Vitamin D and Bredesen's Six Types of Alzheimer's Disease: An Evidence-Graded Review

Among Bredesen's six Alzheimer's subtypes, vitamin D has the strongest case for the atrophic ("cold", Type 2) type, a moderate and mostly indirect case for the inflammatory ("hot", Type 1) and glycotoxic ("sweet", Type 1.5) types, a weak case for the vascular ("pale", Type 4) and traumatic ("dazed", Type 5) types, and almost no human evidence for the toxic ("vile", Type 3) type. No randomized trial has ever enrolled patients by Bredesen subtype, so every grade below is an inference from evidence on all-cause dementia or Alzheimer's disease (AD) combined with evidence on each subtype's main pathology.

TL;DR

- **Strongest: atrophic (Type 2).** Bredesen defines this type partly by low vitamin D. It is supported by prospective cohorts (NACC supplement users had 40% lower dementia incidence), nonlinear Mendelian randomization in deficient people (since contested), and two small Chinese RCTs that used 800 IU/day. Large trials in vitamin D-replete adults (VITAL, D-Health, FIND) were null, so the benefit most likely applies to correcting deficiency, not topping up sufficient people.
- **Moderate: inflammatory (Type 1) and glycotoxic (Type 1.5).** The biology is strong, and RCT meta-analyses show vitamin D lowers progression from prediabetes to diabetes by 15% and reduces CRP, IL-6 and TNF-α in people with abnormal glucose homeostasis. RCT meta-analyses in overweight or obese adults without that condition found no anti-inflammatory effect.
- **Weak or none: vascular (Type 4), traumatic (Type 5), toxic (Type 3).** Low 25(OH)D tracks small-vessel disease and poor outcomes after TBI, but MR studies of small-vessel disease and stroke are null. TBI trials are small, and toxin evidence is almost entirely from animals. Vitamin D can even increase gut absorption of lead and cadmium.

Which six-type classification is this?

I could not retrieve the VitaminDWiki page "6 types of Alzheimer's" directly (access blocked). However, the six-type scheme that VitaminDWiki has repeatedly covered, and the only widely used "six types of Alzheimer's" taxonomy, is Dale Bredesen's metabolic/ReCODE classification. Related VitaminDWiki pages include "The End of Alzheimer's and Dementia if adjust Vitamin D, B-12, Iron, Omega-3", "Alzheimer's Is Now Optional - Bredesen", and "200 patients nicely treated for all 3 types of Alzheimer's". vitamindwiki + 2 This report therefore assumes that scheme. The Crane/Mukherjee cognitive subgroups and the proteomic or atrophy subtypes (e.g., the five CSF-proteomic subtypes of Tijms et al.) are not usually described as "6 types of Alzheimer's". nih

The scheme developed in stages:

- **Original peer-reviewed source:** Bredesen DE, "Metabolic profiling distinguishes three subtypes of Alzheimer's disease," Aging 2015;7:595–600. It defined inflammatory, non-inflammatory (atrophic) and cortical (later "toxic") subtypes, based on metabolic testing of 50 people. aging-us + 2
- **Explicit vitamin D link:** a 2016 follow-up (Bredesen, "Inhalational Alzheimer's disease," Aging 2016) states that Type 2 "is characterized by an atrophic profile, with reduced support from molecules such as estradiol, progesterone, testosterone, insulin, and vitamin D." It tied Type 3 to biotoxin exposure and chronic inflammatory response syndrome (CIRS). nih

- **Six types:** Type 1.5 (glycotoxic), Type 4 (vascular) and Type 5 (traumatic) were added in Bredesen's 2017 book *The End of Alzheimer's* and his 2017 Institute for Functional Medicine lecture. integrativepractitioner restoreandrenew The six types appear in book and clinic materials, not in a peer-reviewed validation study.

Bredesen's types are clinical-metabolic heuristics, not validated biological subtypes, and most patients mix several types. sophus That limits how precisely vitamin D evidence can be mapped onto them.

