Vitamin D and Brain Health

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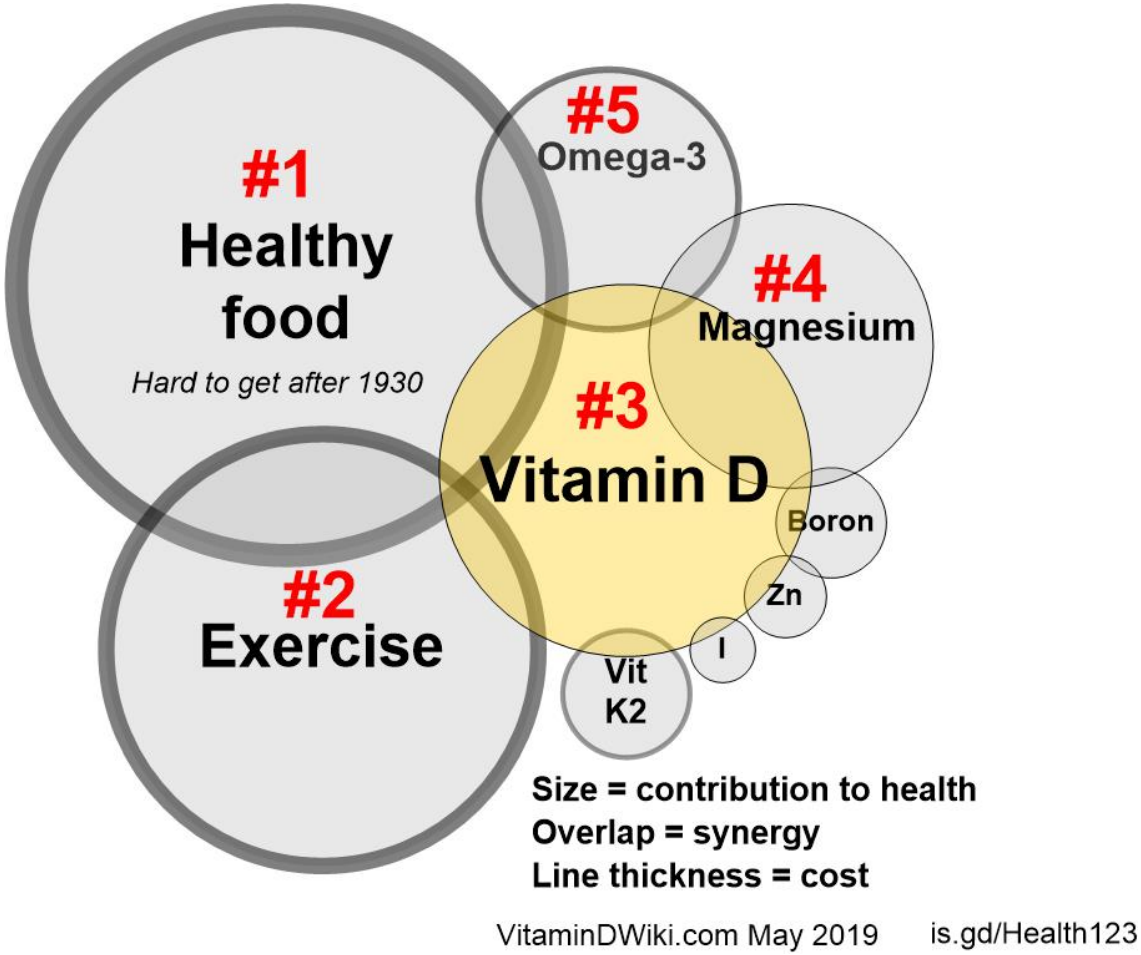
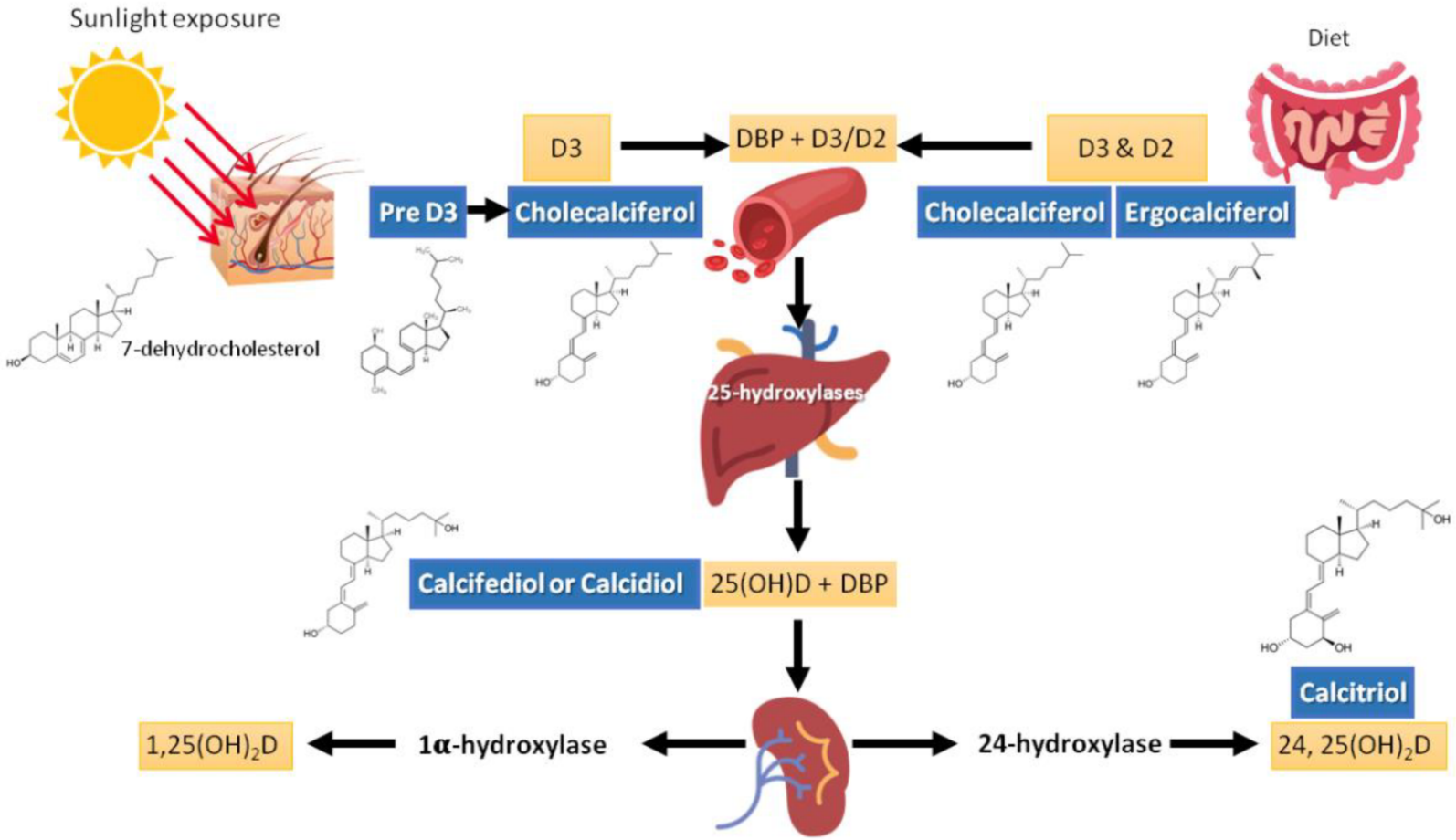
Outline

