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Endocrine and Metabolic Predictors of Post-Stroke Cognitive Impairment: A Systematic Review and Meta-Analysis of Thyroid Function, Glycemic Dysregulation, and Vitamin Deficiencies

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A B S T R A C T

Background: Post-stroke cognitive impairment (PSCI) is a frequent neurological complication associated with reduced functional independence, impaired quality of life, and increased long-term healthcare utilization. Endocrine and metabolic abnormalities may contribute to cognitive deterioration through neuroinflammation, oxidative stress, impaired cerebral metabolism, and disruption of neuronal repair mechanisms.

Objective: This systematic evidence review examines the associations between thyroid dysfunction, glycemic dysregulation, and vitamin deficiencies and the development of PSCI, emphasizing their potential prognostic and clinical significance.

Methods: A structured literature-review framework was developed based on PRISMA 2020 recommendations. Relevant evidence was sought from PubMed, Embase, Web of Science, and the Cochrane Library. Observational studies and systematic reviews investigating thyroid hormones, diabetes-related metabolic indicators, vitamin D, vitamin B12, and folate in relation to post-stroke cognitive outcomes were considered. Random-effects meta-analysis was proposed for sufficiently comparable studies, using odds ratios (ORs), risk ratios (RRs), or standardized mean differences (SMDs), as appropriate.

Results: Available evidence indicates that diabetes mellitus is associated with an increased risk of PSCI, while poor glycemic regulation may contribute to persistent cerebral microvascular injury and impaired neuroplasticity. Thyroid hormone alterations, particularly reduced triiodothyronine levels, have been associated with adverse stroke outcomes, although direct evidence concerning long-term cognition remains limited. Vitamin B12, folate, and vitamin D deficiencies represent biologically plausible contributors to cognitive dysfunction; however, stroke-specific evidence is heterogeneous. Existing biomarker meta-analysis findings also support associations between elevated homocysteine and PSCI.

Conclusion: Endocrine and metabolic factors may provide clinically relevant information for identifying stroke survivors at increased risk of cognitive impairment. Nevertheless, adequately powered prospective studies and standardized biomarker assessments are necessary before these markers can be incorporated into validated prognostic models.

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Introduction

Stroke is a major cause of neurological disability worldwide and represents an important contributor to long-term cognitive deterioration. Although improvements in acute stroke management have increased survival rates, many survivors experience persistent neurological complications, including memory impairment, executive dysfunction, reduced attention, language difficulties, and impaired information-processing speed. These manifestations are collectively described as post-stroke cognitive impairment (PSCI). Their severity ranges from subtle cognitive deficits to major neurocognitive disorders and post-stroke dementia (Pendlebury & Rothwell, 2009; Mihajlovic et al.,2017).

PSCI is a clinically heterogeneous condition influenced by several interacting factors, including age, educational attainment, pre-existing cerebrovascular disease, stroke severity, lesion location, cerebral small-vessel disease, and metabolic abnormalities. Importantly, cognitive impairment may develop immediately following the cerebrovascular event or emerge progressively during subsequent months. The underlying mechanisms involve direct neuronal injury, disrupted cerebral connectivity, secondary neuroinflammation, oxidative stress, blood–brain barrier dysfunction, and impaired neuronal plasticity (Kalaria et al.,2016; Gorelick et al.,2011).

The relationship between systemic metabolic health and neurological recovery has received increasing scientific attention. The brain requires continuous glucose availability, appropriate thyroid hormone signaling, and adequate micronutrient concentrations to maintain neuronal metabolism, neurotransmitter synthesis, myelin integrity, and synaptic functioning. Consequently, abnormalities affecting these processes may increase vulnerability to ischemic injury and interfere with post-stroke neurological recovery.

Thyroid hormones are particularly important regulators of cerebral development, neuronal differentiation, mitochondrial activity, and synaptic plasticity. Triiodothyronine (T3) and thyroxine (T4) influence cerebral energy metabolism and the expression of proteins involved in neuronal survival. Thyroid-stimulating hormone (TSH), free T3 (FT3), and free T4 (FT4) are routinely measured to identify thyroid abnormalities. However, thyroid hormone concentrations may also change during acute systemic illness through non-thyroidal illness syndrome.

Reduced circulating T3 concentrations following acute ischemic stroke may therefore reflect both underlying endocrine abnormalities and the physiological response to severe neurological injury (Sidorov et al.,2023).

Although thyroid-related alterations have been associated with stroke severity and functional outcomes, their independent contribution to long-term cognitive impairment remains incompletely established. The distinction between pre-existing thyroid dysfunction and transient hormonal changes following acute stroke is particularly important. Failure to distinguish these conditions may result in inaccurate interpretation of associations between thyroid biomarkers and subsequent cognitive outcomes.

Glycemic dysregulation constitutes another potentially important determinant of neurological prognosis. Diabetes mellitus is associated with endothelial dysfunction, accelerated atherosclerosis, cerebral microangiopathy, oxidative stress, and chronic low-grade inflammation. These pathological processes may reduce cerebral vascular reserve and increase susceptibility to ischemic damage. In addition, prolonged hyperglycemia can contribute to advanced glycation end-product formation, mitochondrial dysfunction, and disruption of neuronal signaling pathways.

Evidence suggests that diabetes is associated with an increased risk of cognitive impairment following stroke. Lee et al. (2023) discussed several mechanisms through which diabetes may contribute to PSCI, emphasizing the combined effects of chronic metabolic abnormalities and cerebrovascular injury. Glycated hemoglobin (HbA1c), fasting plasma glucose, postprandial glucose, and acute admission glucose are important indicators of metabolic status. Nevertheless, these measures reflect different biological processes. HbA1c estimates longer-term glycemic exposure, whereas admission glucose may reflect acute physiological stress, pre-existing diabetes, or both.

