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Review

From Structure to Function: Cognitive Impairment and Its Heterogeneity in Cerebral Small Vessel Disease

Wei Sun[1], Aini He[1], Benke Zhao[1], Xuefan Yao[1], Xiao Wu[1], Haiqing Song[1*]

[1]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China

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ABSTRACT: Cerebral small vessel disease (CSVD) is a common, age-related microvascular brain disorder and a major vascular cause of cognitive impairment. However, individuals with similar magnetic resonance imaging (MRI) lesion burdens often follow different cognitive trajectories, indicating that conventional imaging captures only late-stage manifestations of a broader pathological cascade. This review focuses on cognitive heterogeneity in CSVD through a heterogeneity-oriented conceptual framework, discussing how divergent cognitive trajectories may arise through the interaction of lesion-related factors, network-mediated consequences, biological and pathological modifiers, and individual susceptibility factors. We highlight the importance of lesion topography, particularly damage to strategic network hubs and connections. Beyond focal lesions, structural network disruption and remote structural and functional abnormalities beyond MRI-visible lesions further shape clinical heterogeneity. We additionally examine biological and pathological modifiers, including molecular biomarkers, heterogeneous neuropathological substrates, and mixed pathology, as well as individual susceptibility factors, such as life-course influences, brain reserve, and resilience. Together, these interacting mechanisms help explain why individuals with comparable structural lesion burdens may experience divergent cognitive trajectories. By reframing CSVD-related cognitive impairment beyond a simple lesion-burden model, this review highlights implications for diagnosis, prognostication, and future individualized approaches to cognitive impairment in CSVD.

Keywords: cerebral small vessel disease, cognitive heterogeneity, network disruption, mixed pathology, brain reserve

1. Introduction

As global life expectancy increases, the burden of age-related cognitive impairment continues to rise [1, 2]. Cerebral small vessel disease (CSVD), which affects the brain's small perforating arterioles, capillaries, and possibly venules, has emerged as a major vascular contributor to cognitive decline [3]. Elucidating the pathophysiological mechanisms that drive small vessel injury is therefore critical for developing effective therapies. Progress has remained limited, however, largely because current imaging and *in vivo* approaches cannot adequately visualize small cerebral vessels. Moreover, despite major advances in reperfusion therapies for large-vessel disease, stroke specialists have achieved relatively little success in treating disorders of the cerebral small vessels [4].

CSVD should be considered a global brain disorder rather than a focal condition, because its localized lesions can affect distant brain regions and disrupt both structural and functional networks. This network-based perspective underscores the potential for conceptual and therapeutic advances by evaluating CSVD-related clinical outcomes in the broader context of small vessel injury. A clearer understanding of how upstream structural damage leads to downstream functional dysfunction is essential to improve clinical outcomes. Nevertheless, the mechanisms by which CSVD causes cognitive impairment remain incompletely defined. Clinicians consistently observe substantial clinical heterogeneity among patients with

***Correspondence should be addressed to:** Dr. Haiqing Song, Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China. Email: songhq@xwhosp.org

similar radiological CSVD features, and in a hospital-based cohort, the 5.5-year cumulative risk of dementia among individuals with CSVD was 11% [5]. These findings indicate that CSVD often remains clinically silent or produces only mild functional deficits in most affected individuals. The pronounced heterogeneity in both structural damage and functional consequences complicates mechanistic insight and hinders accurate diagnosis and effective treatment of CSVD-related cognitive impairment.

Box 1. Distinctive focus of the present review relative to prior reviews.

1. Focuses on cognitive heterogeneity in CSVD rather than providing another broad overview of CSVD-related cognitive impairment.
2. Explores why individuals with apparently similar MRI-visible lesion burdens exhibit markedly different cognitive trajectories.
3. Proposes a heterogeneity-oriented conceptual framework integrating:
   - lesion-related factors
   - network-mediated consequences
   - biological and pathological modifiers
   - molecular biomarkers
   - pathological heterogeneity and mixed pathology
   - individual susceptibility factors
4. Moves beyond a simple lesion-burden model to highlight implications for diagnosis, prognostication, and future individualized approaches.