- Vitamin D overview
- Types of evidence
  - Randomized controlled trials, cohort studies
- Effect of follow-up period in cohort studies
  - Alzheimer's, dementia, cognitive, stroke
- Alzheimer's risk factors and vitamin D
  - Inflammation, insulin resistance, infections, lipids, sleep
- Other brain benefits of vitamin D
- Recommendations

Vitamin D is the Lowest-cost Major Contributor to Health



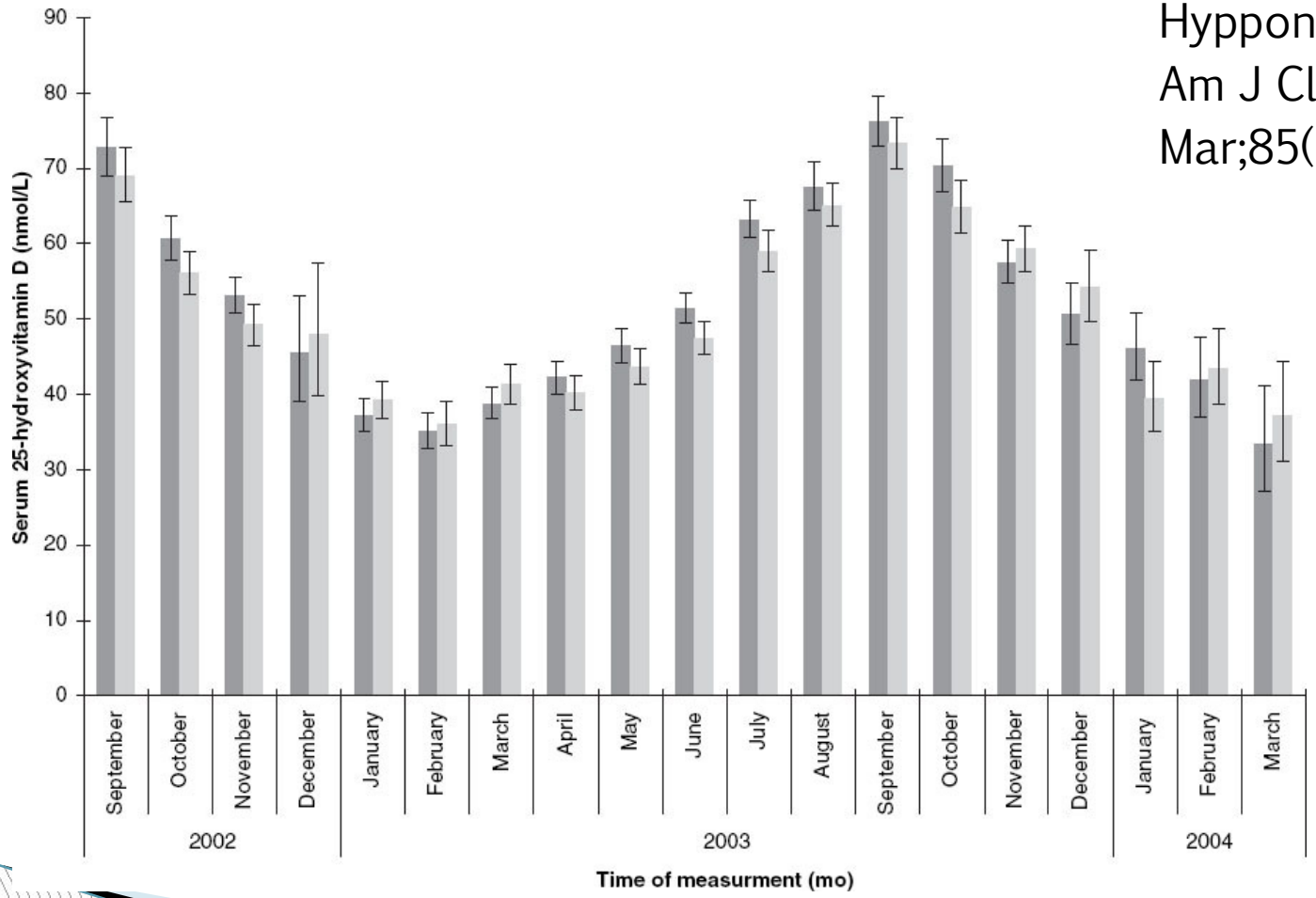
Dominguez et al. Vitamin D Sources, Metabolism, and Deficiency. Metabolites 2021, 11, 255.