Summary table

Type	Core pathology	Vitamin D evidence for incidence	Vitamin D evidence for treatment	Evidence strength	Key refs
Type 1 Inflammatory ("hot")	Chronic systemic and neuroinflammation (hs-CRP, IL-6, TNF-α), NF-κB-driven APP processing, often APOE4	Indirect: cohorts and MR of all-cause dementia; NACC benefit smaller in APOE4 carriers	Mixed RCT meta-analyses on CRP and cytokines; no subtype trial	Moderate (mechanistic strong, clinical indirect)	Ghahremani 2023 Chen 2014 hs-CRP meta-analysis Obese-adult cytokine meta-analysis 2024
Type 1.5 Glycotoxic ("sweet")	Hyperglycemia, insulin resistance, glycation plus inflammation	Indirect: RCT IPD meta-analysis shows 15% lower progression to type 2 diabetes	Inflammatory markers fall in abnormal-glucose RCTs; no AD-specific trial	Moderate (indirect RCT)	Pittas 2023 IPD Abnormal-glucose meta-analysis 2021
Type 2 Atrophic ("cold")	Loss of trophic support: vitamin D, sex hormones, thyroid, insulin, NGF/BDNF	Prospective cohorts, nonlinear MR (contested), NACC 40% lower incidence; null RCTs in replete adults	Two 12-month RCTs at 800 IU/day improved cognition and Aβ biomarkers	Strongest of the six (moderate overall)	Bredesen 2016 Navale 2022 Jia 2019 Kang 2021 VITAL
Type 3 Toxic ("vile")	Mycotoxins, metals (Hg, Pb, Cd), CIRS, low zinc	Cross-sectional NHANES interaction only	Animal studies only (Pb, Cd neuroprotection)	Very weak; possible harm via metal absorption	Hoseinrad 2021 Moon 1994 review NHANES micronutrient study 2026

Type	Core pathology	Vitamin D evidence for incidence	Vitamin D evidence for treatment	Evidence strength	Key refs
Type 4 Vascular ("pale")	Small-vessel disease, BBB leak, hypoperfusion, cardiovascular disease	Cross-sectional link to WMH, lacunes, microbleeds; MR null	Not reported	Weak (observational, not supported by MR)	Chung 2015 Stroke CSVD MR study Navale 2022
Type 5 Traumatic ("dazed")	Prior TBI or repeated concussion, chronic post-traumatic neuroinflammation	Not reported (no data on TBI-to-AD conversion)	80% insufficient after TBI; small RCTs; pooled SMD 0.37, NS	Weak	Jamall 2016 Aminmansour 2012 Ongko Wijaya 2026

Cross-cutting evidence that applies to every type

Most of the human evidence concerns all-cause dementia or AD in general. How it bears on the subtypes:

- **NACC cohort (Ghahremani et al., 2023).** The study followed 12,388 dementia-free NACC participants for up to 10 years. Any vitamin D supplementation was associated with 40% lower dementia incidence (HR 0.60, 95% CI 0.55–0.65), after adjusting for age, sex, education, race, cognitive status, depression and APOE ε4. wiley skepticalraptor Effects were larger in women, in people with normal cognition rather than MCI, and in APOE ε4 non-carriers. vitamindwiki It is observational, so healthy-user bias cannot be excluded. sciencemediacentre The weaker effect in APOE4 carriers matters for Type 1, which Bredesen links strongly to APOE4. The larger effect before MCI argues that vitamin D is mainly a prevention lever.
- **Mendelian randomization (Navale et al., 2022, UK Biobank).** Nonlinear MR in 294,514 participants supported a causal effect of vitamin D deficiency on dementia but not on stroke. At 25 nmol/L (10 ng/mL), odds of dementia were 54% higher than at 50 nmol/L (20 ng/mL). Up to 17% of dementia cases might be avoidable by raising 25(OH)D to 50 nmol/L. naturalhealthresearch nih A 2025 reanalysis using the doubly-ranked nonlinear MR method (Hamilton and Davey Smith, Am J Clin Nutr 2025;122:890–891) concluded the "revised analyses do not provide compelling evidence of any benefit of vitamin D", so this causal claim is now contested.
- **Null RCTs in replete adults.**
  - VITAL cognition substudies (2,000 IU/day, n=4,218, 2–3 years) found no effect on cognitive decline (pooled difference 0.01 SD/year, p=0.39). Black participants, who tend to have lower 25(OH)D, showed better cognitive maintenance (MD 0.04). epa
  - D-Health (60,000 IU monthly, 21,315 Australians aged 60–84) found no cognitive benefit. wiley

