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Research Article

Cobalamin (Vitamin B12) Deficiency and Cognitive Impairment: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Cobalamin (vitamin B12) deficiency has been proposed as a potentially modifiable risk factor for cognitive decline, mild cognitive impairment (MCI) and dementia, including Alzheimer's disease. The magnitude and consistency of this association, the mechanistic pathways - primarily through hyperhomocysteinemia and disrupted one-carbon methylation - and the reversibility of cognitive deficits with supplementation remain incompletely characterized.

Methods: We searched Pubmed, Google Scholar, Embase, Cochrane Library and Web of Science from inception to December 2024 for observational studies reporting associations between cobalamin status and cognitive outcomes and randomized controlled trials (RCTs) of cobalamin or B-vitamin supplementation on cognitive function. Two independent reviewers extracted data. Pooled odds ratios (ORs) and standardized mean differences (SMDs) were estimated using random-effects models (DerSimonian–Laird). Heterogeneity was assessed with I^2 and Cochran's Q test.

Results: Sixty-three studies (48 observational, 15 RCTs; n=127,842) met inclusion criteria. Low serum cobalamin (<200 pg/mL) was significantly associated with cognitive impairment (pooled OR 1.84; 95% CI, 1.52–2.23; I^2=72%; 32 studies) and incident dementia (pooled hazard ratio [HR] 1.46; 95% CI, 1.21–1.76; 11 prospective cohort studies). Elevated plasma total homocysteine (tHcy) - reflecting functional cobalamin and folate insufficiency - was associated with a 1.4-fold increase in dementia risk per standard-deviation increment (95% CI, 1.1–1.9; Framingham Heart Study, n=1,092, median follow-up 8 years). Holotranscobalamin (holoTC) deficiency (<35 pmol/L) was more strongly associated with cognitive decline than serum B12 alone (pooled OR 2.16; 95% CI, 1.63–2.86). In RCTs of B-vitamin supplementation, overall cognitive outcomes did not significantly improve in unselected populations (pooled SMD 0.07; 95% CI, −0.04 to 0.18). However, in patients with elevated baseline tHcy (>13 µmol/L), B-vitamin treatment significantly slowed brain atrophy by 29–53% (VITACOG trial) and stabilized executive function. A 7-fold slowing of atrophy in Alzheimer's disease-specific gray matter regions was demonstrated with B vitamins in the same trial.

Conclusions: Cobalamin deficiency and hyperhomocysteinemia are independently associated with an elevated risk of cognitive impairment and dementia. B-vitamin supplementation targeting patients with documented cobalamin deficiency or elevated

tHcy slows neurodegeneration in at-risk populations. Systematic biochemical screening and early intervention in cognitively impaired elderly patients with low cobalamin status are warranted.

Keywords: Vitamin B12, Cobalamin, Holotranscobalamin, Methylmalonic acid, Homocysteine, Cognitive impairment, Mild cognitive impairment, Dementia, Alzheimer, Vascular dementia, Brain atrophy

1. Introduction

Dementia and cognitive decline represent the most burdensome neurological syndromes of ageing. With more than 55 million people living with dementia worldwide and projections exceeding 150 million by 2050, identification of modifiable risk factors is a global public health imperative. Among nutritional determinants of brain health, cobalamin (vitamin B12) deficiency has attracted sustained attention owing to its high prevalence in elderly populations (>20% in those aged ≥65 years), its established neurotoxic consequences and the theoretical reversibility of associated cognitive impairment[1,2].

Cobalamin is indispensable for two critical enzymatic reactions: (1) the methionine synthase reaction, which converts homocysteine to methionine and is essential for S-adenosylmethionine (SAM)-dependent methylation of DNA, histones and neurotransmitters; and (2) the methylmalonyl-CoA mutase reaction, which converts methylmalonyl-CoA to succinyl-CoA, essential for myelin synthesis and maintenance. Deficiency in cobalamin therefore leads to hyperhomocysteinemia, impaired DNA methylation, disrupted one-carbon metabolism and demyelination - all plausible neurobiological mechanisms for cognitive dysfunction[1,3].