An Example of Serum 25(OH)D Concentration Affecting Gene Expression

- Thirty healthy adults were randomized to receive 600, 4,000 or 10,000 IU/d of vitamin D_3 for 6 months. Circulating parathyroid hormone (PTH), 25(OH)D, calcium and peripheral white blood cells broad gene expression were evaluated. There was a dose-dependent 25(OH)D alteration in broad gene expression with 162, 320 and 1289 genes up- or down-regulated in their white blood cells, respectively.
- Shirvani et al. Sci Rep. 2019;9(1):17685.

Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors



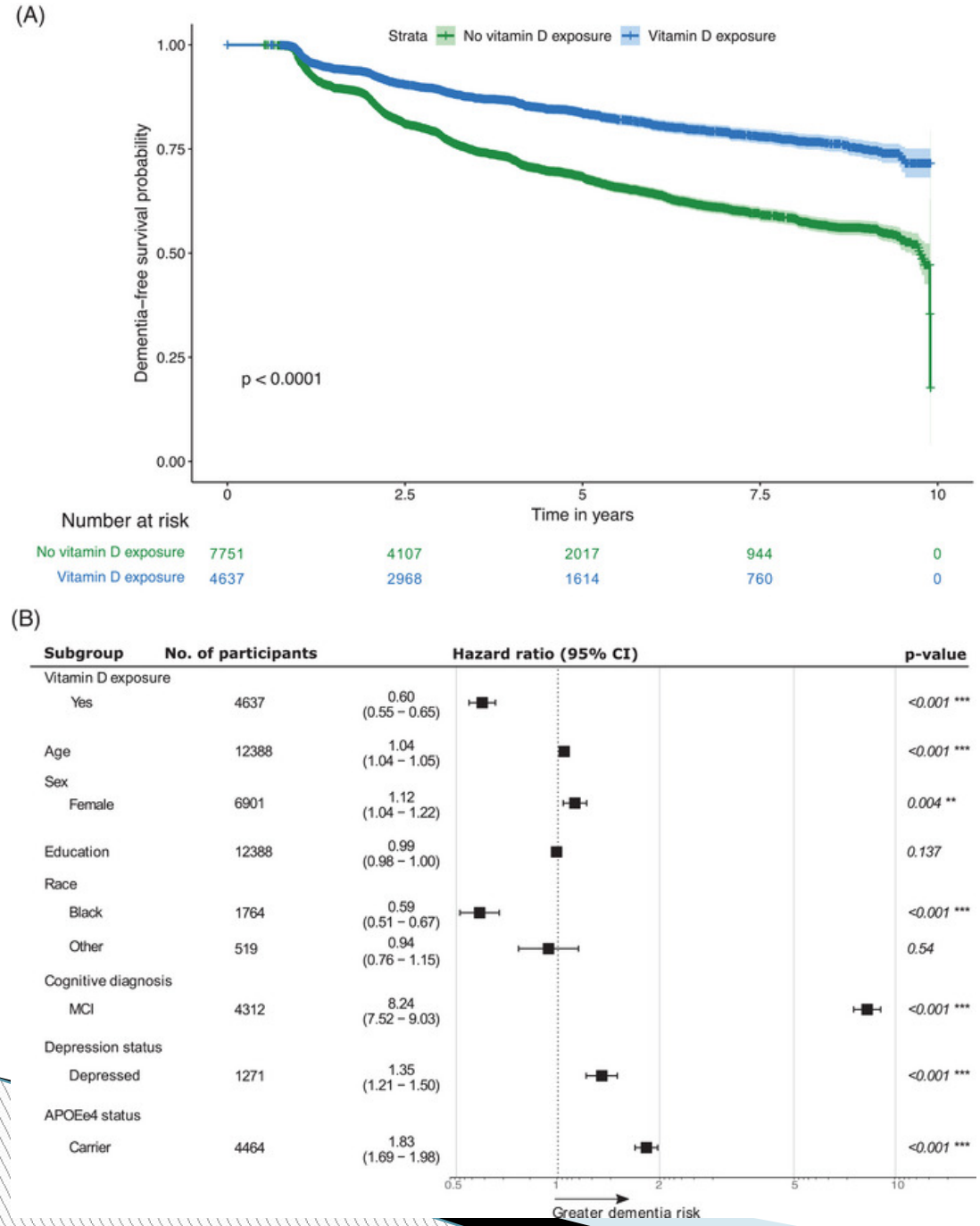
Hypponen, Power.
Am J Clin Nutr. 2007
Mar;85(3):860-8

Distribution of vitamin D status in the UK: a cross-sectional analysis of UK Biobank; 2006-2010

