Vitamin D and ICU delirium: strong associations, elusive proof of causation

Vitamin D deficiency roughly doubles the risk of delirium in hospitalized and ICU patients, according to converging observational, meta-analytic, and genetic evidence. A 2023 meta-analysis of nine studies found severe deficiency (<25 nmol/L) carried an odds ratio of 1.98 for delirium compared with normal levels, PubMed Central PubMed while Mendelian randomization studies in over 300,000 UK Biobank participants suggest this relationship is causal (HR 0.74 per 10 nmol/L genetically instrumented increase, p = 0.0004). PubMed Neurology Yet a critical gap persists: **no randomized controlled trial has tested vitamin D supplementation specifically for ICU delirium prevention**. Meanwhile, 40–70% of ICU patients are vitamin D deficient at admission, PubMed Central ResearchGate making this a potentially modifiable risk factor of enormous scale. The biological plausibility is strong — vitamin D modulates at least five of the six established pathogenic pathways for delirium Journal of Cardiothoracic a… — but the supplementation evidence needed to close the loop remains absent.

The epidemiological case is substantial but not unanimous

The observational literature tilts strongly toward an inverse association between vitamin D levels and delirium incidence, though a handful of smaller studies found null results. The most rigorous synthesis comes from **Fu et al. (2023, PLOS ONE)**, who pooled nine observational studies and found a dose-dependent relationship: severe vitamin D deficiency (<25 nmol/L) versus normal (>75 nmol/L) yielded an **OR of 1.98 (95% CI: 1.41–2.79; I^2 = 25%)**, PubMed Central while moderate deficiency (25–50 nmol/L) produced an **OR of 1.50 (95% CI: 1.12–2.00)**. PubMed Central Insufficiency (50–75 nmol/L) did not reach significance, PubMed Central suggesting a threshold effect rather than a linear gradient at higher levels. PubMed

Individual studies reinforce this pattern with varying effect sizes. Velayati et al. (2020) followed 398 CABG patients and found severe deficiency (<10 ng/mL) tripled delirium odds Journal of Cardiothoracic a… (**OR 3.18, 95% CI: 1.29–7.78**) Journal of Cardiothoracic a… after multivariate adjustment. ScienceDirect Perfusion.com Qiu et al. (2022), studying 632 surgical ICU patients at the Cleveland Clinic, identified **30 ng/mL as a critical threshold** PubMed — below which delirium risk climbed linearly, above which no further protection was observed. PubMed Among 310 critically ill elderly COVID-19 patients, Gholi et al. (2022) found vitamin D deficiency carried a **54% higher delirium hazard** (HR 1.54, 95% CI: 1.02–2.33). PubMed ScienceDirect In 1,029 elderly hip fracture patients, deficiency increased delirium odds by 52% (OR 1.52, 95% CI: 1.01–2.31). PubMed Central

Counterbalancing these positive findings, **Morandi et al. (2013)** in a small Vanderbilt cohort of 120 medical ICU patients found no association PubMed (OR 1.01, 95% CI: 0.98–1.02), PubMed and **Jia et al. (2024)** in a secondary analysis of 390 cardiac surgery patients similarly reported null results (adjusted OR 0.99 per 1 ng/mL increase). PubMed Central These negative studies were notably smaller and assessed delirium over shorter time windows. A separate meta-analysis by Hung et al. (2022, J Clin Anesth), pooling seven studies with 2,673 patients, confirmed that preoperative deficiency significantly raised the risk of postoperative delirium and cognitive dysfunction ScienceDirect (**pooled OR 1.54, $p < 0.01$**). ResearchGate

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Mendelian randomization provides the strongest causal signal

The gold-standard evidence for causality in this domain comes from two Mendelian randomization analyses exploiting the natural randomization of vitamin D–related genetic variants. **Bowman et al. (2019, Neurology)** analyzed 313,121 European-descent participants aged ⩾60 from the UK Biobank, identifying 544 incident delirium cases. Neurology Neurology Genetic variants that raise circulating vitamin D were protective: **HR 0.74 per 10 nmol/L increase (95% CI: 0.62–0.87; $p = 0.0004$)**, with no evidence of pleiotropy confounding the result. PubMed Neurology This design minimizes reverse causation — the possibility that illness causes low vitamin D rather than the reverse. PubMed Central

Pilling et al. (2021, JAGS) extended this work with 351,320 participants and up to 14 years of follow-up, finding 3,634 incident delirium cases. Observationally, vitamin D deficiency (<25 nmol/L) versus sufficiency (>50 nmol/L) carried a **hazard ratio of 2.49 (95% CI: 2.24–2.76; $p = 3 \times 10^{-68}$)**. PubMed Central Wiley Online Library Instrumental variable analysis again confirmed the genetic association. Together, these studies represent the most compelling evidence that low vitamin D causally contributes to delirium risk, though they reflect community-dwelling populations rather than ICU cohorts specifically.