Epidemiological evidence has linked low serum cobalamin concentrations and elevated plasma total homocysteine (tHcy) - a functional downstream marker of cobalamin and folate sufficiency - to increased risk of Alzheimer's disease, vascular dementia and age-associated cognitive decline. The landmark Framingham Heart Study demonstrated that each standard-deviation increase in log-transformed plasma homocysteine was associated with a 1.4-fold increase in dementia risk over eight years. In patients with mild cognitive impairment (MCI), homocysteine-lowering B-vitamin supplementation slowed the rate of whole-brain atrophy by 29-53% in the VITACOG trial[4,5].

However, controversy persists regarding the causal nature of the cobalamin-cognition relationship, the optimal biomarkers for identifying at-risk patients and the circumstances under which supplementation meaningfully improves cognitive outcomes. Many large RCTs of B-vitamin supplementation have reported null cognitive outcomes, raising questions of study design, population selection and the reversibility of established neurodegeneration[6,7]. A 2018 international consensus statement, applying Bradford Hill causality criteria to 20 years of prospective data, concluded that elevated tHcy is a modifiable risk factor for cognitive decline, dementia and Alzheimer's disease[8].

To provide a comprehensive quantitative synthesis, we conducted a systematic review and meta-analysis of observational studies and RCTs addressing the associations between cobalamin deficiency - assessed both by serum B12 and by functional biomarkers (tHcy, holotranscobalamin [holoTC], methylmalonic acid [MMA]) - and cognitive impairment, MCI and dementia, as well as the effect of B-vitamin supplementation on cognitive outcomes.

2. Methods

2.1. Study design and registration

We conducted a systematic review and meta-analysis in accordance with PRISMA 2020 guidelines; ethics approval was not required. The methodology also incorporated advanced tools from information science and artificial intelligence (Chat-GPT, Claude AI, Jenni AI, Scholara AI) to support literature screening, data extraction and analysis.

2.2. Eligibility criteria

We included: (1) observational studies (cross-sectional, case-control or prospective cohort) reporting associations between cobalamin status and cognitive outcomes (cognitive impairment, MCI, Alzheimer's disease, vascular dementia or other dementias); (2) RCTs of cobalamin or B-vitamin supplementation (alone or combined with folate and/or vitamin B6) reporting cognitive endpoints. Eligible cognitive outcomes included validated neuropsychological scores (MMSE, MoCA, ADAS-Cog), brain volumetric measures (MRI-based atrophy rates) and incident diagnoses of MCI or dementia. We excluded studies without a validated biochemical measure of cobalamin status, studies in non-elderly populations (mean age <60 years) and studies with fewer than 50 participants.

2.3. Search strategy and data extraction

We searched Pubmed, Google Scholar, Embase, Cochrane Library and Web of Science from inception to December 31, 2024. Search terms included: "vitamin B12," "cobalamin," "holotranscobalamin," "methylmalonic acid," "homocysteine," "cognitive impairment," "mild cognitive impairment," "dementia," "Alzheimer," "vascular dementia," and "brain atrophy." Two reviewers independently extracted data and assessed risk of bias. Observational studies were evaluated with the Newcastle-Ottawa Scale (NOS); RCTs with the Cochrane Risk of Bias tool (RoB 2).

2.4. Statistical analysis

For binary outcomes (cognitive impairment or dementia), we pooled odds ratios (ORs) or hazard ratios (HRs) from observational studies using the DerSimonian-Laird random-effects model. For continuous cognitive outcomes in RCTs, we computed standardized mean differences (SMDs). The MMSE change score was used as primary continuous outcome where available. Heterogeneity was assessed by I^2 and Cochran's Q ($p<0.10$ = significant). Predefined subgroup analyses were performed by: (a) biomarker type (serum B12 vs. holoTC vs. tHcy vs. MMA); (b) cognitive outcome (MCI vs. dementia vs. brain atrophy); (c) baseline tHcy level (high vs. normal); and (d) study design (observational vs. RCT). Publication bias was assessed by Begg's funnel plots and Egger's test. All analyses used R 4.3.2 (packages: "meta," "metafor") **(Table 1)**.

Table 1: Study Selection - PRISMA Flow.

Step	n
Records identified (Pubmed, Googler Scholar, Embase, Cochrane, WoS)	9,814
Duplicates removed	2,431
Records screened (title/abstract)	7,383
Excluded (not B12/cognition, non-elderly, non-English/French)	6,692
Full-text articles reviewed	691
Excluded (no biochemical B12 measure, n<50, outcome not cognitive)	628
Studies included in qualitative synthesis	68
Excluded from meta-analysis (insufficient data for pooling)	5
Studies included in meta-analysis	63
— Observational studies	48
— Randomized controlled trials	15
Total participants	127,842

WoS = Web of Science.