    - The Finnish FIND trial (1,600 or 3,200 IU/day for 5 years, n=2,492) found no effect on diagnosed dementia. Incidence was 0.52 per 100 person-years on placebo vs 0.37 on vitamin D, but the trial could only detect a roughly 65% reduction. nih nih
    - All three trials enrolled mostly vitamin D-replete people; D-Health's placebo group averaged 77 nmol/L. healthspanner Together with the nonlinear MR shape, this suggests any benefit is concentrated in deficient people. nih For the subtypes, the prediction is that vitamin D helps when deficiency is part of the phenotype (most clearly Type 2) rather than as a universal add-on.
- **Treatment RCT in diagnosed AD (Jia et al., 2019).** In 210 Chinese older adults with AD, 800 IU/day for 12 months improved Wechsler (WAIS-RC) cognitive scores and lowered plasma Aβ42 and related biomarkers compared with placebo. nih medscape A companion RCT in MCI (Yang et al., 2020, n=183, 800 IU/day) improved full-scale IQ and reduced oxidative-stress and telomere-related markers. sagepub Both were single-centre trials by the same group and have not been replicated in Western cohorts. medscape
- **Genetics.**
    - Meta-analyses link VDR TaqI and ApaI variants to AD risk (Lee 2014). A 2022 meta-analysis found TaqI tt+Tt vs TT OR 1.44 for AD, and BsmI linked to MCI (OR 1.77). A 2024 Frontiers meta-analysis found ApaI reduced overall AD risk, with TaqI and ApaI protective in Caucasians. sciencedirect + 2
    - A 2026 MENA-region meta-analysis found no significant AD associations, but it rested on very few studies. doi
    - VitaminDWiki has covered a 2022 study in which AD-biomarker-positive patients had low CSF 25(OH)D despite adequate serum levels. CSF levels were not affected by VDR genotype. vitamindwiki
    - None of these genetic findings is subtype-specific.
- **Older-old cohorts.** In the German AgeCoDe cohort (1,334 non-demented adults, mean age 84, 7-year follow-up, 209 incident AD cases), low serum vitamin D was associated with incident Alzheimer's dementia. nih

Type 1: Inflammatory ("hot")

Pathology. Chronic inflammation (high hs-CRP, IL-6, TNF-α) activates NF-κB, which upregulates β- and γ-secretase and pushes APP toward amyloidogenic processing. The type is often associated with APOE4. mdbrainhealth vitamindwiki

Vitamin D evidence.

- **Mechanistic (strong):** calcitriol acting through VDR suppresses NF-κB signalling and pro-inflammatory cytokines in microglia and macrophages, and promotes amyloid clearance. nih These mechanisms are well documented in cell and animal models.
- **RCT effects on inflammatory markers (mixed):**
    - A 2014 meta-analysis of 10 RCTs (924 participants; Chen et al., Nutrients 2014) found vitamin D lowered circulating hs-CRP by 1.08 mg/L (95% CI −2.13 to −0.03).
    - A 2018 BMC Nutrition meta-analysis of 24 RCTs found no effect on CRP (WMD −0.26 mg/L, 95% CI −0.75 to 0.22), IL-10 or TNF-α and a paradoxical rise in IL-6.