- Underweight (N=2301)
- < 25 nmol/L; 25-50 nmol/L; >50 nmol/L
- 18% 37% 45%
- Healthy weight (N=144 591)
- 11% 37% 52%
- Overweight (N=189 583)
- 12%) 42% 46%
- Obese (N=110 292
- 19% 48% 33%
- Lin et al. BMJ Open 2021;11:e038503

Types of Evidence re Vitamin D Benefits

- Observational studies
  - Prospective cohort studies
  - Cross-sectional studies
- Randomized controlled trials (RCTs)
  - Most vitamin D RCTs have been based on guidelines for pharmaceutical drugs. As a result, they are poorly designed, conducted, and analyzed for nutrients such as vitamin D: participants had high baseline 25(OH)D concentrations; those in the treatment arm were given low vitamin D doses; those in the control arm also took vitamin D; results not analyzed with respect to achieved 25(OH)D concentration
- Mechanisms

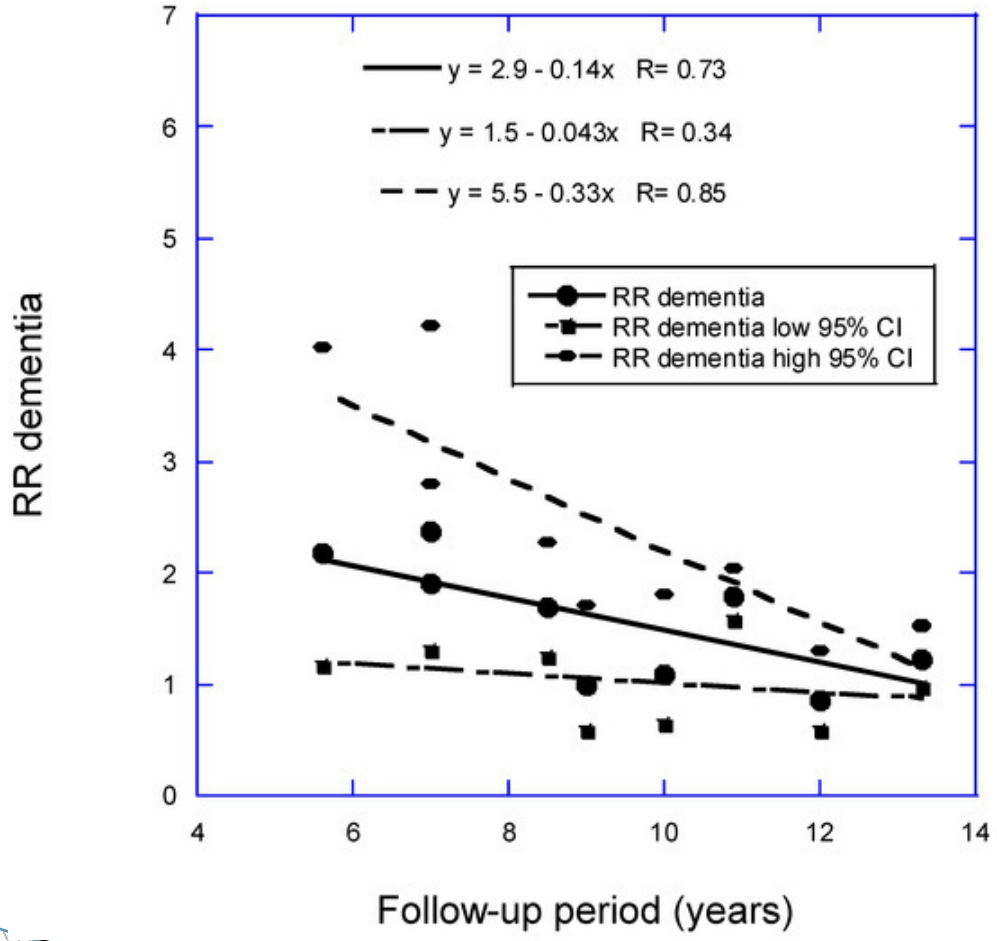


Longitudinal study involving 12,388 dementia-free persons in 40 centers in the US with mean age 71 years at baseline, followed for ten years.

Any vitamin D supplementation vs. none was associated in a 40% reduced risk of dementia (Alzheimer's disease and vascular dementia). Females, those without mild cognitive impairment, and those without ApoE ε4 had greater reductions.

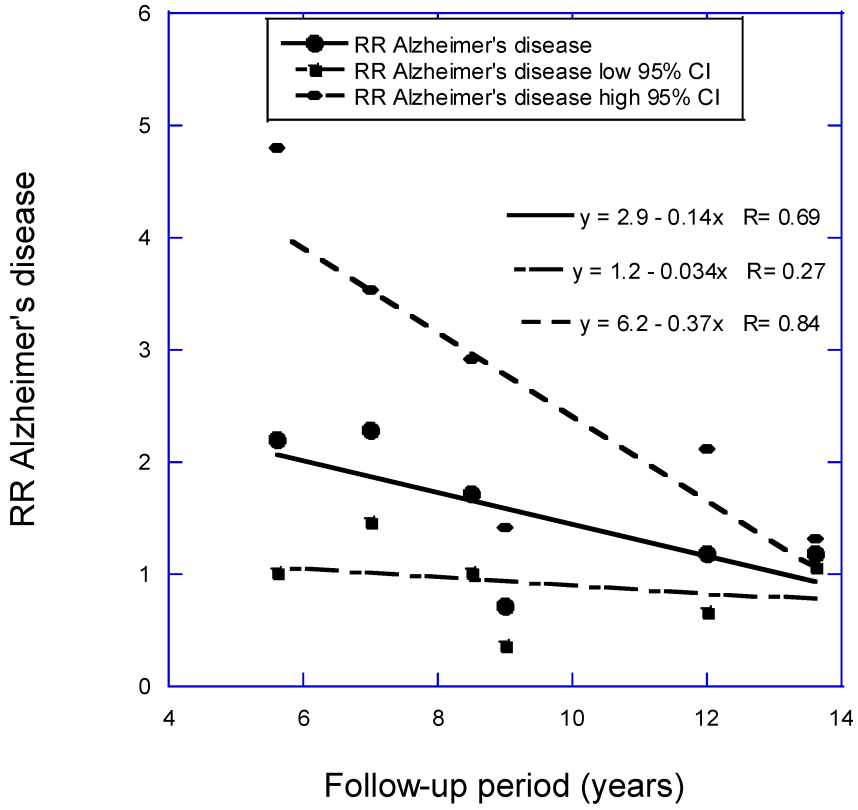
Ghahremani et al. Vitamin D supplementation and incident dementia: Effects of sex, APOE, and baseline cognitive status Alzheimers Dement (Amst). 2023;15(1):e12404.