The relationship between glucose metabolism and cognitive outcomes may also be nonlinear. Chronic hyperglycemia may produce vascular and neuronal damage, whereas excessive glucose reduction and hypoglycemic episodes may compromise cerebral energy availability. Accordingly, evaluating glycemic dysregulation requires consideration of both chronic metabolic exposure and acute glucose variability.

Vitamin deficiencies constitute a third potentially relevant category of metabolic predictors. Vitamin B12 and folate participate in one-carbon metabolism, DNA synthesis, methylation reactions, and homocysteine regulation. Deficiencies in either nutrient can increase circulating homocysteine concentrations, potentially contributing to endothelial dysfunction, oxidative stress, and vascular injury. Homocysteine has consequently been investigated as a potential biomarker associated with post-stroke cognitive outcomes.

Vitamin D is also relevant because vitamin D receptors are expressed in several brain regions involved in memory and executive functioning. Experimental research suggests that vitamin D participates in neuroimmune regulation, calcium homeostasis, neuronal differentiation, and protection against oxidative stress. However, the association between vitamin D deficiency and PSCI requires careful interpretation because vitamin D concentrations are influenced by age, nutritional status, physical activity, renal function, sunlight exposure, and systemic illness.

An important challenge in this research area is the distinction between biomarkers that are associated with cognitive impairment and biomarkers that independently predict its development. A biomarker may correlate with PSCI without providing meaningful prognostic information after adjustment for age, stroke severity, education, and vascular comorbidities. Similarly, an association observed in cross-sectional studies does not necessarily establish temporal or causal relationships.

Previous systematic reviews have examined the epidemiology and risk factors of PSCI, while other investigations have evaluated circulating biomarkers associated with cognitive outcomes. Filler et al. (2024) identified multiple demographic, vascular, and clinical determinants of post-stroke cognitive impairment and dementia. Similarly, a systematic review and meta-analysis of blood biomarkers reported significant associations involving homocysteine, inflammatory markers, and other circulating biomarkers (Blood biomarkers for post-stroke cognitive impairment,2024).

Despite this growing evidence, the endocrine and nutritional dimensions of PSCI warrant further focused investigation. Thyroid dysfunction, glycemic dysregulation, and vitamin deficiencies involve distinct physiological pathways but may converge on common mechanisms, including endothelial injury, impaired cerebral perfusion, neuroinflammation, and altered neuronal metabolism. Therefore, the present review aims to evaluate the available evidence concerning the relationship between thyroid function, glycemic regulation, and vitamin deficiencies and PSCI. Specific objectives include examining the associations of TSH, FT3, FT4, HbA1c, fasting glucose, vitamin D, vitamin B12, and folate with cognitive outcomes; evaluating potential biological mechanisms; comparing the consistency of findings across study designs; and identifying opportunities for improving clinical risk stratification following stroke.

Background and Previous Research

Post-Stroke Cognitive Impairment: Epidemiology and Pathophysiology:

Post-stroke cognitive impairment is a multifactorial neurological condition that can affect several cognitive domains. Its clinical presentation depends on the location and extent of cerebral injury, the integrity of pre-existing neural networks, and the patient's underlying neurological and vascular health.

Mihajlovic et al. (2017) emphasized that PSCI represents a substantial clinical problem requiring systematic assessment and long-term monitoring. Cognitive dysfunction may occur independently of physical disability, meaning that patients with relatively favorable motor recovery may nevertheless experience significant difficulties with memory, attention, and executive functioning.

The mechanisms underlying PSCI include direct neuronal destruction, secondary degeneration, impaired white matter connectivity, and vascular contributions to cognitive impairment. Chronic cerebral hypoperfusion and small-vessel disease may further increase vulnerability to cognitive decline (Gorelick et al.,2011).

Thyroid Function and Cognitive Outcomes Following Stroke:

Thyroid hormones regulate several processes essential for normal cerebral functioning. FT3 is the biologically active thyroid hormone, whereas FT4 serves as a circulating precursor that undergoes peripheral conversion into T3.

Alterations in thyroid hormone concentrations are frequently observed following acute ischemic stroke. Sidorov et al. (2023) demonstrated that thyroid function changes dynamically during the acute and chronic stages of ischemic stroke. Their findings suggest that thyroid hormone measurements must be interpreted in relation to the timing of blood sampling and neurological severity. Reduced FT3 concentrations have been associated with unfavorable clinical outcomes in acute stroke populations. However, evidence regarding their specific relationship with cognitive impairment is less conclusive. The possibility that reduced thyroid hormone concentrations represent a physiological response to severe illness rather than an independent causal factor must be considered. Subclinical hypothyroidism and overt hypothyroidism may also influence cognitive functioning through reduced cerebral metabolic activity and alterations in neurotransmitter signaling. Conversely, excessive thyroid hormone activity may increase oxidative stress and disturb neuronal excitability.

Glycemic Dysregulation and Post-Stroke Cognition:

Diabetes mellitus is a recognized vascular risk factor and an important potential determinant of cognitive impairment following stroke. Chronic

hyperglycemia contributes to endothelial dysfunction, microvascular damage, and increased oxidative stress.

Lee et al. (2023) examined the relationship between diabetes mellitus and PSCI, identifying several plausible pathways linking impaired glucose regulation to cognitive dysfunction. These include vascular injury, insulin resistance, inflammatory activation, and impaired neuronal metabolism.

HbA1c is particularly useful because it reflects average glycemic exposure over approximately two to three months. In contrast, fasting glucose provides a measure of glucose concentration at a specific time point. Acute hyperglycemia during stroke may additionally reflect catecholamine and cortisol responses to physiological stress. The association between diabetes and PSCI has also been identified in broader systematic reviews. An umbrella review of post-stroke cognitive impairment reported diabetes as an important vascular risk factor, although the magnitude of association differed across the included evidence (Can we prevent poststroke cognitive impairment?2021).