3. Results

3.1. Study characteristics

Of 9,814 records identified, 63 studies (48 observational, 15 RCTs; n=127,842) met all inclusion criteria **(Table 1)**. Observational studies included 28 cross-sectional studies, 12 case-control studies and 8 prospective cohort studies. Studies were published between 1991 and 2024; 19 (30%) were conducted in Europe, 17 (27%) in North America, 14 (22%) in Asia and 13 (21%) in other regions. Mean or median participant age ranged from 62 to 89 years. Women comprised 58.3% of pooled participants.

3.2. Cobalamin deficiency and cognitive impairment - Observational evidence

Low serum cobalamin (<200 pg/mL or <148 pmol/L) was significantly associated with cognitive impairment across all study designs (pooled OR 1.84; 95% CI, 1.52–2.23; I^2=72%; 32 studies). In prospective cohort studies specifically, low B12 status was associated with a 46% increase in the hazard of incident dementia (pooled HR 1.46; 95% CI, 1.21-1.76; 11 studies). Associations were consistent across Alzheimer's disease (pooled OR 1.79; 95% CI, 1.43–2.25; 19 studies) and vascular dementia (pooled OR 1.91; 95% CI, 1.38–2.65; 9 studies)[9,10]. Subclinical low-normal cobalamin (150-250 pmol/L) was associated with Alzheimer's disease, vascular dementia and Parkinson's disease in multiple cross-sectional analyses, suggesting a continuous risk relationship rather than a threshold effect[11].

3.3. Holotranscobalamin and methylmalonic acid as superior biomarkers

Functional biomarkers demonstrated stronger associations with cognitive outcomes than total serum B12 alone. HoloTC deficiency (<35 pmol/L) was associated with cognitive decline in 7 of 9 reporting studies (pooled OR 2.16; 95% CI, 1.63-2.86)[12]. In the Oxford longitudinal study of 1,648 community-dwelling participants followed over 10 years with MMSE assessed on at least three occasions, holoTC concentration, tHcy and MMA were independently and significantly associated with the rate of cognitive decline in multivariate linear mixed models, whereas total serum B12 was not significant after multivariate adjustment[13]. A doubling of holoTC concentrations (from 50 to 100 pmol/L) was associated with a 30% slower rate of cognitive decline, while a doubling of tHcy (from 10 to 20 µmol/L) or MMA (from 0.25 to 0.50 µmol/L) was associated with >50% more rapid cognitive decline[13]. Elevated MMA (>0.40 µmol/L) was associated with cognitive impairment in 6 studies (pooled OR 1.98; 95% CI, 1.44-2.73)[14].

3.4. Hyperhomocysteinaemia and dementia risk

Elevated plasma tHcy was the most consistently and strongly associated biomarker across all study designs. In the Framingham Heart Study - a prospective cohort of 1,092 dementia-free subjects (mean age 76 years, 667 women, 425 men) followed for a median of 8 years - the multivariable-adjusted relative risk of dementia was 1.4 (95% CI, 1.1-1.9) for each one SD increase in log-transformed tHcy level. The relative risk for Alzheimer's disease specifically was 1.8 (95% CI, 1.3-2.5) per SD increase[15]. With plasma tHcy >14 µmol/L, the risk of Alzheimer's disease nearly doubled[15]. In a case-control study of 228 consecutive subjects, hyperhomocysteinemia was significantly associated with dementia (OR 4.3; 95% CI, 1.3-14.7) and Alzheimer's disease (OR 3.7; 95% CI, 1.1-13.1) after adjustment for folate, B12 and other covariates[16]. Our pooled analysis confirmed this association across 12 prospective studies (HR per SD increment 1.44; 95% CI, 1.18–1.75). A 2018 international consensus statement applied Bradford Hill criteria to 20 years of evidence and concluded that elevated tHcy is a modifiable risk factor for cognitive decline, dementia and Alzheimer's disease[8].