Abbreviations: CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging.

Although previous reviews have comprehensively summarized the diagnosis, pathophysiology, neuroimaging, and management of CSVD-related cognitive impairment [6], a clinically important but unresolved question remains: why do individuals with apparently comparable structural lesion burdens often exhibit markedly different cognitive trajectories? Conventional magnetic resonance imaging (MRI)-visible lesions likely capture only part of the disease spectrum and incompletely explain this clinical heterogeneity. Rather than providing another broad overview of CSVD-related cognitive impairment, this review focuses on the transition from structural injury to functional dysfunction through a heterogeneity-oriented conceptual framework. Specifically, we discuss how cognitive heterogeneity in CSVD may arise through the interaction of lesion-related factors, network-mediated consequences, biological and pathological modifiers, and individual susceptibility factors. By reframing CSVD-related cognitive impairment beyond a simple lesion-burden model, this review aims to provide a more integrated conceptual perspective on the mechanisms underlying divergent clinical outcomes and to highlight implications for diagnosis, prognosis, and therapeutic development (Box 1).

2. From structural damage to cognitive impairment in CSVD

A major clinical challenge in CSVD is that tissue sampling for definitive diagnosis is rarely feasible. Neuroimaging, by contrast, is widely available, and established standards guide its use for CSVD diagnosis. The Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) group introduced standardized terminology and minimum imaging criteria for suspected CSVD. Neuroimaging, particularly MRI, reveals characteristic features of CSVD. White matter hyperintensity (WMH) commonly raises suspicion for CSVD, while additional findings with higher specificity but uncertain sensitivity include recent small subcortical infarct, lacune, perivascular spaces (PVS), cerebral microbleed (CMB), cortical superficial siderosis (CSS), cortical cerebral microinfarct, and brain atrophy [7, 8].

MRI-visible lesions reflect only a limited portion of the brain injury caused by CSVD and typically represent relatively late and often irreversible stages of the disease process. Nonetheless, when considered together, these radiological markers show strong associations with cognitive and functional decline [9]. Meta-analyses consistently demonstrate a robust link between WMH and cognitive impairment, indicating that greater baseline WMH burden, faster progression, and periventricular distribution increase the risk of incident dementia [10, 11]. To date, at least twenty cohort studies - mainly from Europe and North America, with two from East Asia - have examined the association between WMH and future dementia, and all support this relationship [12]. Incident lacunes also predict dementia onset [13], and pooled analyses indicate that lacunar infarcts confer a significantly increased or borderline significant risk of dementia [14, 15]. Approximately 30 percent of patients who experience a lacunar stroke develop cognitive impairment within four years of the index event, a rate comparable to that observed after non-lacunar stroke (23 percent). This similarity suggests that progressive CSVD, rather than the acute infarct itself, primarily drives cognitive decline [16].

Cortical microinfarcts, although markedly underdetected by routine MRI, represent the most common form of cerebral infarction. They frequently are associated with cerebral amyloid angiopathy (CAA), occur at high prevalence among cognitively impaired individuals, and show strong, independent associations

with adverse cognitive outcomes [17-19]. According to the Boston criteria, most individuals older than 55 years with multiple strictly lobar CMB, even in the absence of intracerebral hemorrhage or alternative diagnoses, are presumed to have CAA. These individuals face an estimated annual hemorrhage risk of 5 percent and appear to experience more severe cognitive decline and higher dementia rates than patients with deep CMB [20]. Global brain atrophy commonly occurs in CSVD but largely reflects the combined effects of aging and coexisting neurodegenerative processes [21, 22]. Although smaller brain volumes correlate with cognitive impairment, the lack of adequate Alzheimer's disease (AD)–specific control groups in most studies limits causal inference [23]. Enlarged PVS have also been associated with poorer cognitive performance, but inconsistent findings weaken their utility as a reliable biomarker [21, 24]. Nevertheless, several longitudinal cohort studies have linked greater PVS burden to increased dementia risk [25, 26].