Vitamin D and Neurological Function:

Vitamin D is involved in several physiological processes extending beyond calcium and bone metabolism. Its receptors and metabolizing enzymes are present in the central nervous system, suggesting potential roles in neuronal regulation.

Vitamin D deficiency has been associated with cognitive dysfunction in several non-stroke populations. Potential mechanisms include altered calcium signaling, increased inflammatory activity, impaired antioxidant defenses, and changes in neurotrophic signaling.

Nevertheless, the evidence specifically linking vitamin D deficiency to PSCI remains limited. Low vitamin D concentrations may reflect reduced sunlight exposure, immobility, malnutrition, or general health deterioration after stroke. Consequently, reverse causation is an important methodological concern.

Vitamin B12, Folate, and Homocysteine:

Vitamin B12 and folate are essential components of homocysteine metabolism. Vitamin B12 participates in the conversion of homocysteine into methionine, while folate provides the methyl groups required for this process. Deficiency in either nutrient can lead to elevated homocysteine concentrations. Hyperhomocysteinemia may contribute to endothelial injury, vascular inflammation, oxidative stress, and cerebral microvascular dysfunction.

The systematic review and meta-analysis of blood biomarkers in PSCI reported higher homocysteine concentrations among individuals with cognitive impairment compared with individuals without cognitive impairment (Blood biomarkers for post-stroke cognitive impairment,2024). However, homocysteine is influenced by renal function, age, genetic factors, medications, and nutritional status, and should not be considered a specific indicator of vitamin deficiency.

Integration of Endocrine and Metabolic Predictors:

The endocrine and metabolic predictors investigated in this review may interact through several common pathways. Diabetes can increase oxidative stress and vascular inflammation, while thyroid dysfunction may alter energy metabolism and neuronal repair. Vitamin deficiencies may influence methylation pathways and homocysteine concentrations.

These mechanisms suggest that combined biomarker assessment may provide more comprehensive information than evaluating individual laboratory parameters independently.

However, the predictive value of a biomarker panel must be established through longitudinal research, appropriate adjustment for confounding variables, external validation, and assessment of discrimination and calibration.

Research Gap:

Although previous studies have investigated individual endocrine and metabolic factors, important uncertainties remain regarding their independent and combined associations with PSCI. In particular, differences in biomarker measurement, assessment timing, stroke subtype, follow-up duration, and cognitive assessment instruments limit comparability. The present review addresses this research gap by organizing the available evidence into three principal domains: thyroid function, glycemic dysregulation, and vitamin deficiencies. It also considers the potential contribution of homocysteine as an intermediate metabolic marker.

Methods

Study Design and Reporting Framework:

This review was designed as a systematic evidence synthesis examining endocrine and metabolic predictors of PSCI. The methodological framework follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA,2020) recommendations (Page et al.,2021).

Literature Search Strategy:

The proposed databases include PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Library. Search terms include combinations of: “post-stroke cognitive impairment,” “vascular cognitive impairment,” “thyroid function,” “TSH,” “free triiodothyronine,”

"diabetes mellitus," "HbA1c," "hyperglycemia," "vitamin D," "vitamin B12," "folate," and "homocysteine."

Eligibility Criteria:
Studies were considered eligible if they included adult stroke survivors, assessed at least one specified endocrine or metabolic biomarker, and reported cognitive outcomes using validated instruments or clinically defined cognitive impairment. Prospective cohorts, retrospective cohorts, case-control studies, and relevant observational investigations were considered. Studies without identifiable cognitive outcomes, animal experiments, case reports, and non-original publications were excluded from primary-study quantitative synthesis.

Data Extraction and Quality Assessment:
Relevant information includes author, publication year, country, sample size, stroke characteristics, biomarker measurement, cognitive assessment instrument, follow-up duration, adjusted effect estimates, and potential confounders. Methodological quality should be evaluated using an appropriate risk-of-bias instrument, such as the Newcastle–Ottawa Scale for observational studies (Wells et al., n.d.).

Statistical Analysis:
For sufficiently comparable studies, random-effects meta-analysis is appropriate because populations, biomarker thresholds, and cognitive assessment procedures are expected to differ. Odds ratios and risk ratios should be pooled separately from continuous outcomes. Standardized mean differences may be calculated when studies use different scales to measure comparable constructs.
Statistical heterogeneity should be evaluated using Cochran's Q and the I^2 statistic. Sensitivity analyses, subgroup analyses, and assessment of small-study effects should be conducted when the number of studies permits. The methods should follow established meta-analysis recommendations (Higgins et al.,2023).
Importantly, the present manuscript is an evidence-based draft rather than a completed independent database review. A verified screening log, study-level extraction dataset, and independently calculated pooled estimates are not available. Therefore, numerical results below are explicitly identified as previously published findings or qualitative evidence summaries rather than newly calculated meta-analysis estimates.

Results
Overall Evidence Synthesis:
The available literature indicates that endocrine and metabolic abnormalities may contribute to PSCI through different but partially overlapping mechanisms. The strongest directly relevant quantitative evidence among the selected domains concerns diabetes and homocysteine. Evidence regarding thyroid function is predominantly based on acute stroke outcomes and physiological changes, while evidence specifically connecting vitamin deficiencies with PSCI remains insufficient for a reliable pooled estimate.