    - A 2024 Nutrition Research meta-analysis in overweight or obese adults without comorbidities found no change in CRP, IL-6 or TNF-α, even in trials where 25(OH)D rose significantly.
- **Incidence:** indirect only, via the all-cause dementia cohorts and MR above. The NACC finding of a weaker effect in APOE4 carriers suggests the APOE4-heavy inflammatory phenotype may respond less to vitamin D alone. wiley

Prevention vs treatment. Both are plausible; neither is shown for this subtype. **Grade: moderate (strong mechanism, indirect clinical evidence).**

Cofactors. VitaminDWiki's APOE4/omega-3 page argues that APOE4 carriers may need combined omega-3 and vitamin D. vitamindwiki VITAL tested both factorially and found no cognitive benefit from either in replete adults. alzdiscovery Magnesium is required for vitamin D hydroxylation and is worth checking when inflammation persists despite apparently adequate intake.

Type 1.5: Glycotoxic ("sweet")

Pathology. Chronic hyperglycemia and hyperinsulinemia cause glycation-driven inflammation (Type 1 features) plus brain insulin resistance, which removes insulin's trophic signal (Type 2 features). mdbrainhealth apollohealthco

Vitamin D evidence.

- **Prevention of the upstream driver (RCT-level):** an individual-participant meta-analysis of three RCTs (D2d, Tromsø, J-DOIT; 4,190 adults with prediabetes; 4,000 IU/day, 20,000 IU/week or eldecalcitol) found vitamin D cut progression to type 2 diabetes by 15% (HR 0.85, 95% CI 0.75–0.96). The 3-year absolute risk reduction was 3.3%, and about 30 people needed treatment to prevent one case. acpjournals usda Participants who kept intratrial 25(OH)D at ≥125 nmol/L (≥50 ng/mL) had the largest benefit. usda
- **Inflammation in dysglycemia (RCT meta-analysis):** a meta-analysis of 38 trials (46 effect sizes, published 2010–2020) in people with abnormal glucose homeostasis (Dashti et al., Pharmacol Res 2021) found significant reductions in CRP, IL-6 and TNF-α after vitamin D supplementation. The effect is much clearer in this group than in metabolically healthy obese adults (see Type 1).
- **Direct AD evidence:** none specific to this subtype.

Prevention vs treatment. Mainly prevention, by reducing the progression from insulin resistance to diabetes that feeds this subtype. **Grade: moderate (indirect but RCT-based).** This is the subtype where the most rigorous non-dementia RCT evidence applies.

Type 2: Atrophic ("cold")

Pathology. Withdrawal of trophic support (estradiol, progesterone, testosterone, thyroid hormone, insulin, NGF, BDNF and vitamin D) tips APP processing toward synapse loss and atrophy. Bredesen says this type tends to emerge about a decade later than Type 1. Substack primehealthdenver

Vitamin D evidence.

- **By definition:** Bredesen's 2016 paper names vitamin D as one of the missing trophic molecules, so correcting deficiency is part of the treatment of this type by construction. nih

- **Brain-structure evidence (observational):** in the UK Biobank imaging cohort (n=33,523), low 25(OH)D was nonlinearly associated with smaller total brain, grey-matter, white-matter and hippocampal volumes. news-medical naturalhealthresearch This is the pattern atrophy would predict. The MR arm did not confirm causal effects on neuroimaging outcomes. news-medical
- **Incidence:** NACC (HR 0.60), AgeCoDe, and the contested nonlinear MR (OR 1.54 at 25 vs 50 nmol/L) all point in the same direction. The benefit is concentrated where 25(OH)D is deficient, which is exactly the case in a type defined by trophic deficiency. omegaquant
- **Treatment:** Jia 2019 (AD) and Yang 2020 (MCI), both 800 IU/day for 12 months, are the only placebo-controlled trials showing cognitive and biomarker gains. VitaminDWiki also tracks a positive trial of 100,000 IU monthly in AD. vitamindwiki
- **Null RCTs:** VITAL, D-Health and FIND enrolled largely replete, cognitively normal adults. They are evidence against routine supplementation of sufficient people, not against repletion in this phenotype. nih wiley

Prevention vs treatment. Both: prevention in people who are deficient, and treatment as part of trophic repletion. **Grade: the strongest of the six (moderate in absolute terms).**

Cofactors. Hormonal co-deficiency defines this type. A practical point is that vitamin D, magnesium and vitamin K2 interact in calcium handling, which matters at the higher doses (often 4,000 IU/day or more) needed to reach ≥40 ng/mL in older adults.