Consistent with the associations between MRI-visible markers and cognitive decline, cognitive impairment represents a major clinical consequence of CSVD. Beyond overt dementia, milder forms of cognitive impairment are substantially more common and may still impose considerable functional disability [27]. CSVD-related cognitive impairment most commonly presents as a characteristic subcortical cognitive syndrome, predominantly involving executive dysfunction, slowed processing speed, attentional deficits, and impaired working memory. Episodic memory is relatively preserved in earlier stages but may become affected as disease severity increases or additional pathology accumulates. This cognitive pattern resembles the frontal–subcortical syndrome observed in disorders affecting frontal–subcortical circuits [28, 29]. Accordingly, cognitive assessments emphasizing executive function and processing speed may improve detection of probable CSVD-related cognitive impairment, particularly in earlier disease stages. In clinical practice, probable CSVD-related cognitive impairment may be suggested by predominant executive dysfunction and slowed processing speed disproportionate to memory impairment, together with MRI evidence of CSVD burden. By contrast, prominent episodic memory impairment, language dysfunction, or visuospatial deficits out of proportion to vascular lesion burden may raise suspicion for coexisting neurodegenerative pathology.

However, increasing evidence suggests that cognitive impairment in CSVD is broader and more heterogeneous than the traditional subcortical profile alone would imply. Considerable overlap exists across dementia syndromes, partly reflecting the multifactorial nature of age-related cognitive decline and the frequent coexistence of neurodegenerative pathology [30]. Recent meta-analytic evidence indicates that CSVD-related cognitive impairment may extend beyond executive dysfunction and slowed processing speed, with deficits observed across multiple cognitive domains [31, 32]. Whether impairments in non-executive domains reflect downstream consequences of disruption in key cognitive systems or more generalized multisystem involvement remains uncertain. Severe CAA, for example, has been associated with relatively greater visuospatial dysfunction, potentially reflecting the posterior predominance of amyloid-related vascular injury [33, 34]. Accordingly, cognitive profiles extending beyond the characteristic subcortical pattern should prompt consideration of coexisting vascular and neurodegenerative pathology. Where available, amyloid-β and tau biomarkers, together with CAA-sensitive MRI markers (e.g., lobar cerebral microbleed and cortical superficial siderosis according to the Boston criteria), may facilitate differentiation between predominant CSVD and mixed vascular–neurodegenerative disease. Longitudinal multimodal phenotyping, integrating repeated clinical, cognitive, imaging, and biomarker assessments, may further improve diagnostic classification and clarify the relative contribution of vascular and neurodegenerative processes over time [35, 36]. Together, these findings suggest that although a subcortical cognitive profile remains clinically characteristic of CSVD, the spectrum of cognitive impairment is likely more heterogeneous than previously recognized.

3. Mechanisms linking structural damage to cognitive impairment in CSVD

Pathophysiologically, CSVD arises from concurrent structural and functional abnormalities of the cerebral microvasculature. Microcirculatory injury in CSVD involves tightly coupled structural damage and physiological dysfunction. Structurally, small vessels develop wall thickening, increased rigidity, luminal stenosis, and, in some cases, microvascular rupture. Functionally, these changes lead to impaired cerebrovascular autoregulation, reduced neurovascular coupling (NVC), blood–brain barrier (BBB) disruption and leakage, and are increasingly associated with impaired interstitial fluid drainage [37-45]. Endothelial injury plays a central role in these processes, with additional contributions from mural cells, including vascular smooth muscle cells and pericytes, which together regulate microvascular integrity and function [46-49].

