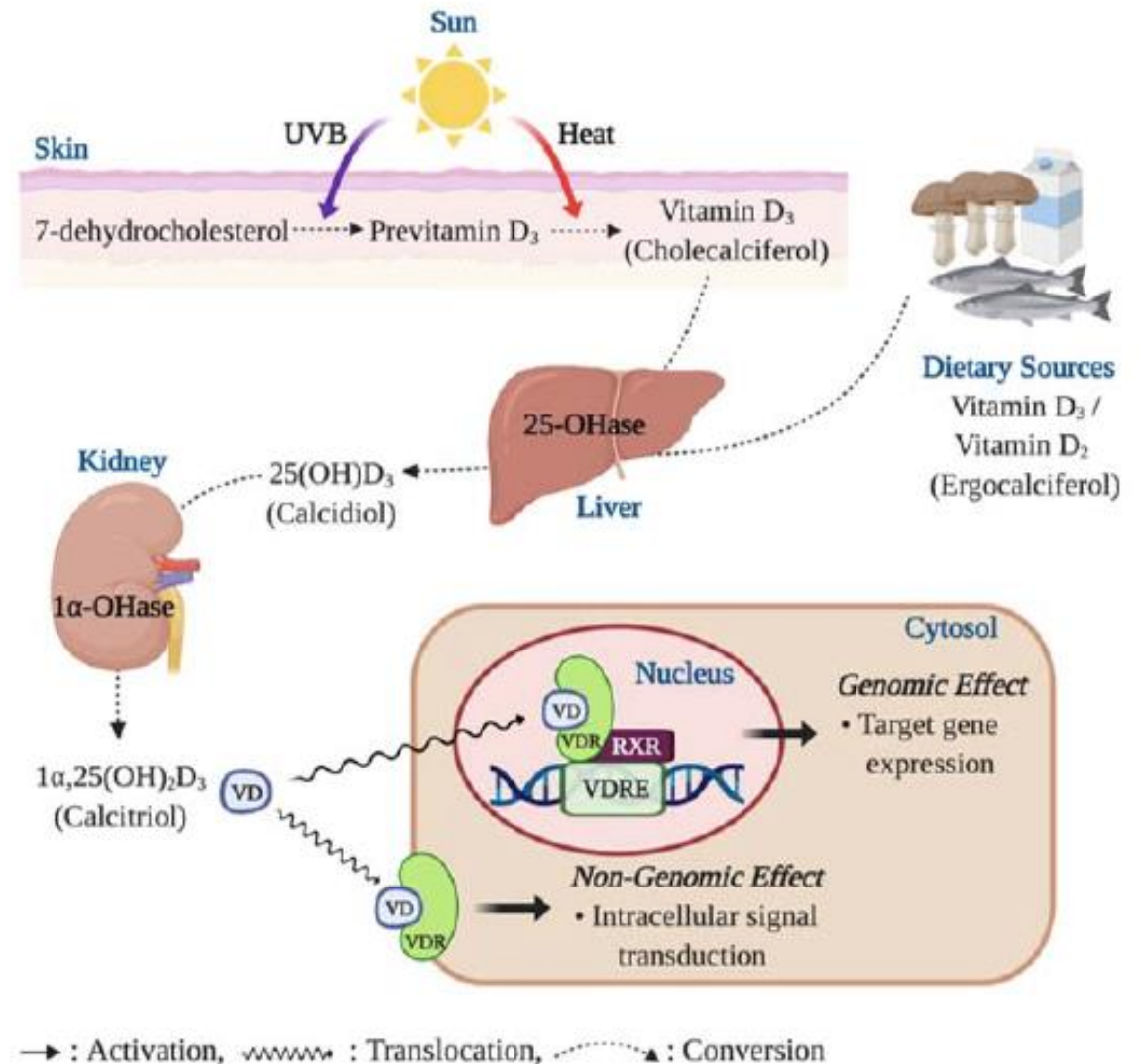
- **Relationships with commercial interests:** none
- **Editorial Board:** Nutrients (Micronutrients Subsection)
- **Author:** publications on vitamin D and cognition