Grant WB. Follow-Up Period Affects the Association between Serum 25-Hydroxyvitamin D Concentration and Incidence of Dementia, Alzheimer's Disease, and Cognitive Impairment. Nutrients. 2024; 16(18):3211.



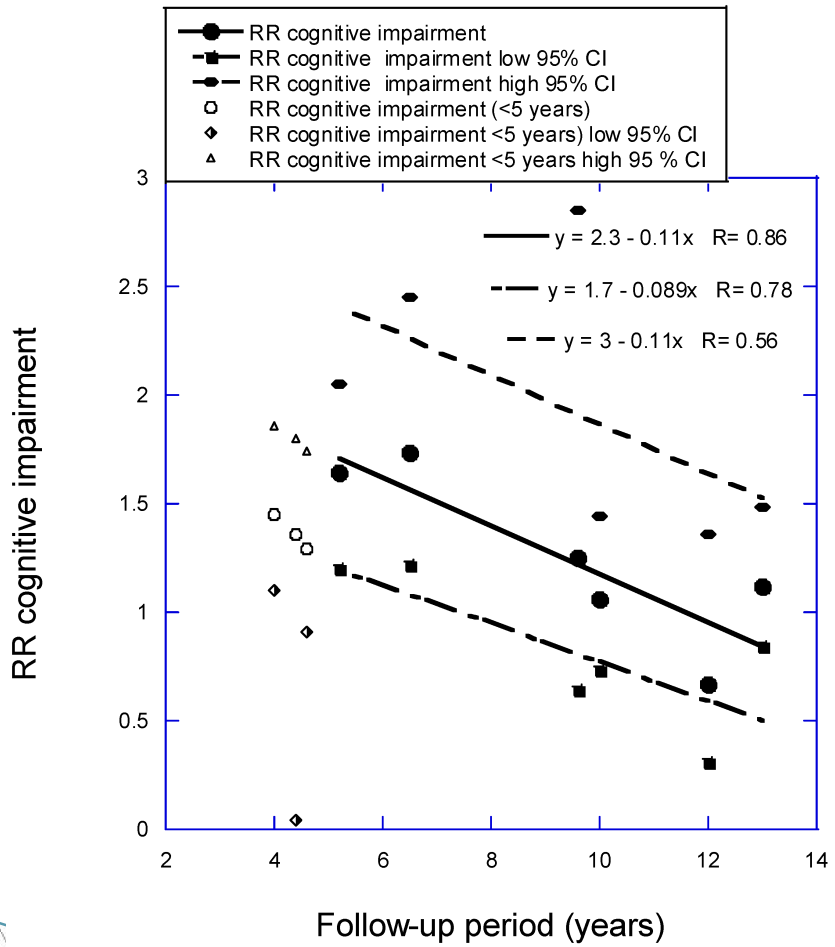
As follow-up period increases, the measured relative risk for dementia for low vs. high 25(OH)D (<25 or 50 nmol/L vs. >50 nmol/L) decreases since 25(OH)D concentrations change with time. The middle line is the regression fit to the RR; the outer two lines are the fit to the 95% confidence interval. The spread is larger for shorter follow-up times due to lower number of events. Above about 12 years, the RR is near 1.0 (i.e., no effect).

Grant WB. Follow-Up Period Affects the Association between Serum 25-Hydroxyvitamin D Concentration and Incidence of Dementia, Alzheimer's Disease, and Cognitive Impairment. Nutrients. 2024; 16(18):3211.