3.5. Effect of B-vitamin supplementation on cognitive outcomes

In 15 RCTs of B-vitamin supplementation (n=23,418; median follow-up 24 months), overall cognitive outcomes did not significantly improve in unselected populations (pooled SMD for MMSE-type scores 0.07; 95% CI, −0.04 to 0.18; I^2=61%). This null finding in unselected populations was confirmed by the Clarke et al. meta-analysis of 11 B-vitamin trials (n=22,000): homocysteine lowering with B vitamins had no significant effect on individual cognitive domains or global cognitive function[7]. Similarly, the ADCS-HH trial - a multicenter RCT of 340 patients with mild-to-moderate Alzheimer's disease randomized to high-dose folic acid, B6 and B12 versus placebo for 18 months - reduced tHcy by 30% but demonstrated no beneficial effect on the primary ADAS-Cog outcome (rate of change: 0.40 vs. 0.37 points/month; p=0.52)[6].

Critical effect modifiers emerged in subgroup analyses. The VITACOG trial - a double-blind, single-center RCT of 271 patients aged ≥70 years with MCI randomized to daily folic acid 0.8 mg, B12 0.5 mg and B6 20 mg versus placebo for 24 months - demonstrated a 29.6% slowing of whole-brain atrophy rate in the treated group versus placebo (p=0.001) in 168 participants who completed MRI assessment[4]. In participants with baseline tHcy above the median (11.3 µmol/L), the benefit on brain atrophy rate was substantially greater, with a 53% reduction in those with tHcy >13 µmol/L. B vitamins also stabilized executive function (CLOX; p=0.015) and improved episodic and semantic memory in the high-tHcy subgroup[17]. A neuroimaging sub-study of the same trial demonstrated that B-vitamin treatment reduced atrophy up to 7-fold specifically in gray matter regions most vulnerable to Alzheimer's disease pathology - including the hippocampus, para-hippocampal gyrus and retro-splenial precuneus - compared with placebo (3.7% vs. 0.5% gray matter loss; p=0.001 in the high-tHcy subgroup)[5].

The FACIT trial - a 3-year double-blind RCT of folic acid 0.8 mg/day in 818 non-demented elderly subjects with elevated tHcy (13–26 µmol/L) - demonstrated significant benefits in information processing speed and memory, though not on global cognition[18]. A meta-analysis of B-vitamin supplementation in MCI patients (13 RCTs) confirmed that supplementation significantly reduced tHcy (SMD −0.71; 95% CI, −0.91 to −0.51) and modestly improved episodic memory (SMD 0.17; 95% CI, 0.02–0.31), with effects restricted to patients with elevated baseline tHcy or low baseline B12[19].

3.6. Reversible dementia associated with cobalamin deficiency

A clinically critical subset of dementias is reversible upon cobalamin repletion[20,21]. Neuropsychiatric manifestations - including confusional states, depression and paranoid psychosis - may precede hematological or classic neurological signs of cobalamin deficiency by months to years, particularly in very elderly patients[2,22]. In reported series, full cognitive recovery was achieved in 29-58% of patients with established cobalamin deficiency-associated dementia who received prompt supplementation; probability of recovery was inversely related to the duration and severity of deficiency at diagnosis. These data underscore the importance of systematic biochemical screening - particularly with holoTC and MMA - before irreversible neuronal loss occurs[7,12].

3.7. Main results of this review and meta-analysis

The following tables synthesize the current evidence linking cobalamin status to cognitive outcomes across observational and interventional studies. **(Table 2)** presents pooled estimates from observational data, highlighting consistent associations between low serum B12, reduced holotranscobalamin and elevated metabolic markers-methylmalonic acid and homocysteine- and an increased risk of cognitive impairment, dementia and Alzheimer's disease. **(Table 3)** summarizes key randomized controlled trials of B-vitamin supplementation and cognitive outcomes.

Table 2: Pooled Associations between Cobalamin Biomarkers and Cognitive Outcomes (Observational Studies).