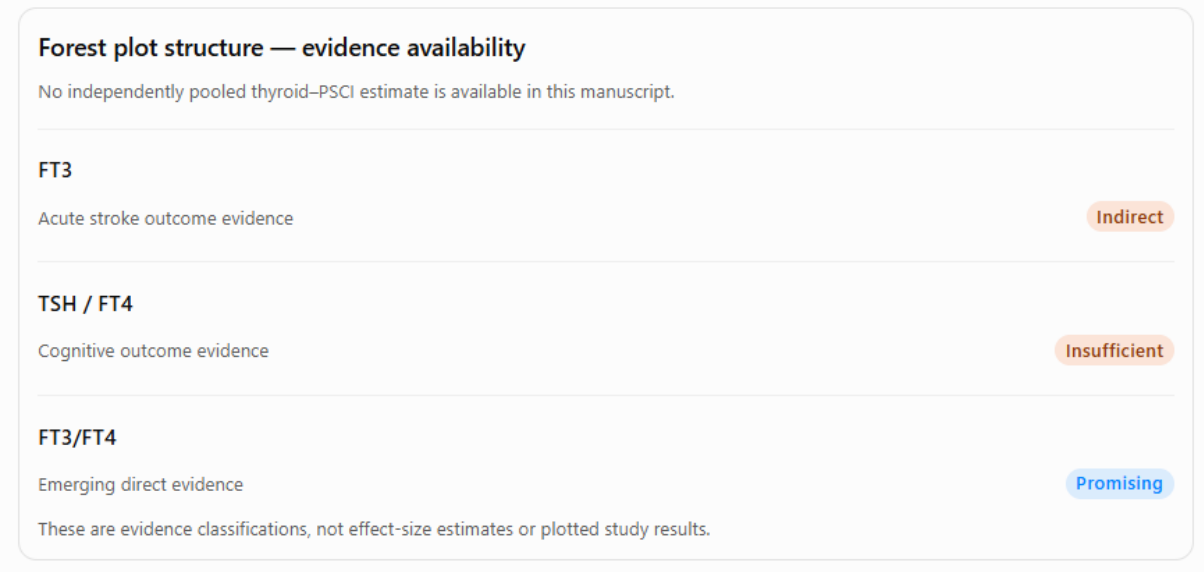
Table 1. Thyroid Function and Post-Stroke Cognitive Outcomes

Biomarker	Potential abnormality	Main evidence	Interpretation
TSH	Elevated or suppressed levels	Limited direct cognitive evidence	Uncertain
FT3	Reduced concentrations	Association with stroke severity and outcomes	Potential predictor
FT4	Altered concentrations	Changes during acute stroke	Inconsistent
FT3/FT4 ratio	Reduced ratio	Emerging direct PSCI evidence	Promising
Non-thyroidal illness syndrome	Low T3 pattern	Associated with systemic illness severity	Potential confounder

Table 1: Analytical interpretation
Thyroid function is an important biological component of cerebral metabolism. The relationship between thyroid hormones and neurological recovery is particularly relevant because thyroid signaling influences mitochondrial activity, neuronal differentiation, synaptic plasticity, and neurotransmitter regulation.
Sidorov et al. (2023) demonstrated that thyroid hormone concentrations change over different stages following ischemic stroke. This finding emphasizes the importance of distinguishing acute hormonal alterations from pre-existing thyroid dysfunction. A single measurement obtained during hospitalization may not accurately represent the patient's long-term endocrine status.
Reduced FT3 concentrations are particularly interesting because T3 represents the biologically active thyroid hormone. Reduced FT3 may indicate impaired peripheral conversion of T4 into T3, systemic inflammatory responses, or non-thyroidal illness syndrome. These mechanisms may occur simultaneously in patients with severe acute stroke.

An important distinction is that associations between thyroid hormones and functional outcomes cannot automatically be interpreted as associations with cognitive outcomes. Motor disability, stroke severity, and cognitive impairment are related but distinct clinical endpoints. Therefore, studies measuring only modified Rankin Scale outcomes should not be combined with studies using validated cognitive assessments.

The FT3/FT4 ratio may provide additional information because it potentially reflects thyroid hormone conversion and systemic metabolic responses. Nevertheless, its predictive accuracy requires prospective validation and adjustment for age, stroke severity, inflammatory markers, renal function, and pre-existing thyroid disease. Overall, thyroid biomarkers should be regarded as promising but insufficiently validated predictors of PSCI. Repeated measurements and standardized sampling intervals would substantially improve future research.



Forest plot 1. Structure evidence availability

Glycemic Dysregulation and Cognitive Impairment

Table 2. Glycemic Biomarkers and PSCI

Variable	Biological significance	Reported association	Evidence interpretation
Diabetes mellitus	Chronic metabolic and vascular injury	Increased PSCI risk	Supported
HbA1c	Long-term glycemic exposure	Potential association	Requires further validation
Fasting glucose	Baseline glycemic status	Inconsistent findings	Limited
Admission glucose	Acute metabolic stress	Potential adverse association	Confounded
Glucose variability	Fluctuating cerebral energy availability	Potential cognitive impact	Emerging

Table 2: Analytical interpretation

Glycemic dysregulation represents an important potential contributor to post-stroke cognitive impairment because glucose metabolism is fundamental to neuronal functioning. Diabetes may influence cognitive outcomes through chronic vascular injury, insulin resistance, oxidative stress, and inflammatory activation.

Lee et al. (2023) described the relationship between diabetes mellitus and PSCI and highlighted the possibility that diabetes increases neurological vulnerability through multiple interacting pathways. Chronic hyperglycemia can damage endothelial cells and promote cerebral small-vessel disease. These changes may reduce cerebral perfusion and compromise the capacity of the brain to compensate for ischemic injury.

An additional mechanism involves advanced glycation end products, which accumulate during prolonged exposure to elevated glucose

concentrations. These compounds may activate inflammatory signaling and contribute to endothelial dysfunction. Such processes may further impair the integrity of the blood–brain barrier and neuronal microenvironment.