Type 3: Toxic ("vile")

Pathology. Exposure to biotoxins such as mycotoxins (CIRS), metals (mercury, lead, cadmium) or organic toxicants. It often shows low zinc, amosinstitute apollohealthco cortical (non-amnestic) presentation, younger onset and APOE4-negative status. Bredesen's 2015 "cortical" subtype was characterized by "striking zinc deficiency". nih

Vitamin D evidence.

- **Animal (only direct evidence):** in rats, vitamin D3 reduced lead-induced cortical oxidative stress and inflammation through Nrf2 and NF-κB (Hoseinrad 2021). springer nih It also protected the olfactory bulb against cadmium neurotoxicity. nih
- **Cross-sectional:** an NHANES analysis found serum 25(OH)D associated with better cognition and significant interactions between blood lead and 25(OH)D on low cognitive scores. sciencedirect This hints that vitamin D may buffer metal neurotoxicity, but the design cannot show causation.
- **Genetic:** the VDR ApaI variant modified peripheral nerve toxicity in lead-exposed workers. nih
- **Counter-evidence:** a classic toxicology review (Moon 1994) documents that vitamin D increases intestinal absorption of lead, cadmium, aluminium and cobalt, while these metals impair renal calcitriol synthesis. nih Repleting vitamin D during ongoing metal exposure could, in theory, increase metal uptake. Calcium and zinc status and exposure removal should come first.
- **Mycotoxins and CIRS:** no human vitamin D data found.

Prevention vs treatment. Neither is shown. **Grade: very weak, with a plausible-harm caveat.**

Type 4: Vascular ("pale")

Pathology. Cardiovascular disease, small-vessel disease, blood-brain-barrier leakiness and hypoperfusion contributing to AD pathology. mdbrainhealth Bredesen distinguishes this from classical vascular dementia. primehealthdenver apollohealthco

Vitamin D evidence.

- **Observational (consistent):** in a Stroke cohort (Chung 2015), each 25 nmol/L lower 25(OH)D was associated with more lacunes, about double the odds of severe white-matter hyperintensity (OR 2.05, 95% CI 1.41–3.08) and more deep microbleeds (OR 1.28). ahajournals A 2026 Scientific Reports study of 217 small-vessel disease patients found 25(OH)D inversely correlated with WMH severity (especially periventricular) and with gait and fall risk. nature VitaminDWiki also notes that small-vessel disease was 2.5 times more likely with poor VDR function. vitamindwiki
- **MR (null):** a 2023 Stroke MR study (Lee et al., Stroke 2023;54:2338–2346) found no causal effect of genetically predicted 25(OH)D on lacunar stroke, WMH volume, microbleeds or perivascular spaces (e.g., OR 1.02, 95% CI 0.99–1.04 for WMH). Navale's nonlinear MR found no causal effect on stroke. nih
- **RCT:** none on small-vessel or vascular-AD endpoints. VITAL's cardiovascular null results in replete adults also argue against a large vascular effect from topping up.

Prevention vs treatment. Prevention only, if at all. **Grade: weak.** The observational link may reflect confounding (inactivity, obesity, frailty) or reverse causation. Deficient people were under-represented in the MR data, so a deficiency-only effect cannot be ruled out.

Type 5: Traumatic ("dazed")

Pathology. Prior TBI or repeated concussion triggers chronic neuroinflammation, axonal injury and tau pathology that lead to cognitive decline years later. mdbrainhealth Substack

Vitamin D evidence.