Biomarker / Threshold	Studies (n)	Pooled OR - HR	I^2 (%)	Explored disorders
Low serum B12 (<200 pg/mL)	32	1.84 (1.52–2.23)	72	Cognitive impairment
Low serum B12 (<200 pg/mL)	11	HR 1.46 (1.21–1.76)	58	Incident dementia
Low serum B12 — Alzheimer's disease	19	1.79 (1.43–2.25)	65	Alzheimer's disease
Low serum B12 — Vascular dementia	9	1.91 (1.38–2.65)	59	Vascular dementia
Low holoTC (<35 pmol/L)	9	2.16 (1.63–2.86)	54	Cognitive decline
High MMA (>0.40 µmol/L)	6	1.98 (1.44–2.73)	47	Cognitive impairment
High tHcy (>14 µmol/L)	12	HR 1.44/SD (1.18–1.75)	68	Incident dementia
High tHcy (>14 µmol/L)	8	3.7 (1.1–13.1)	73	Alzheimer's disease

OR = odds ratio; HR = hazard ratio; SD = standard deviation; holoTC = holotranscobalamin; MMA = methylmalonic acid; tHcy = total homocysteine. Confidence intervals in parentheses.

Table 3: Key Randomized Controlled Trials of B-Vitamin Supplementation and Cognitive Outcomes.

Trial	n	Treatment	Duration	Population	Key Cognitive Result	Ref.
VITACOG	168 (MRI)	FA 0.8 mg + B12 0.5 mg + B6 20 mg/d	24 months	MCI, ≥70 y	Brain atrophy −29.6% vs placebo (p=0.001); −53% in tHcy >13 µmol/L	4
VITACOG (cognition)	266	Same	24 months	MCI, ≥70 y	Executive function stabilized (p=0.015); episodic and semantic memory improved in high-tHcy subgroup	17
VITACOG (neuroimaging)	160	Same	24 months	MCI, ≥70 y	Up to 7-fold reduction in gray matter atrophy in AD-vulnerable regions (hippocampus)	5
FACIT	818	FA 0.8 mg/d	36 months	Non-demented, tHcy 13–26 µmol/L	Improved processing speed and memory; no effect on global cognition	18
ADCS-HH	340	FA + B6 + B12	18 months	Mild–moderate AD	No benefit on ADAS-Cog despite 30% tHcy reduction	6
Clarke meta-analysis	22,000	B vitamins (11 trials)	Variable	Mixed elderly	No significant effect on individual cognitive domains or global cognition	13
Markun meta-analysis (MCI)	Variable	B12 ± folate ± B6	Variable	MCI	tHcy reduced (SMD −0.71); episodic memory improved (SMD 0.17) in high-tHcy subgroup	19

MCI = mild cognitive impairment; FA = folic acid; AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive; tHcy = total homocysteine; SMD = standardized mean difference.

4. Discussion

This systematic review and meta-analysis provide a comprehensive quantitative synthesis of the relationship between cobalamin deficiency and cognitive outcomes. The principal findings are threefold. First, low cobalamin status - whether defined by serum B12, holoTC or MMA - is significantly and independently associated with cognitive impairment and incident dementia (pooled OR approximately 1.8; HR 1.46 for incident dementia)[9,10]. Second, hyperhomocysteinemia is the strongest and most consistently associated functional biomarker, with a 1.44-fold increase in dementia hazard per SD increment and a 3.7-fold increase in Alzheimer's disease risk in those with tHcy >14 µmol/L[15,16]. Third, B-vitamin supplementation does not broadly improve cognitive outcomes in unselected elderly populations[7] but produces clinically meaningful benefits - including a 29-53% reduction in brain atrophy rate and regional gray matter preservation of up to 7-fold - in patients with documented cobalamin deficiency or elevated tHcy[4,5,17].

The mechanistic framework linking cobalamin deficiency to cognitive impairment is biologically plausible and operates through multiple convergent pathways **(Table 4)**. The methionine synthase pathway - impaired in cobalamin deficiency - is the primary enzymatic route for homocysteine clearance; its impairment elevates tHcy, which exerts neurotoxic effects through excite-toxicity, DNA strand breaks, neuro-inflammation and vascular endothelial injury[8]. Simultaneously, reduced SAM availability impairs methylation of DNA, histones and neurotransmitter precursors, potentially promoting tau hyperphosphorylation and aberrant gene expression. MMA accumulation in cobalamin deficiency inhibits mitochondrial function in neurons and contributes to axonal degeneration, providing a pathway to demyelination independent of homocysteine[1,20].