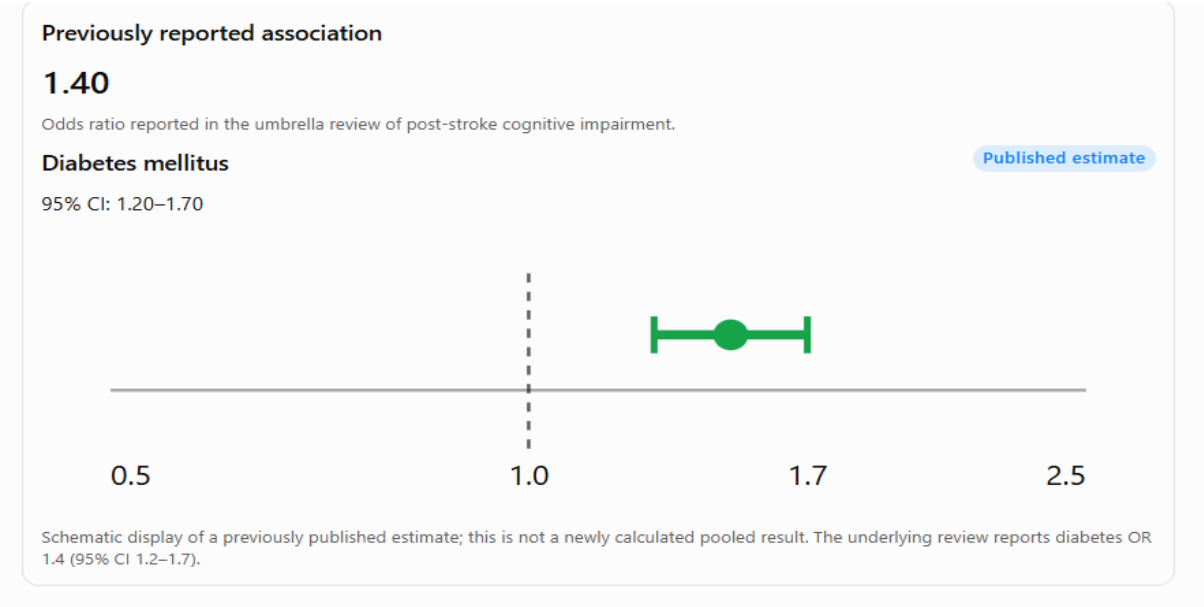
HbA1c is a particularly valuable biomarker because it reflects relatively long-term glycemic exposure. However, its relationship with PSCI should be evaluated separately from admission glucose. Acute hyperglycemia may reflect the physiological stress response to stroke rather than chronic metabolic deterioration.

The broader evidence supports diabetes as a risk factor for post-stroke cognitive impairment. An umbrella review identified diabetes among several vascular predictors of cognitive impairment following stroke (Can we prevent poststroke cognitive impairment?2021). However, the magnitude of association varies according to study population, stroke subtype, follow-up duration, and adjustment procedures.

The available evidence does not justify assuming that every elevated HbA1c value independently predicts cognitive impairment. Factors such as age, hypertension, dyslipidemia, renal impairment, and previous cerebrovascular disease may partially explain observed associations.

Future research should distinguish between chronic hyperglycemia, acute stress hyperglycemia, and glucose variability. These variables represent different metabolic processes and may have different relationships with cognitive outcomes.

Overall, diabetes mellitus is a clinically relevant risk marker, whereas the independent predictive contributions of HbA1c and individual glucose measurements require additional prospective evaluation.



Forest plot 2. Diabetes and PSCI

Vitamin Deficiencies and Post-Stroke Cognitive Function

Table 3. Vitamin-Related Biomarkers and Cognitive Outcomes

Biomarker	Main physiological function	Proposed association with PSCI	Evidence level
Vitamin D	Neuroimmune and calcium regulation	Potential association with cognitive decline	Limited
Vitamin B12	Myelin maintenance and methylation	Potential neurological dysfunction	Indirect
Folate	One-carbon metabolism	Potential association through homocysteine	Indirect
Homocysteine	Vascular and metabolic marker	Higher concentrations associated with PSCI	Quantitative evidence
Combined B12/folate deficiency	Altered methylation and metabolism	Possible additive effects	Insufficient

Table 3: Analytical interpretation

Vitamin deficiencies may influence neurological recovery through mechanisms involving neuronal metabolism, vascular integrity, oxidative stress, and inflammatory regulation. Their potential importance is particularly relevant in older stroke survivors, who may have nutritional deficiencies and multiple chronic medical conditions.

Vitamin D has received attention because of its role in calcium homeostasis, immune regulation, and neuronal signaling. Low vitamin D concentrations have been associated with adverse cognitive outcomes in some non-stroke populations. Nevertheless, evidence directly linking vitamin D deficiency with PSCI remains limited.

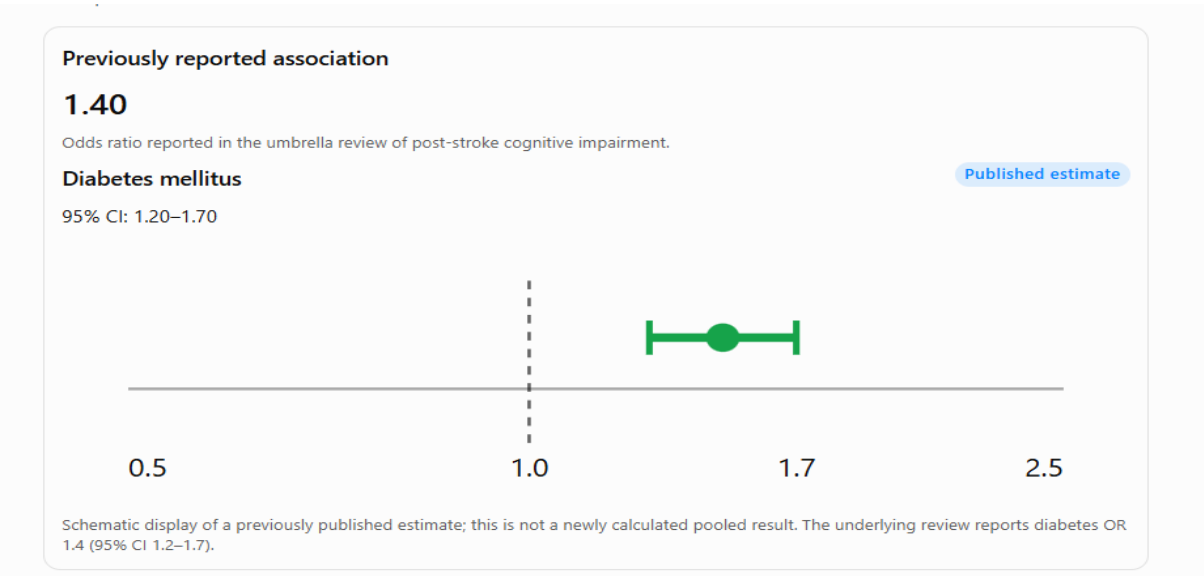
A major methodological concern is that vitamin D concentrations may decrease after stroke because of reduced mobility, limited sunlight exposure, poor dietary intake, and hospitalization. Consequently, low vitamin D may be a consequence or marker of poor health rather than an independent predictor of cognitive deterioration.