# Learning Objectives

- 1) Describe how vitamin D acts in the brain and how this might relate to cognition and dementia.
- 2) Discuss evidence from the literature on vitamin D and its association with cognition and dementia.
- 3) Discuss practical implications

# What is Vitamin D?

- Fat-soluble steroid pro-hormone, **Calciferol** (skin synthesis, diet)
  - D3: cholecalciferol; D2: ergocalciferol
- **25(OH)D (calcidiol)** [measured in blood]
- **1,25-dihydroxyvitamin D (calcitriol)** [active form]
  - **Genomic** receptor binding (nucleus) modulates transcription of multiple genes
  - **Non-genomic** receptor binding (cell wall) causes rapid rise in intracellular calcium concentrations (causes rapid effects)
  - **Epigenetic** effects at different stages of development



# How Much?

- Recommendations differ; are based on *bone* health

Institute of Medicine (IOM)	Endocrine Society
25(OH)D $\geq$ 50 nmol/L	25(OH)D $\geq$ 75 nmol/L
600 IU/day ages 1-70 yrs	400-1000 IU/d ages 1-18
800 IU/day ages >70	1500-2000 IU/d adults*
	*Obese adults require 2-3 times more

- Many experts hypothesize that optimal 25(OH)D for all health outcomes is around 100 - 120 nmol/L; Endocrine Society's "preferred range" is 100-150 nmol/L [Kimball, Holick Eur J Clin Nutr 2020, 74:1514-1518.]

# What Does Vitamin D Do in the Brain?

- The brain possesses 1- $\alpha$ -hydroxylase and vitamin D receptors (VDR) [Eyles et al 2005]
- Vitamin D increases acetylcholine levels via increasing ChAT [Sonnenberg et al 1986]
- Vitamin D increases hippocampal neuron densities [Landfield 1998]
- Vitamin D has neuroprotective effects by:
  - Limiting excess calcium influx [Brewer et al 2001]
  - Upregulating neurotrophic factors and inducing calcium binding proteins
  - Aiding detoxification (increases glutathione [Garcion et al 2002; Deluca et al 2013])

# Other Mechanisms

- Vasoprotective actions: decreases endothelial dysfunction, [Kim et al (2020)] advanced glycation end-products (AGEs) [Krul-Poel et al 2015]
- Anti-inflammatory effects [Yu et al (2022)]
- Favorably alters the microbiome [Bosman et al (2019)]
- Enhances breakdown, clearance of amyloid-beta [Masoumi et al (2009); Ito et al (2011)]
- Reduced formation of A-beta plaques and peptides [Yu et al (2011)]
- Provides neuroprotection against amyloid-beta-induced tau hyperphosphorylation [Lin et al (2020)]

# Questions

- 1) Is vitamin D status associated with cognition;
- 2) and cognitive decline in aging?
  
- 3) Is vitamin D status associated with risk of dementia?
  
- 4) Does vitamin D supplementation improve cognition?
  
- 5) Does vitamin D supplementation decrease risk of dementia?

Which cognitive domains?

How much (dose-response)?

Who benefits most?