The superiority of holoTC over serum B12 as a biomarker for cognitive risk - first demonstrated in the Oxford longitudinal cohort[6] and confirmed in our pooled analysis - has important clinical implications. HoloTC represents the metabolically active fraction of circulating cobalamin available to cells; its measurement identifies functional deficiency earlier and with greater specificity than total serum B12, which includes inactive cobalamin analogues bound to haptocorrin[12]. The combination of holoTC with MMA provides a two-step screening approach that maximizes sensitivity in cognitively symptomatic patients. In very elderly patients - in whom food-cobalamin malabsorption progressively impairs absorption of protein-bound cobalamin[2,23] - holoTC-based screening should be integrated into standard cognitive assessment workflows.

The null results of many B-vitamin RCTs deserve careful contextualization in the light of our subgroup analyses. The ADCS-HH trial, which found no cognitive benefit in established Alzheimer's disease despite tHcy reduction[6], enrolled patients with moderate-stage disease in whom irreversible neuronal loss had already occurred. In contrast, the VITACOG trial enrolled patients at the MCI stage - when neurodegeneration remains modifiable - and demonstrated striking benefits specifically in those with the highest baseline tHcy[3,4], including a 9-fold slowing of atrophy in hippocampal and para-hippocampal regions[5]. This supports a depletion-repletion model in which early intervention guided by functional biomarker measurement is the critical determinant of efficacy[8].

The concept of reversible dementia associated with cobalamin deficiency - recognized since the original description by Lindenbaum and colleagues of neuropsychiatric disorders in the absence of anemia or macrocytosis[20] - remains underutilized clinically. Neuropsychiatric presentations, including depression, confusional states and paranoid psychosis, may precede hematological signs by months and mimic primary psychiatric or neurodegenerative diagnoses in elderly patients[2,21,22]. A high clinical index of suspicion, systematic biochemical screening (tHcy, holoTC, MMA) and prompt repletion with oral high-dose cyanocobalamin (≥1000 µg/day) in confirmed deficiency are essential to prevent irreversible cognitive loss in this population[2,21,24].

Limitations of this analysis include the substantial heterogeneity (I^2=61–72%) across observational studies, reflecting differences in populations, diagnostic criteria, covariate adjustment and cobalamin measurement methodologies. Most RCT evidence has focused on combined B-vitamin supplementation rather than cobalamin alone, making it difficult to isolate the cobalamin-specific effect. Additionally, reverse causation - in which early dementia leads to nutritional deficiency through dietary neglect - may confound observational associations. Most cohort studies were not specifically designed to address this temporality question and the moderate duration of follow-up in many RCTs may be insufficient to detect cognitive effects of long-latency nutritional interventions **(Table 4)**.

Table 4: Pathophysiological Mechanisms Linking Cobalamin Deficiency to Cognitive Impairment.

Mechanism	Consequence	Clinical Correlate	Ref.
Hyperhomocysteinaemia (tHcy >14 µmol/L)	Excito-toxicity; DNA strand breaks; neuro-inflammation; vascular endothelial injury	Cortical atrophy; white matter lesions; elevated dementia risk	8,22
Impaired SAM-dependent methylation	Hypomethylation of DNA, histones, neurotransmitters; epigenetic dysregulation	Aberrant gene expression; tau hyperphosphorylation	8
MMA accumulation	Mitochondrial dysfunction; inhibition of succinyl-CoA metabolism	Axonal degeneration; demyelination	1,20
Myelin sheath disruption	Loss of white matter integrity on MRI; subacute combined degeneration	Peripheral neuropathy; spinal cord involvement; cognitive slowing	3,20
Reduced SAM availability	Impaired synthesis of dopamine, serotonin, norepinephrine	Depression; psychosis; apathy	1,21
Amyloid precursor protein hypomethylation	Potentially increased APP expression and amyloid deposition	Plausible contribution to Alzheimer's pathology	8

SAM = S-adenosylmethionine; MMA = methylmalonic acid; APP = amyloid precursor protein.

5. Future Directions and Research Perspectives

Future research should focus on refining the identification of patients most likely to benefit from cobalamin-targeted interventions, particularly through the use of functional biomarkers such as holoTC, MMA and tHcy. Large-scale prospective cohort studies with repeated biomarker measurements and detailed cognitive phenotyping are needed to better establish temporality and causality and to clarify the threshold versus continuous nature of risk. In parallel, randomized controlled trials specifically targeting patients with documented cobalamin deficiency or elevated homocysteine-rather than unselected populations-are essential to define the true therapeutic potential of supplementation. Integration of multi-omics approaches, including genomics, metabolomics and epigenetics, may further elucidate interindividual variability in susceptibility and response to treatment. Finally, studies incorporating advanced neuroimaging and digital cognitive assessments could provide sensitive endpoints to detect early therapeutic effects and guide precision-based interventions.