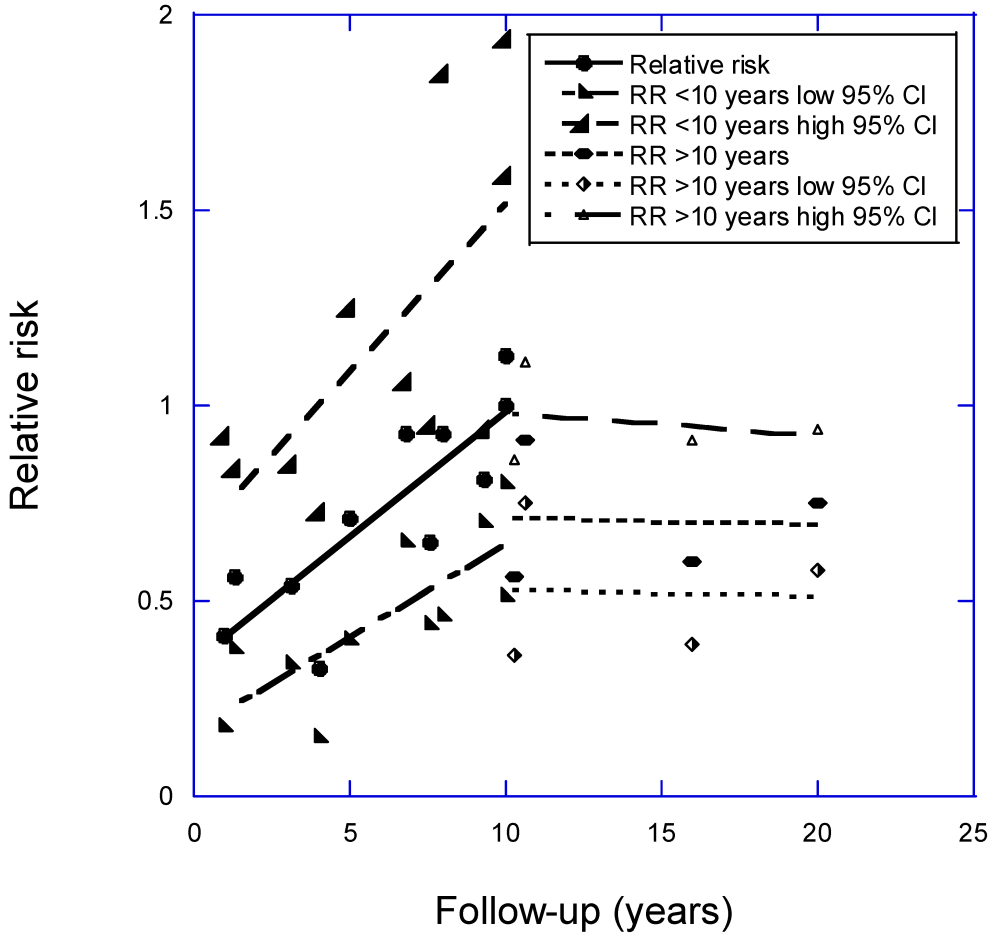
Relative risk for Alzheimer's disease for low vs. high 25(OH)D concentration (<25 or 50 nmol/L vs. >50 nmol/L) as a function of follow-up years.

Grant WB. Follow-Up Period Affects the Association between Serum 25-Hydroxyvitamin D Concentration and Incidence of Dementia, Alzheimer's Disease, and Cognitive Impairment. Nutrients. 2024; 16(18):3211.



Relative risk for cognitive impairment for low vs. high 25(OH)D concentration (<25 or 50 nmol/L vs. >50 nmol/L) as a function of follow-up years.

Grant, W. B., & Boucher, B. J. (2024). How Follow-Up Period in Prospective Cohort Studies Affects Relationship Between Baseline Serum 25(OH)D Concentration and Risk of Stroke and Major Cardiovascular Events. Nutrients, 16(21), 3759.



Relative risk for stroke for high vs. low 25(OH)D concentration

Risk Factors for Alzheimer's Disease Affected by Vitamin D

- Inflammation
- Insulin resistance
- Type 2 diabetes mellitus
- Atherosclerosis
- Infections
- Periodontal disease
- Sleep disturbance

Inflammation Context in Alzheimer's Disease, a Relationship Intricate to Define

- Importantly, Amyloid beta (Aβ) and tau species are able to activate astrocytes and microglia, which release several proinflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β), together with reactive oxygen and nitrogen species, triggering neuroinflammation. However, this inflammatory response has a dual function: it can play a protective role by increasing Aβ degradation and clearance, but it can also contribute to Aβ and tau overproduction and induce neurodegeneration and synaptic loss.
- Moreover, diseases related to systemic or local inflammation, including infections, cerebrovascular accidents, and obesity, have been proposed as risk factors for the development of AD.
- Novoa et al. Biol Res. 2022;55(1):39.

Vitamin D as a Modulator of Neuro-inflammation: Implications for Brain Health

- Vitamin D's mechanisms of action include cytokine modulation and regulation of nuclear and mitochondrial genes. It adjusts inflammatory mediators and antioxidants, resulting in neuroprotective effects. Additionally, vitamin D impacts neurotransmitter synthesis and brain plasticity.
- Menéndez SG, Manucha W. Curr Pharm Des. 2024;30(5):323-332.

Insulin Resistance and Alzheimer's

- Insulin and insulin-like growth factor-1 receptors are expressed on all cell types in the central nervous system. Insulin is known to regulate glucose metabolism, support cognition, enhance the outgrowth of neurons, modulate the release and uptake of catecholamine, and regulate the expression and localization of gamma-aminobutyric acid. Insulin is also able to freely cross the blood–brain barrier from the circulation. In addition, changes in insulin signaling, caused inter alia insulin resistance, may accelerate brain aging, and affect plasticity and possibly neurodegeneration.
- Sędzikowska A, Szablewski L. Insulin and Insulin Resistance in Alzheimer's Disease. Int J Mol Sci. 2021; 22(18):9987.

Insulin Resistance

- Insulin resistance occurs when body cells fail to respond properly to insulin, forcing the pancreas to produce excess insulin to manage blood sugar, often leading to prediabetes and type 2 diabetes. Key symptoms include fatigue, increased hunger/thirst, belly fat, and skin tags. It is primarily caused by obesity, inactivity, and genetics, and treated through diet, exercise, and medication

How Vitamin D Reduces Insulin Resistance

- One of the molecular mechanisms by which vitamin D participates in insulin secretion by pancreatic β-cells is the regulation of intracellular Ca2+ concentration.
- It has also been observed that vitamin D might decrease insulin resistance indirectly via the renin-angiotensin-aldosterone system (RAAS).
- Vitamin D mediated increase in insulin sensitivity occurs via binding of 1,25(OH)2D (calcitriol) to vitamin D receptors.