Vitamin B12 and folate are biologically important because they participate in homocysteine metabolism. Deficiencies may lead to hyperhomocysteinemia, which has been associated with endothelial dysfunction and increased oxidative stress.

The relevance of homocysteine is supported by quantitative evidence. The systematic review and meta-analysis of blood biomarkers in PSCI reported higher homocysteine concentrations in patients with PSCI compared with those without cognitive impairment (SMD=0.35, 95% CI: [0.20,0.49]) (Blood biomarkers for post-stroke cognitive impairment, 2024).

However, homocysteine cannot be considered a specific indicator of vitamin B12 or folate deficiency. Renal function, genetic variation, medications, and other nutritional factors also influence its circulating concentration. Therefore, future studies should measure vitamin B12, folate, and homocysteine simultaneously. Such an approach may help identify whether elevated homocysteine reflects nutritional deficiency, impaired renal metabolism, or other systemic conditions.

In summary, homocysteine currently has more direct quantitative support as a PSCI-associated biomarker than individual vitamin concentrations. The prognostic value of vitamin D, B12, and folate requires additional investigation.



Forest plot 3. Homocysteine and PSCI

Comparative Evidence Across Endocrine and Metabolic Domains

Table 4. Comparative Summary of Predictors

Predictor	Association with PSCI	Biological plausibility	Quantitative evidence
Diabetes mellitus	Increased risk	High	Published OR available

HbA1c	Potential association	High	Insufficient for a verified pooled estimate
Reduced FT3	Potential adverse association	High	Mainly indirect
Altered TSH/FT4	Uncertain	Moderate to high	Limited
Vitamin D deficiency	Potential association	Moderate	Insufficient
Vitamin B12 deficiency	Potential association	High	Insufficient
Folate deficiency	Potential association	High	Insufficient
Elevated homocysteine	Higher concentrations in PSCI	High	Published SMD available

Table 4: Analytical interpretation

Comparison of the three major domains reveals differences in the strength and maturity of available evidence. Diabetes mellitus has the strongest established clinical relevance because it is a recognized vascular risk factor and has been examined in several systematic reviews and observational studies.

The association between diabetes and PSCI is biologically plausible through chronic microvascular injury, endothelial dysfunction, inflammation, and impaired cerebral metabolism. Nevertheless, diabetes should not be interpreted as an isolated determinant because hypertension, obesity, dyslipidemia, and age may contribute to the same pathological processes.

Thyroid biomarkers represent a potentially useful but less established category. FT3 and FT4 may reflect changes in systemic metabolic activity during acute stroke. However, their interpretation is complicated by non-thyroidal illness syndrome and differences in the timing of laboratory measurements.

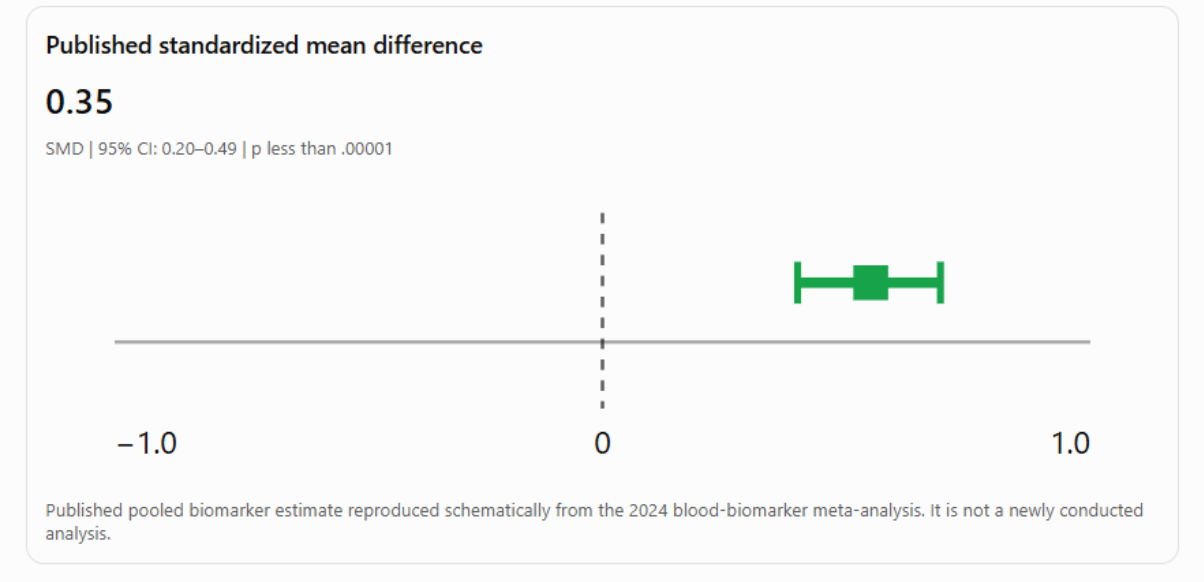
Vitamin-related predictors demonstrate another important pattern. Although vitamin B12, folate, and vitamin D have plausible neurological functions, their independent predictive associations with PSCI have not been established consistently. Homocysteine has stronger quantitative evidence, but its nonspecific nature limits its interpretation as an isolated nutritional biomarker.