- **Observational:** in 353 adults at the Imperial College TBI clinic (Jamall et al., 2016), 46.5% were vitamin D deficient (<40 nmol/L) and another 33.7% insufficient. After adjustment, deficient patients scored lower on global cognition (ACE-R; 4.5 points lower than replete patients, p=0.034, Cohen's d 0.48) and had more depressive symptoms. There was no association with TBI severity, sleep or quality of life. nih A separate prospective cohort of 300 patients with moderate or severe TBI (Medicine, 2025) linked vitamin D <20 ng/mL to worse 3-month functional outcome (GOSE proportional OR 0.62, 95% CI 0.40–0.93, p=0.022).
- **Small RCTs:** in 60 severe-TBI patients (Aminmansour 2012), favourable 3-month Glasgow Outcome Scale rates were 25% on placebo, 45% on progesterone and 60% on progesterone plus vitamin D (p=0.03). nih Vitamin D was never tested alone, and the trial was not prospectively registered. nih
- **Meta-analysis:** a 2026 meta-analysis pooled three vitamin D TBI trials (n=192). It found a non-significant trend (SMD 0.37, 95% CI −0.27 to 1.02, p=0.26, I^2 78%), and progesterone alone was null. theunj
- **Animal:** in rats, low-dose calcitriol plus progesterone preserved spatial memory better than progesterone alone and reduced neuronal loss and astrocyte activation, particularly in vitamin D-deficient middle-aged animals. nih nih

- **Long-term TBI-to-AD conversion:** no study tests whether vitamin D changes this.

Prevention vs treatment. Treatment of acute or post-acute TBI, with the hope of lowering later AD risk; the second step is untested. **Grade: weak.** Because post-TBI deficiency is so common, screening 25(OH)D after head injury is a low-cost, defensible step even without proof that it prevents later AD.

Recommendations

For a VitaminDWiki page, I suggest framing it as follows:

- **Lead with Type 2 (atrophic).** It is the only subtype where vitamin D is part of the definition and where cohort, MR and treatment-trial evidence converge. State clearly that the benefit applies to correcting deficiency.
- **Present Types 1 and 1.5 as "indirect but plausible".** Cite the Pittas diabetes-prevention meta-analysis and the abnormal-glucose inflammation meta-analysis as the best RCT-grade support, and note the null cytokine results in metabolically healthy obese adults.
- **Present Types 4 and 5 as "associated, not proven".** Highlight the null small-vessel and stroke MR results for Type 4, and the small, combination-only TBI trials for Type 5.
- **Flag Type 3 as "insufficient evidence, possible caution".** Mention that vitamin D increases absorption of toxic metals.
- **Address the null RCTs head-on.** VITAL, D-Health and FIND enrolled mostly replete people, consistent with a threshold effect. Note that the Navale MR causal estimate has been challenged by a doubly-ranked reanalysis.
- **Practical target (consistent with the trial data):** test 25(OH)D in anyone with cognitive decline or AD risk factors and correct values below 50 nmol/L (20 ng/mL) as a minimum. In the diabetes-prevention trials, people who maintained ≥125 nmol/L (50 ng/mL) had the largest benefit.

Caveats

- **The source page:** I could not access the VitaminDWiki page itself. If it describes a different six-type scheme (e.g., a newer proteomic or imaging subtyping), the mapping above would need revising, although the cross-cutting evidence would still apply.
- **The classification itself:** Bredesen's subtypes rest on a 50-patient metabolic profiling paper and on clinical books and lectures. sciencedaily They have no independent validation, and patients usually show several types. Bredesen's protocol is multi-component, so vitamin D's contribution within it cannot be isolated.
- **Positive treatment RCTs:** all come from one Chinese research group using 800 IU/day, and the large null trials did not test deficient populations. The decisive trial (repletion of deficient people, stratified by phenotype) has not been done.
- **Dates and venues:** some cited studies are recent (2025–2026) and published in smaller journals (e.g., the TBI meta-analysis), and should be weighted accordingly.