- Szymczak-Pajor et al. Int J Mol Sci. 2020;21(18):6644.

Type 2 Diabetes Mellitus (T2DM)

- People with T2DM have a 30% increased risk of developing Alzheimer's disease.
- Athanasaki et al. Biomedicines, 2022:10(4), 778.
- It may be due to effects of T2DM or due to having shared risk factors.
- Hamzé et al. Type 2 Diabetes Mellitus and Alzheimer's Disease: Shared Molecular Mechanisms and Potential Common Therapeutic Targets. Int J Mol Sci. 2022; 23(23):15287.

Intratrial Exposure to Vitamin D and New-Onset Diabetes Among Adults With Prediabetes

- The D2d study compared the effect of daily supplementation with 100 µg (4,000 IU) of vitamin D_3 versus placebo on new-onset diabetes in adults with prediabetes. Intratrial vitamin D exposure was calculated as the cumulative rolling mean of annual serum 25(OH)D measurements.
- The hazard ratios for diabetes among participants treated with vitamin D who maintained intratrial 25(OH)D levels of 100-124 and ≥125 nmol/L were 0.48 (0.29-0.80) and 0.29 (0.17-0.50), respectively, compared with those who maintained a level of 50-74 nmol/L.
- Dawson-Hughes et al. Diabetes Care. 2020;43(12):2916-2922.

Association between Atherosclerosis and Alzheimer's Disease: A Systematic Review and Meta-analysis

- Atherosclerosis is a disease of the arteries characterized by the deposition of plaques of fatty material on their inner walls.
- Atherosclerosis is associated with many vascular factors, such as hypertension, diabetes mellitus, dyslipidemia, and smoking.
  An analysis of the prevalence of atherosclerosis was made for ten studies (1,698 cases and 6,452 controls). Compared with controls, AD group showed a significantly higher prevalence of atherosclerosis (OR = 1.46; 95% CI, 1.26–1.68).
- Xie et al. Brain Behav. 2020;10(4):e01601

How Vitamin D Reduces Risk of Atherosclerosis

- Vitamin D supplementation lowers the levels of total cholesterol, triglycerides, and LDL-cholesterol and increases the levels of HDL-cholesterol. Vitamin D is also involved in the development of atherosclerosis at the site of the blood vessels. Deficiency of this vitamin has been found to increase adhesion molecules or endothelial activation and, at the same time, supplementation is linked to the lowering presence of adhesion surrogates. Vitamin D can also influence the vascular tone by increasing endothelial nitric oxide production. Deficiency can lead, at the same time, to oxidative stress and an increase in inflammation as well as the expression of particular immune cells that play a pivotal role in the development of atherosclerosis in the intima of the blood vessels, i.e., monocytes and macrophages. Vitamin D is also involved in atherogenesis through inhibition of vascular smooth muscle cell proliferation.
- Surdu AM, et al. Vitamin D and Its Role in the Lipid Metabolism and the Development of Atherosclerosis. Biomedicines. 2021; 9(2):172.

Infectious Agents and Alzheimer's Disease

- Recent reports have shown that viruses (e.g., Herpes simplex type 1, 2, 6A/B; human cytomegalovirus, Epstein-Barr virus, hepatitis C virus, influenza virus, and severe SARS-CoV-2), bacteria, as well as eukaryotic unicellular parasites (e.g., Toxoplasma gondii) may factor into cognitive decline within the context of AD. Microorganisms may trigger pathological changes in the brain that resemble and/or induce accumulation of Aβ peptides and promote tau hyperphosphorylation. Further, the mere presence of infectious agents is suspected to induce both local and systemic inflammatory responses promoting cellular damage and neuronal loss.
- Piekut et al. J Integr Neurosci. 2022;21(2):73.

Vitamin D Reduces Risk of Infections and Infectious Diseases

- Re: antiviral activity of vitamin D in a lung epithelial cell. These mechanisms include induction of cathelicidin antimicrobial peptide (CAMP) expression as well as 1,25(OH)2D-mediated suppression of inflammatory cytokines IL-5 and IFN-γ, ICAM-1, and PAFR. The mature form of CAMP, LL37, binds to viral dsRNA, which enables efficient binding to endosomal toll-like receptor 3 (TLR3), augmenting TLR3 signaling and subsequent viral clearance. An additional mechanism for viral removal is the induction of autophagy by 1,25(OH)2D.
- Ismailova, White. Reviews in Endocrine and Metabolic Disorders (2022) 23:265–277

Analysis the Link between Periodontal Diseases and Alzheimer's Disease: A Systematic Review

- Five studies were included. The selected studies described in their results an increase in the bacterium F. nucleatum in Alzheimer's disease patients (adjusted p = 0.02), and its incidence was linked to two bacteria, C. rectus and P. gingivalis (adjusted HR = 1.22 [1.04-1.43]) as well as A. naeslundii (crude HR = 2.0 [1.1-3.8]). The presence of periodontitis at baseline was associated with a six-fold increase in the rate of cognitive decline over a 6-month follow-up period. The current review suggests an association between periodontal disease and Alzheimer's disease. The treatment of periodontal disease could be a way to explore Alzheimer's disease prevention.
- Borsa et al. Int J Environ Res Public Health. 2021;18(17):9312.