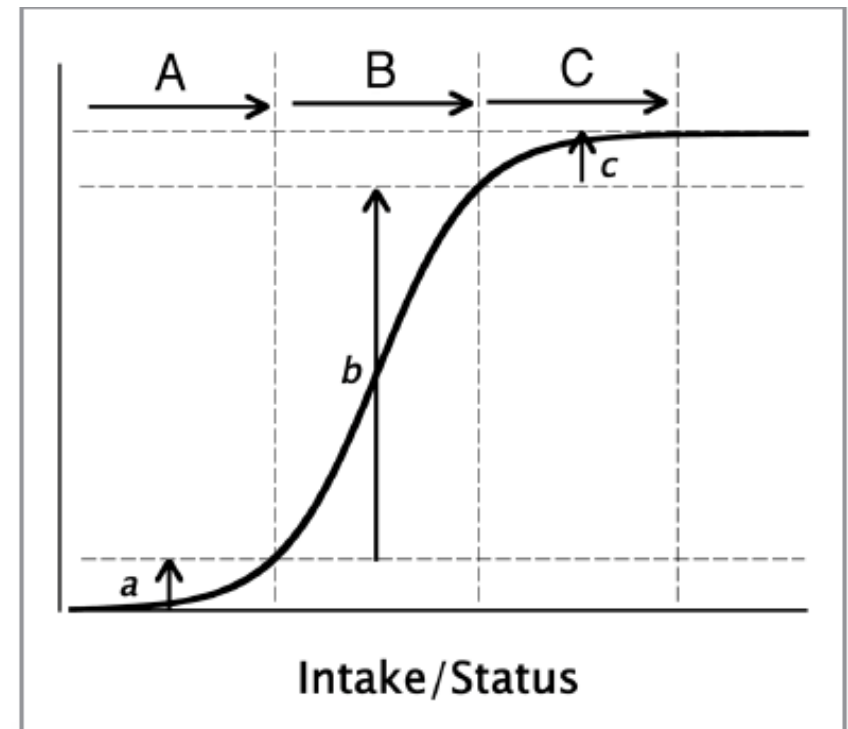
# Questions & Answers

- 1) Is vitamin D status associated with cognition; **yes**
- 2) and cognitive decline in aging? **yes**
  - Which cognitive domains? **Global cognition, executive functioning, (visual) memory**
  - How much (dose-response) and who benefits most? **~60-70 nmol/L (or more); Older individuals (65yrs+), women > men**
- 3) Is vitamin D status associated with risk of dementia? **yes**
  - How much (dose-response) and who benefits most? **Increased risk of dementia (and AD) with deficient levels (<25 nmol/L) and likely insufficient levels (<50-75 nmol/L); Unclear**
- 4) Does vitamin D supplementation improve cognition? **possibly**
  - Which cognitive domains? **global cognition, (visual memory, executive functioning)**
  - How much (dose-response) and who benefits most? **Unclear but likely boosting deficient/insufficient at baseline; vulnerable populations (?MCI, AD), ?Black > white**
- 5) Does vitamin D supplementation decrease risk of dementia? **unclear**
  - How much (dose response) and who benefits most? **Unclear, perhaps women > men, APOE4 noncarriers > carriers, cognitively well at baseline > MCI**

# Why Vitamin D Supplement Trials Often Fail

Lappe, Heaney *Dermato-Endocrinol* 2012;4(2):95-100; Boucher *Endocrine Connections* 2020;9, R195-R206.

- VitD RCTs have used designs evolved for testing *drugs* not nutrients
- Nutrient-specific issues
  - Sigmoid response and starting level
  - Adequacy of dose/exposure
  - Low dose control group, additional vitD intake
  - Co-nutrient optimization
  - Population heterogeneity



Lappe et al (2012)

# Practical Implications

- There is biological plausibility that vitamin D is important for brain health, cognition and prevention of dementia
- Low 25(OH)D levels are associated with worse cognition and dementia and increased risk of developing cognitive decline and dementia
- Raising 25(OH)D levels to overcome insufficiency *may* improve/maintain cognition with aging
- We don't know (yet) if it will prevent/delay dementia
- Maintaining adequate levels of vitamin D throughout earlier life will “improve the likelihood of successful brain aging” (Latimer et al PNAS 2014)

# Practical Implications

- To avoid insufficiency, most people will need to supplement in winter and many will need to continue supplementing during the rest of the year
- ~1500-2000\* IU/d to achieve and maintain  $\geq 75$  nmol/L
  - (~4000\* IU/d for  $\geq 100$  nmol/L)
- Take with fat; adequate intake of other nutrients
- Most people do not require follow-up measurement of 25(OH)D (toxicity extremely rare) unless risk factors for deficiency (see below)

\*May need up to up to 2-3 x more if: obesity, diabetes, GI malabsorption, certain medications (anti-epileptics, glucocorticoids, antifungals, AIDS medications)

[Kimball & Holick Eur J Clin Nutr (2020);74:1514-1518.]