White matter lesion formation constitutes a central pathological hallmark of cognitive impairment in CSVD. Because white matter supports communication across

neural circuits, these lesions serve as clinically meaningful indicators of CSVD-related brain dysfunction [50, 51]. Despite clear evidence of microcirculatory injury in CSVD, whether vascular dysfunction represents a primary cause or a downstream consequence of brain damage, and how directly it drives clinical manifestations, remain unresolved. Emerging methodological approaches may help address this long-standing "chicken-and-egg" question. Recent large cross-sectional cohort studies demonstrate that reduced carbon dioxide (CO_2) reactivity in white matter or subcortical gray matter associates with greater CSVD burden, including WMH, lacunes, CMB, PVS, and brain atrophy, as well as with impaired cognitive performance [37, 38]. Additional imaging studies in patients show that decreases in cerebral blood flow (CBF) accompanied by increases in oxygen extraction fraction (OEF) correlate with higher WMH density, supporting a role for chronic hypoxia–ischemia in CSVD pathogenesis and WMH formation [52, 53]. Experimental studies in mice further suggest that NVC deficits may arise primarily from vascular, rather than neuronal, dysfunction. Specifically, age-related deterioration reflects a decline in vasoresponsivity rather than reduced neuronal activity [54].

Pathologically, white matter lesions encompass a spectrum of processes, including demyelination, astrogliosis, and axonal loss. Converging evidence from longitudinal cohort, human imaging, and experimental animal studies suggests that these changes may reflect the combined effects of chronic cerebral hypoperfusion, BBB leakage, and secondary increases in oxidative stress and inflammation [27, 55]. These insults are thought to contribute to cellular dysfunction, mitochondrial impairment, and activation of pro-apoptotic signaling pathways, ultimately driving white matter injury [56-58]. The resulting structural damage is likely to compromise the integrity of long-range white matter tracts that support efficient interregional communication. As injury accumulates, axonal signal transmission becomes delayed or disorganized, disrupting information flow across large-scale brain networks, particularly fronto-subcortical and cortico-cortical circuits that underlie executive function, attention, and memory [59, 60]. However, the precise causal relationships among vascular dysfunction, white matter injury, and network disruption remain incompletely understood. Further longitudinal, multimodal, and mechanistic studies are needed to establish the temporal sequence of these pathological processes.

Diffuse cerebrovascular endothelial failure is widely considered a key mechanism underlying CSVD-related brain injury. Endothelial damage may disrupt BBB integrity, allowing blood-derived components to extravasate into the brain parenchyma. This leakage is proposed to promote local vascular alterations and widespread tissue injury by triggering brain inflammation, characterized by early activation and sustained accumulation of microglia and macrophages. Human and experimental studies further suggest that cerebral microhemorrhages are associated with more severe neuroinflammation, as microhemorrhages themselves provoke persistent local inflammatory responses, while the breakdown of extravasated erythrocytes promotes iron deposition and the inflammatory milieu further alters cerebral iron metabolism. The cerebral cortex and deep nuclei are essential for normal cognitive function, and inflammation and iron deposition in these regions cause neuronal damage that directly impairs cognition [61-63]. However, the interactions among endothelial failure, BBB leakage, neuroinflammation, and iron dysregulation remain incompletely understood, and further studies are needed to clarify how these processes interact during disease progression.

BBB leakage also increases interstitial fluid accumulation. In parallel, the glymphatic system, a perivascular clearance pathway involved in cerebrospinal fluid (CSF)–interstitial fluid exchange, has been identified to be present in both animals and humans [64, 65]. Experimental animal and human imaging studies suggest that impaired fluid transport through the glymphatic system may contribute to PVS enlargement and interstitial fluid buildup within the white matter [66, 67]. Additional human imaging studies further report associations between enlarged PVS and neuroinflammatory markers, raising the possibility that impaired waste clearance and resulting oxidative stress and inflammatory responses may promote myelin degeneration and reactive gliosis, progressively weakening the structural integrity of long-range white matter and subcortical fiber tracts [68]. More recently, longitudinal cohort studies using diffusion tensor image analysis along the perivascular space (DTI-ALPS), an indirect MRI-based surrogate of glymphatic function, show that decreased DTI-ALPS are related to progression of MRI markers of CSVD, along with CSVD-related cognitive decline over time [69, 70]. These findings may support a role for impaired glymphatic clearance in CSVD progression and cognitive deterioration. However, because current imaging approaches do not directly quantify glymphatic function and much of the available evidence remains associative, the mechanistic contribution of glymphatic dysfunction to CSVD-related cognitive impairment remains incompletely established and warrants further investigation.