Five convergent biological mechanisms explain why vitamin D matters for the brain

The pathophysiology of delirium involves neuroinflammation, cholinergic deficiency, blood-brain barrier disruption, oxidative stress, and neurotransmitter imbalance. PubMed Central Vitamin D directly modulates at least five of these pathways, providing robust biological plausibility.

Neuroinflammation suppression is perhaps the most potent mechanism. The vitamin D receptor (VDR) physically binds IKKβ protein, blocking TNF-α–induced NF-κB activation

PubMed Central — the master inflammatory transcription factor. Vitamin D downregulates pro-inflammatory cytokines **IL-6, TNF-α, and IL-1β** while upregulating anti-inflammatory IL-10. ScienceDirect ScienceDirect It suppresses the NLRP3 inflammasome and shifts microglia from pro-inflammatory M1 to neuroprotective M2 phenotype PubMed Central via TLR4/MyD88/NF-κB pathway inhibition. Since the neuroinflammatory cascade — peripheral immune signals activating brain parenchymal cells — is considered a primary driver of ICU delirium, ScienceDirect this mechanism is directly relevant. PLOS +2

Cholinergic enhancement addresses the leading neurotransmitter hypothesis of delirium. The active form of vitamin D ($1,25(OH)_2D_3$) elevates choline acetyltransferase (ChAT) activity MDPI by **12–45%** in specific brain nuclei, including the arcuate-median eminence and bed nucleus of the stria terminalis PubMed (Sonnenberg et al., 1986). VDR-knockout mice show significant decreases in brain acetylcholine levels. MDPI Vitamin D also modulates acetylcholinesterase activity and prevents pathological AChE increases in Alzheimer's models. Taylor & Francis Online This is critical because **cholinergic deficiency** is the dominant neurotransmitter theory of delirium, PubMed Central and anticholinergic medications are established delirium precipitants. Frontiers ScienceDirect

Blood-brain barrier integrity is maintained by vitamin D through upregulation of tight junction proteins — ZO-1, occludin, and claudin-5. Won et al. (2015) demonstrated that calcitriol prevented hypoxia-induced barrier dysfunction in brain endothelial cells PLOS via VDR-mediated NF-κB signaling. Frontiers Vitamin D also regulates **aquaporin-4**, the principal brain water channel protein implicated in glymphatic clearance of neurotoxic waste. Journal of Cardiothoracic a… BBB disruption permits peripheral inflammatory mediators to access brain parenchyma, triggering the neuroinflammatory cascade central to delirium. Frontiers +3

Neurotrophic support operates through vitamin D's upregulation of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor (GDNF). PubMed Central Direct intrahippocampal injection of calcitriol induces NGF expression in adult rats. PubMed Central NGF is critical for survival of basal forebrain cholinergic neurons — the same neurons whose dysfunction underlies delirium. BDNF supplementation via vitamin D in aging rats mitigated age-related cognitive decline. PubMed

Oxidative stress reduction rounds out the mechanistic picture. Vitamin D activates the Nrf2/HO-1 antioxidant pathway, PubMed Central PubMed Central upregulates glutathione, superoxide dismutase, catalase, and glutathione peroxidase, and inhibits inducible nitric oxide synthase in microglia. NCBI +2 ICU patients face overwhelming oxidative stress from sepsis, surgery, and mechanical ventilation. Vitamin D's antioxidant actions directly counter this pathogenic mechanism.

Vitamin D deficiency is near-universal in the ICU

The prevalence data underscore the scale of the problem. Across multiple studies and geographic regions, **40–70% of ICU patients have vitamin D deficiency** (25(OH)D < 20 ng/mL), PubMed Central Nature with typical median levels of **18–22 ng/mL**. A Taiwanese multicenter study of 538 patients reported a median of 18.3 ng/mL (IQR 13.7–23.9), with **59% deficient** — compared to 22.4% in the general population of the same region. PubMed Central In critically ill cancer patients, deficiency prevalence reaches **74%**, and severe deficiency (≤12 ng/mL) affects **54%**. MDPI

Septic patients fare worst: Biomedcentral a Korean cohort reported median levels of just **13 ng/mL**, MDPI while Australian data showed sepsis patients at **7.9 ± 3 ng/mL** versus 24.6 ± 6.7 ng/mL in controls. ResearchGate Contributing factors include pre-existing deficiency from chronic disease and limited sun exposure, acute metabolic dysregulation during critical illness, hepatic and renal dysfunction impairing vitamin D hydroxylation, hemodilution from aggressive fluid resuscitation, and impaired gastrointestinal absorption. PubMed Central Notably, vitamin D levels drop rapidly after ICU admission independent of pre-illness status, suggesting that critical illness itself depletes vitamin D stores. PubMed Central