Vitamin D Reduces Risk of Periodontal Disease - Mechanisms

- Modulation of microbial biofilm
- Immunomodulation
- Regulation of T-cell function
- Promotion of epithelial barrier integrity
- Inhibition of osteoelastogenesis
- Reduction in oxidative stress
- Reductions ins systemic and local inflammation
- Moszura et al. Nutrients 2026, 18(4), 577

Sleep Disorders Increase the Risk of Dementia, Alzheimer's Disease, and Cognitive Decline: a Meta-analysis

- Studies reporting risk estimates for dementia, AD, or cognitive decline associated with obstructive sleep apnea, insomnia, and other sleep disorders (e.g., restless legs syndrome, circadian rhythm sleep disorders, excessive daytime sleepiness) were included. Meta-analyses were performed. Thirty-nine cohort studies were included, with subgroup analyses showing significant associations between all-cause dementia and obstructive sleep apnea (HR 1.33, 95% CI 1.09–1.61), insomnia (HR 1.36, 95% CI 1.19–1.55), and other sleep disorders (HR 1.33, 95% CI 1.24–1.43). Obstructive sleep apnea increased the risk for AD (HR 1.45, 95% CI 1.24–1.69), though its association with vascular dementia did not reach statistical significance (HR 1.35, 95% CI 0.99–1.84). Insomnia was significantly associated with increased risk for both vascular dementia (HR 1.59, 95% CI 1.01–2.51) and AD (HR 1.49, 95% CI 1.27–1.74).
- Ungvari et al. Geroscience. 2025. PMID: 40214959

Vitamin D Reduces Risk of Sleep Disturbance

- Over an average follow-up of 13 years, we documented 2,704 cases of sleep disorders and found that higher serum 25(OH)D concentrations were significantly associated with reduced sleep disorder risk. In fully adjusted models, sufficient serum 25(OH)D concentrations reduced sleep disorder risk by 48% in prediabetes (HR = 0.52; 95% CI: 0.41-0.65) and 52% in diabetes (HR = 0.48; 95% CI: 0.34-0.67). Subgroup analysis found that adequate 25(OH)D concentrations were associated with improved sleep health especially in people ≤60 years of age, women, BMI≥30 kg/m², and those who had never smoked.
- Liu et al. Front Endocrinol (Lausanne). 2025:16:1524368.
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Parkinson’s Disease and Vitamn D

- Parkinson's disease (PD) is a neurodegenerative brain disease developed due to dopaminergic neuron loss in the substantia nigra (SN). Vitamin D (VD), VD receptor (VDR), and VD metabolites are highly expressed in the human brain and play a critical role in maintaining different brain functions. VDRs are highly expressed in the SN that regulates the activity of dopaminergic neurons and synaptic plasticity. VD exerts protective and therapeutic effects against the development of PD by modulating dopaminergic neurons of SN. VD reduces oxidative stress and neuroinflammation in PD because of its anti-inflammatory and antioxidant activities.
- Al-Kuraishy et al. Naunyn Schmiedebergs Arch Pharmacol. 2024;397(1):33-40.

Vitamin D Protects against Depression: Evidence from an Umbrella Meta-analysis

- Ten meta-analyses of randomised controlled trials (RCTs) revealed significant reduction in depression symptoms comparing participants on vitamin D supplements to those on placebo (Pooled standardised mean difference: - 0.40; 95 % CI: - 0.60, - 0.21).
- Four meta-analyses of cohort studies (with one having two subgroups) revealed that participants with lower levels of serum vitamin D were at increased odds of depression than those with higher levels of serum vitamin D (Pooled odds ratio: 1.60; 95 % CI: 1.08, 2.36).
- Musazadeh et al. Pharmacol Res. 2023:187:106605

Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines - 1

- Vitamin D offers numerous under-recognized health benefits beyond its well-known role in musculoskeletal health. It is vital for extra-renal tissues, prenatal health, brain function, immunity, pregnancy, cancer prevention, and cardiovascular health. Existing guidelines issued by governmental and health organizations are bone-centric and largely overlook the above mentioned extra-skeletal benefits and optimal thresholds for 25(OH)D. In addition, they rely on RCTs, which seldom show benefits due to high baseline 25(OH)D concentrations, moderate supplementation doses, and flawed study designs.
- Grant, et al. Nutrients. 2025;17(2):277.

Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines - 2

- This review emphasizes the findings from prospective cohort studies showing that higher 25(OH)D concentrations reduce the risks of eight major diseases and mortality, including pregnancy and birth outcomes.
- Raising serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L) can significantly reduce the burden of disease for eight of the top ten causes of death in the US: heart disease, cancer, COVID-19, stroke, chronic lower respiratory diseases, Alzheimer's disease and other dementias, diabetes mellitus, and kidney disease.

Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines - 3

- Serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L) are achievable for many people through daily supplementation with 2000 IU/day (50 mcg/day) of vitamin D_3, perhaps 4000-5000 IU/day for those obese. Furthermore, a daily dose between 4000 and 6000 IU of vitamin D_3 to achieve serum 25(OH)D levels between 40 and 70 ng/mL (100 – 175 nmol/L) would provide greater protection against many adverse health outcomes.
- Note, if a person has not been supplementing with vitamin D, a bolus dose (e.g., 10,000 IU/day for 10-15 days) could be used to rapidly increase 25(OH)D.

For More Information

- Search Google Scholar (Scholar.google.com)
- https://vitamindwiki.com/
- VitaminDWiki continues to be the world's most comprehensive website on Vitamin D. It has >14,400 curated pages of evidence-based studies, overviews, charts, and meta-analyses. (Click here for 340+ diseases and health topics related to Vitamin D).
- https://www.grassrootshealth.net/