Loss of microvascular homeostasis may promote chronic focal hypoperfusion and ischemia, increase susceptibility to microhemorrhages, impair interstitial

waste clearance, and induce secondary metabolic dysfunction and sustained pro-inflammatory signaling. Together, these processes are thought to preferentially damage cortical, subcortical, and limbic regions that are critical for cognitive function. Over time, the cumulative burden of microvascular injury and progressive network disintegration depletes cognitive reserve, ultimately resulting in CSVD-related cognitive impairment (Fig. 1).

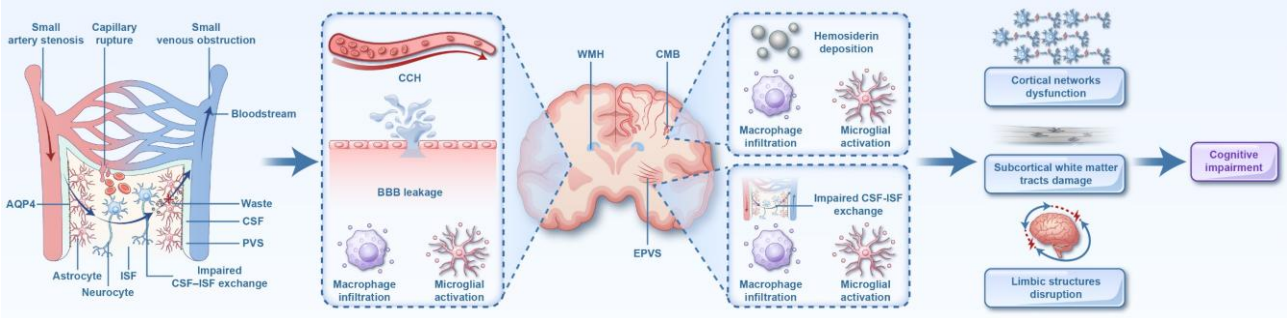

Figure 1. Schematic overview of the putative cascade linking microvascular dysfunction, glymphatic impairment and cognitive decline in CSVD. Hemodynamic and drainage disturbances–such as small artery stenosis, capillary rupture, small venous obstruction, and impaired CSF–ISF exchange–are proposed to converge on neurovascular unit dysfunction and reduced perivascular clearance. These processes are reflected by characteristic neuroimaging markers of CSVD, including WMH, CMB, and EPVS. In this framework, WMH are associated with CCH and BBB leakage, accompanied by macrophage infiltration and microglial activation. CMB are linked to microhemorrhagic injury with perivascular hemosiderin deposition and neuroinflammatory responses. EPVS are considered an imaging correlate of impaired CSF–ISF exchange and concomitant neuroinflammation. The cumulative burden of these vascular and clearance-related abnormalities contributes to cortical network dysfunction, subcortical white matter tract damage, and limbic system disruption, ultimately leading to cognitive impairment. Abbreviations: AQP4, aquaporin-4; BBB, blood–brain barrier; CCH, chronic cerebral hypoperfusion; CMB, cerebral microbleed; CSF, cerebrospinal fluid; CSVD, cerebral small vascular disease; EPVS, enlarged perivascular space; ISF, interstitial fluid; PVS, perivascular space; WMH, white matter hyperintensity.

At the cortical level, converging studies show that reduced functional connectivity within the frontoparietal control network (FPCN), dorsal attention network (DAN), and default mode network (DMN) scales with the severity of cognitive impairment in CSVD. Because these networks depend on long-range cortico-cortical connections, their disruption leads to domain-specific cognitive deficits. Reduced DMN connectivity associates with impaired episodic memory, whereas disconnection of the FPCN and DAN contributes to executive dysfunction and attentional deficits, respectively. Beyond cortico-cortical networks, injury to strategic subcortical white matter tracts plays a critical role in CSVD-related cognitive impairment. Diffusion tensor imaging (DTI) studies consistently identify the corpus callosum, anterior thalamic radiation (ATR), superior longitudinal fasciculus (SLF), cingulum bundle, and projection fibers of the internal capsule as particularly vulnerable. Microstructural damage within these tracts mediates the relationship between overall CSVD burden and deficits in processing speed, executive function, attention, and working memory, with ATR injury emerging as an especially strong predictor. The thalamus and hippocampus, as key nodes within subcortical and limbic circuits, also represent strategically important structures affected by CSVD. Thalamic atrophy and disrupted thalamocortical connectivity show strong associations with global cognitive impairment and reduced attentional control, whereas hippocampal vulnerability resulting from either direct microinfarcts or secondary degeneration driven by white matter damage contributes to episodic memory decline (Table 1).