The VDR is expressed widely in the brain — in neurons and glia of the **hippocampus (CA1, CA2), hypothalamus, substantia nigra, cortex, amygdala, and thalamus** PubMed nih — confirming that vitamin D functions as a neurosteroid with direct CNS activity. Journal of Cardiothoracic a… The brain also possesses local activation machinery (CYP27B1 in microglia and pericytes), nih meaning that peripheral deficiency likely translates to central deficiency. MDPI

No data exist on vitamin D and delirium subtypes

Despite the clear clinical relevance, **no published study has examined whether vitamin D levels differentially predict hyperactive, hypoactive, or mixed delirium**. All existing studies treat delirium as a binary outcome. This is a notable gap because the subtypes differ substantially in prevalence and prognosis. In a systematic review of 131 studies comprising 13,902 delirious ICU patients (Krewulak et al., 2022), hypoactive delirium was the most common subtype at **50.3%**, followed by mixed (27.7%) and hyperactive (22.7%). Mixed delirium carried the worst outcomes across all metrics. PubMed Central Springer Given that hypoactive delirium is associated with older age and worse pre-morbid cognition Oxford Academic — populations also at highest risk for vitamin D deficiency — a mechanistic link is plausible but undemonstrated.

Sepsis encephalopathy and post-ICU cognition remain underexplored

Sepsis-associated encephalopathy (SAE), affecting up to 50% of sepsis patients, Nature shares pathophysiological mechanisms with delirium including neuroinflammation, BBB disruption, and microglial activation. PubMed PubMed Central Preclinical evidence is promising: Sun et al. (2025) showed that calcitriol reduced neuronal pyroptosis markers by ~40% and increased survival from **41% to 72%** in a mouse sepsis model, with corresponding cognitive improvement. PubMed ScienceDirect However, no human clinical trial has tested vitamin D for SAE prevention or treatment.

For **post-ICU cognitive impairment**, the most relevant evidence comes from the VIOLET-BUD trial (Han et al., 2021), an ancillary study of the large VIOLET RCT. Among 95 vitamin D-deficient critically ill adults randomized to 540,000 IU vitamin D_3 versus placebo, global cognition scores at approximately 14 months were nearly identical (**79.6 vs. 82.1**; adjusted OR 0.83, 95% CI: 0.50–1.38). Elsevierpure One executive function subscale was actually lower in the treatment group. ScienceDirect This null result dampens enthusiasm for high-dose supplementation as a cognitive rescue strategy, though the small sample size, single-dose design, and late outcome assessment limit its conclusions.

Vitamin D's relationship with **sepsis outcomes** more broadly is better established. De Haan et al. (2014) pooled 14 observational studies (n = 9,715) and found deficiency increased infection risk (**RR 1.49**), sepsis risk (**RR 1.46**), and in-hospital mortality (**RR 1.79**). PubMed PubMed Central The VITdAL-ICU trial (Amrein et al., 2014) showed no overall mortality benefit from high-dose supplementation, Nature but a pre-specified subgroup with severe deficiency (<12 ng/mL) showed hospital mortality of **28.6% versus 46.1%** PubMed (HR 0.56, 95% CI: 0.35–0.90) — a hypothesis-generating finding that has not been confirmed in larger trials. PubMed Central

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Conclusion

The evidence linking vitamin D deficiency to ICU delirium is compelling across multiple lines of inquiry but incomplete at the interventional level. Observational data consistently show **1.5- to 3-fold increases** in delirium risk among deficient patients, PubMed Central PLOS Mendelian randomization supports causality, Neurology and five distinct biological mechanisms provide robust plausibility. The near-universal prevalence of vitamin D deficiency in ICU populations (40–70%) PubMed Central makes this a potentially high-impact modifiable risk factor. Nature +2 Yet the field lacks the decisive evidence: **a well-powered RCT testing vitamin D supplementation for ICU delirium prevention as a primary endpoint**. The failure of the VIOLET-BUD ancillary study to improve post-ICU cognition — though limited in design — adds a note of caution about translating associative evidence into therapeutic benefit. ScienceDirect Future trials will need to address timing of

supplementation (pre-admission vs. early ICU), dosing strategies (loading dose vs. daily), baseline vitamin D stratification, and delirium subtype differentiation. Frontiers Until such trials are completed, vitamin D deficiency should be viewed as a robust risk marker for ICU delirium, with correction of severe deficiency a reasonable clinical practice given its low cost and safety profile, MDPI even as definitive proof of delirium prevention remains outstanding. PubMed Central Neurology