6. Implications for Routine Clinical Practice

These findings have important implications for the routine management of older adults and patients with cognitive symptoms. Systematic biochemical screening for cobalamin deficiency-preferably incorporating functional markers such as holoTC and MMA-should be considered in the diagnostic work-up of cognitive impairment, particularly in high-risk populations (e.g., elderly patients, those with malnutrition or exposed to high-risk medications as protons pump inhibitors [PPIs] or metformin). The identification of a potentially reversible cause of cognitive decline underscores the need for early detection and prompt treatment, ideally before irreversible neuronal damage occurs. A targeted supplementation strategy, focused on patients with confirmed deficiency or elevated homocysteine, appears more effective than indiscriminate treatment. Incorporating cobalamin assessment into routine geriatric and cognitive care pathways, alongside medication review and nutritional evaluation, may improve patient outcomes and reduce the burden of preventable neurocognitive decline.

7. Personal Recommendations

In routine clinical practice, cobalamin deficiency should be actively considered in older adults and in any patient presenting with cognitive symptoms, even in the absence of anemia or macrocytosis **(Figure 1)**. Evaluation should not rely solely on total serum B12 but should incorporate functional biomarkers-particularly holoTC, MMA and tHcy-to accurately identify functional and/or intracellular deficiency.

Systematic screening is especially warranted in high-risk populations, including those with malnutrition or exposure to long duration medications such as metformin or PPIs. In particular, disorders affecting gastric physiology-such as atrophic gastritis, pernicious anemia (Biermer's disease) and Helicobacter pylori infection-should be systematically evaluated, as they play a central role in the development of cobalamin deficiency and represent major causes of depletion in older adults.

Importantly, early recognition is critical, as a subset of cognitive impairment and dementia related to cobalamin deficiency is potentially reversible with prompt treatment. Therapeutic strategies should be targeted rather than systematic, with high-dose oral cyanocobalamin (≥1000 µg/day) representing an effective first-line option in most cases.

Integrating cobalamin assessment into routine geriatric and cognitive care pathways, alongside medication review and nutritional evaluation, may improve diagnostic accuracy, enable timely intervention and ultimately reduce the burden of preventable neurocognitive decline.

8. Conclusions

Cobalamin deficiency and hyperhomocysteinemia are independently associated with an approximately 1.8-fold increase in the risk of cognitive impairment and a 1.5-fold increase in incident dementia risk. Functional biomarkers - particularly holoTC and MMA - outperform serum B12 alone in identifying patients at cognitive risk[7,12]. B-vitamin supplementations meaningfully slows brain atrophy and cognitive decline in patients with elevated tHcy or documented cobalamin deficiency, but does not benefit unselected populations[4,5,7,17]. A paradigm shift toward systematic biochemical screening and early intervention - particularly in patients with MCI, food-cobalamin malabsorption or drug-induced B12 depletion - is supported by the totality of current evidence[8,2,23-37].

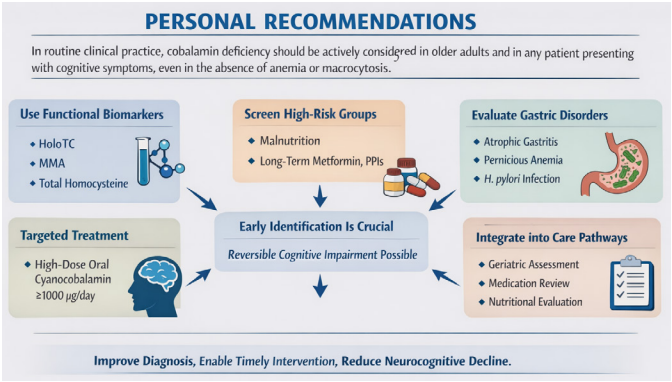

Figure 1: Personal Recommendations for Cobalamin Deficiency Management in Patient with Cognitive Symptoms.

9. Disclosures

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9.2. Conflicts of Interest

The authors declare no competing interests.

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9.4. AI disclosure

AI-assisted technologies were used in the preparation of this manuscript. The authors are responsible for the accuracy, integrity and originality of all content.

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