4. Heterogeneity of cognitive impairment in CSVD

Although structural damage defines CSVD, its functional consequences - particularly cognitive impairment - represent the primary clinical concern. Structural neuroimaging markers of CSVD correlate with cognitive deficits [101], but they explain only part of the marked heterogeneity in clinical outcomes, as many individuals retain normal cognition despite substantial lesion burden [102-105]. These findings indicate that the progression from structural injury to functional decline is not linear and reflects a complex interplay of interacting neurobiological processes [47].

Cognitive heterogeneity in CSVD can be conceptualized as arising from four interacting levels of influence. Firstly, lesion-related factors determine the immediate impact of vascular injury according to lesion location and involvement of strategic brain regions. Secondly, network-mediated consequences propagate the effects of focal lesions through structural and functional disconnection. Thirdly, biological and pathological modifiers, including molecular biomarkers, pathological heterogeneity, and coexisting neurodegenerative

pathology, influence the tissue response to vascular injury and may amplify or attenuate its cognitive consequences. Finally, individual susceptibility factors, such as cognitive reserve and resilience, determine the extent to which pathological changes translate into clinical impairment. Together, these interacting mechanisms help explain why individuals with apparently similar MRI-visible lesion burdens may exhibit markedly different cognitive trajectories.

Table 1. Major structural correlates of cognitive impairment in CSVD.

Affected structure	Specific sites affected	Cognitive domains impacted	Representative evidence
Cortical networks	DMN	Memory, general cognition executive function, processing speed	Sun et al. 2011 [71]; Yi et al. 2012 [72]; Schaefer et al. 2014 [73]; Zhou et al. 2016 [74]; Ding et al. 2017 [75]; Liu et al. 2019 [76]; Schlemm E et al. 2022 [77]; Wei HL et al. 2024 [78]; Hu Y et al. 2025 [79]
	FPCN	Executive function, working memory	Kim et al. 2016 [80]; Liu et al. 2019 [76]
	DAN	Executive function, attention switching	Ding et al. 2018 [81]; Liu et al. 2019 [76]; Hu Y et al. 2025 [79]
	SN	Executive function, general cognition	De Marco et al. 2017 [82]; Benson et al. 2018 [83]; Chen et al. 2019 [84]; Wei HL et al. 2024 [78]
	SMN	Executive function	Wu et al. 2015 [85]; Zhou et al. 2020 [86]
	VN	General cognition	Xin H et al. 2022 [87]
Subcortical white matter tracts	Corpus callosum	Global cognition, interhemispheric transfer, processing speed, executive function	Reijmer et al. 2015 [88]; Biesbroek JM et al. 2017 [89]; Biesbroek et al. 2017 [90]; Ban S et al. 2019 [91]; Jacobs HIL et al. 2022 [92]; Dobrynina et al. 2024 [93]
	ATR	Executive function, attention, processing speed	Biesbroek JM et al. 2016 [94]; Biesbroek JM et al. 2017 [89]; Biesbroek et al. 2017 [90]; Biesbroek JM, et al. 2020 [95]; Jacobs HIL et al. 2022 [92]
	SLF	Processing speed, executive function, working memory	Biesbroek JM et al. 2017 [89]; Ban S et al. 2019 [91]; Biesbroek JM, et al. 2020 [95]
	Cingulum bundle	Memory, executive control, attention	Biesbroek JM et al. 2017 [89]; Ban S et al. 2019 [91]; Jacobs HIL et al. 2022 [92]
	Internal capsule projection fibers	Processing speed, motor control, executive function	Hu et al. 2022 [96]; Jacobs HIL et al. 2022 [92]; da Silva PHR et al. 2023 [97]; Sui et al. 2025 [98]
Subcortical nuclei and limbic structures	Thalamus	Memory (anterior), attention/executive (medial), visuospatial (posterior)	Li et al. 2023 [99]; da Silva PHR et al. 2023 [100]
	Hippocampus and fornix	Episodic memory, learning	Ban S et al. 2019 [91]; Jacobs HIL et al. 2022 [92]