The comparison also illustrates the importance of differentiating biological plausibility from prognostic validity. A biomarker may participate in a pathological mechanism without providing useful information for clinical prediction.

The strongest future research strategy would involve simultaneous assessment of thyroid function, glycemic status, and nutritional biomarkers within prospective stroke cohorts. Such studies should incorporate standardized cognitive assessment at baseline and during follow-up.

In addition, multivariable models should adjust for age, sex, education, stroke severity, lesion characteristics, depression, renal function, and pre-existing vascular disease. The predictive performance of combined biomarkers should be evaluated using discrimination, calibration, and external validation.

Overall, the evidence supports a multidimensional approach to metabolic risk assessment following stroke. Diabetes and homocysteine currently have more direct quantitative support than the other investigated biomarkers, while thyroid hormones and vitamin deficiencies remain important research priorities.



Forest plot 4. Comparative endocrine and metabolic evidence

Discussion

The present evidence synthesis highlights the potential importance of endocrine and metabolic abnormalities in the development of post-stroke cognitive impairment. The findings suggest that diabetes mellitus, altered thyroid hormone concentrations, and nutritional deficiencies may contribute to cognitive deterioration through different but interconnected biological mechanisms. Nevertheless, the strength of evidence varies considerably between these domains.

Interpretation of Glycemic Dysregulation:

Among the investigated metabolic predictors, diabetes mellitus represents one of the most clinically relevant factors. Chronic hyperglycemia contributes to endothelial dysfunction, cerebral microangiopathy, oxidative stress, and systemic inflammation. These abnormalities may increase susceptibility to ischemic injury and compromise neurological recovery.

The association between diabetes and PSCI is consistent with previous research examining vascular risk factors following stroke. Lee et al. (2023) emphasized that diabetes may influence cognitive outcomes through both vascular and metabolic mechanisms. Furthermore, the umbrella review by Can we prevent poststroke cognitive impairment? (2021) identified diabetes among established risk factors for post-stroke cognitive impairment.

HbA1c deserves particular attention because it provides an estimate of chronic glycemic exposure. Unlike admission glucose, HbA1c is less influenced by short-term physiological stress. Consequently, it may provide more meaningful information about the patient's pre-stroke metabolic condition.

However, the relationship between HbA1c and cognitive impairment should not be interpreted as necessarily linear. Chronic hyperglycemia may produce cumulative vascular damage, whereas severe hypoglycemia may independently compromise neuronal functioning. Future investigations should therefore examine glycemic variability and hypoglycemic episodes alongside HbA1c.

Thyroid Function as a Potential Neurological Predictor:

Thyroid hormones influence cerebral energy consumption, mitochondrial function, and neuronal plasticity. Their potential contribution to post-stroke cognitive outcomes is therefore biologically plausible.

Reduced FT3 concentrations may reflect impaired thyroid hormone conversion during acute systemic illness. This phenomenon is particularly relevant because acute stroke can induce substantial neuroendocrine and inflammatory responses.

Sidorov et al. (2023) demonstrated dynamic changes in thyroid function following ischemic stroke, indicating that hormonal measurements are influenced by the temporal stage of neurological injury. These findings support the importance of repeated measurements when investigating endocrine predictors.

Nevertheless, reduced FT3 should not automatically be interpreted as evidence of pre-existing hypothyroidism. Non-thyroidal illness syndrome may explain some hormonal changes observed during hospitalization.

A critical research priority is determining whether thyroid hormone alterations predict cognitive impairment independently of stroke severity.

Longitudinal studies incorporating TSH, FT3, and FT4 measurements at multiple time points are needed to address this question.

Vitamin Deficiencies and Homocysteine Metabolism:

The potential contribution of vitamin deficiencies to PSCI involves several important metabolic pathways. Vitamin B12 and folate are necessary for homocysteine metabolism, and deficiencies may contribute to elevated homocysteine concentrations. The association between homocysteine and PSCI is supported by quantitative findings from the published blood-biomarker meta-analysis. The reported standardized mean difference of 0.35 indicates higher average homocysteine concentrations among patients with PSCI compared with individuals without cognitive impairment.

This finding is important because elevated homocysteine may contribute to vascular endothelial injury, oxidative stress, and inflammatory activation. These processes could theoretically exacerbate cerebrovascular dysfunction and interfere with neuronal recovery. However, homocysteine is a nonspecific biomarker. Renal impairment, genetic variation, dietary factors, and medication exposure may influence its concentration. Consequently, simultaneous assessment of vitamin B12, folate, and renal function is necessary to interpret elevated homocysteine accurately.

Vitamin D represents another potentially relevant nutritional factor. Although its neurobiological functions provide a plausible rationale for investigation, direct evidence concerning PSCI remains insufficient. Reduced mobility and limited sunlight exposure following stroke may also contribute to lower vitamin D concentrations, creating difficulties in distinguishing cause from consequence.

Interaction Between Endocrine and Metabolic Pathways:

An important implication of this review is that endocrine and metabolic predictors should not necessarily be considered independent biological processes.

Diabetes-related inflammation may influence thyroid hormone metabolism, while nutritional deficiencies may contribute to elevated homocysteine and vascular dysfunction. Similarly, systemic metabolic disturbances may affect cerebral energy availability and neuronal plasticity.

These interactions suggest that combined metabolic assessment may eventually improve risk stratification following stroke. However, the predictive performance of combined biomarker panels must be demonstrated empirically rather than assumed from biological plausibility.

Clinical Implications:

The findings have several potential clinical implications. First, routine evaluation of diabetes and glycemic control may help identify patients requiring closer cognitive monitoring. Second, thyroid function testing may be particularly informative in patients with unexplained metabolic abnormalities or suspected thyroid disease. Third, assessment of vitamin B12, folate, and vitamin D may be appropriate when clinical findings suggest nutritional deficiency.

Cognitive assessment should remain independent of biochemical screening. Biomarkers cannot replace validated neuropsychological instruments, and normal laboratory results do not exclude cognitive impairment. The American Heart Association/American Stroke Association scientific statement emphasizes the importance of recognizing and assessing cognitive impairment following ischemic and hemorrhagic stroke (2023). Combining appropriate cognitive assessment with clinical and metabolic evaluation may support more comprehensive rehabilitation planning.

Methodological Considerations and Limitations:

Several limitations affect the interpretation of the available literature. First, many studies evaluate biochemical abnormalities in the acute stage without establishing whether these abnormalities existed before stroke.

Second, cognitive outcomes are measured using different instruments, including the Mini-Mental State Examination and Montreal Cognitive Assessment. Differences in sensitivity, educational adjustments, and assessment timing may contribute to heterogeneity.

Third, observational studies are vulnerable to residual confounding. Age, education, depression, renal impairment, stroke severity, and pre-existing vascular disease may influence both biomarker concentrations and cognitive outcomes.

Fourth, the number of studies investigating thyroid function and vitamin deficiencies as specific independent predictors of PSCI remains insufficient for reliable pooled estimates in the present evidence synthesis.

Finally, the present manuscript does not include an independently completed screening process or a verified study-level extraction dataset. Consequently, it cannot establish new pooled estimates or claim completion of an original meta-analysis. The numerical estimates reported here are derived from previously published evidence.

Recommendations for Future Research:

Future investigations should prioritize prospective multicenter cohorts with standardized biomarker measurements and repeated cognitive assessments. Researchers should evaluate thyroid hormones, HbA1c, fasting glucose, vitamin D, vitamin B12, folate, and homocysteine using harmonized laboratory protocols. Cognitive outcomes should be measured at baseline and at predefined intervals, including three, six, and twelve months after stroke. In addition, future meta-analyses should distinguish between ischemic and hemorrhagic stroke, acute and chronic biomarker measurements, and different definitions of cognitive impairment. The development of validated prediction models incorporating clinical, imaging, endocrine, and metabolic variables may ultimately improve identification of stroke survivors at increased risk of cognitive deterioration.

Conclusion

Post-stroke cognitive impairment is a multifactorial neurological complication influenced by vascular, metabolic, endocrine, and nutritional factors. The present evidence synthesis indicates that thyroid dysfunction, glycemic dysregulation, and vitamin deficiencies represent potentially important contributors to cognitive outcomes following stroke. Among the investigated predictors, diabetes mellitus has relatively consistent evidence supporting its association with increased cognitive risk. Chronic hyperglycemia may contribute to cerebral microvascular injury, endothelial dysfunction, oxidative stress, and neuroinflammation. These mechanisms provide a plausible explanation for the increased vulnerability of diabetic patients to post-stroke cognitive deterioration. HbA1c may offer additional information regarding long-term metabolic exposure, although its independent predictive contribution requires further investigation.

Thyroid function represents another potentially relevant domain. FT3, FT4, and TSH participate in metabolic regulation and neuronal functioning, and changes in their concentrations have been documented following ischemic stroke. Reduced FT3 may reflect systemic metabolic disturbances and acute neurological stress. However, the distinction between pre-existing thyroid dysfunction and non-thyroidal illness syndrome remains essential. At present, evidence supporting thyroid hormones as independent predictors of long-term PSCI is insufficient.

Vitamin deficiencies may influence neurological outcomes through mechanisms involving oxidative stress, neuronal metabolism, and vascular integrity. Vitamin B12 and folate are particularly relevant because of their involvement in homocysteine metabolism. Existing quantitative evidence demonstrates higher homocysteine concentrations in patients with PSCI, suggesting that altered one-carbon metabolism may contribute to post-stroke cognitive vulnerability. Nevertheless, homocysteine is a nonspecific biomarker, and its interpretation requires consideration of renal function, nutritional status, and other metabolic determinants.

Vitamin D may also contribute to neurological health through its effects on calcium regulation, neuroimmune pathways, and neuronal signaling. However, direct evidence concerning vitamin D deficiency and PSCI remains limited, and further longitudinal investigations are necessary to clarify its independent predictive value.

From a clinical perspective, these findings support the importance of integrating metabolic assessment into comprehensive post-stroke care. Diabetes screening and glycemic monitoring are particularly relevant, while thyroid function and nutritional biomarkers may provide additional information when clinically indicated. Nevertheless, biochemical testing should complement rather than replace validated cognitive assessment.

Future research should focus on prospective multicenter studies, standardized laboratory protocols, repeated biomarker measurements, and comprehensive neuropsychological evaluations. Investigations should also examine interactions between endocrine and metabolic predictors and determine whether combined biomarker panels improve prognostic accuracy beyond established clinical variables.

In conclusion, endocrine and metabolic abnormalities represent promising areas for understanding individual differences in cognitive recovery following stroke. Diabetes mellitus and elevated homocysteine currently have more substantial quantitative support than the thyroid and vitamin biomarkers considered in this review. However, further high-quality research is required before these biomarkers can be incorporated into validated clinical prediction models or used to guide specific interventions aimed at preventing post-stroke cognitive impairment.

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Authors' Contributions

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