Abbreviations: ATR, anterior thalamic radiation; CSVD, cerebral small vessel disease; DAN, dorsal attention network; DMN, default mode network; FPCN, frontoparietal control network; SLF, superior longitudinal fasciculus; SMN, sensorimotor network; SN, salience network; VN, visual network.

4.1 Lesion-related factors

Cognitive networks exhibit complex neuroanatomical organization, and lesion location plays a critical role in linking structural damage to cognitive impairment. Importantly, lesions differ markedly in their functional impact, as lesion topography exerts a disproportionate influence on network integrity. The substantial heterogeneity of cognitive outcomes in CSVD is likely to reflect several interacting factors, with lesion topography emerging as a particularly important contributor. Cross-sectional neuroimaging studies show that focal injury to strategically positioned network hubs or critical long-range white matter pathways, often referred to as rich-club or central connections, produces outsized disruption of network integration and information transfer. As a result, these lesions generate widespread functional disconnection and cognitive deficits that total lesion burden alone fails to predict accurately. In particular, the integrity of rich-club connectivity mediates the relationship between WMH burden and higher-order cognitive performance. Greater preservation of rich-club connections attenuates the negative effects of WMH on processing speed and executive function, such that individuals with stronger central connectivity maintain relatively preserved cognition despite comparable lesion loads [106-108]. Complementary evidence further demonstrates that microstructural damage to central network connections, rather than injury confined to peripheral or non-central fibers, specifically mediates the association between WMH volume and executive dysfunction [109]. Owing to their topological centrality

and dense interconnectivity, rich-club pathways exert a pivotal influence on global information integration. Consequently, damage to these structures is associated with more extensive network disruption than equivalent injury to peripheral nodes or connections. Even small, strategically located infarcts near rich-club or central pathways may therefore trigger disproportionately severe and widespread network dysfunction, potentially giving rise to highly heterogeneous clinical phenotypes that diverge from the typical subcortical presentation of CSVD.

Taken together, these findings provide converging evidence that strategic structural injury, particularly to key circuits and white matter tracts selectively disrupts communication among core cognitive networks. Such strategic structural injury may not only contribute to cognitive impairment in CSVD but also partly explain the observed heterogeneity in clinical outcomes. However, most available evidence remains cross-sectional, limiting causal inference regarding the relationship between lesion location, network disruption, and cognitive decline. Further longitudinal multimodal studies are needed to clarify how lesion topography contributes to the progression of network dysfunction and cognitive heterogeneity in CSVD.

4.2 Network-mediated consequences

Evidence from structural network analyses, including multiple large longitudinal cohort studies and cross-sectional imaging investigations, has markedly improved our understanding of how CSVD-related structural damage translates into cognitive dysfunction. Disruption of structural network organization, most commonly reflected by reduced global efficiency, shows strong associations with cognitive impairment, depressive symptoms, and an increased 5-year risk of all-cause dementia in CSVD cohorts [110-114]. Combining diffusion-based tractography with graph-theoretical analysis enables quantification of structural connectivity metrics that reliably predict cognitive decline, conversion to dementia, and even all-cause mortality in individuals with CSVD [115-117]. Importantly, network disruption partially mediates the relationship between conventional MRI markers, such as WMH, and cognitive decline, indicating that lesion burden exerts its clinical effects largely through alterations in network topology [110, 111].

Defining the remote structural and functional brain changes in CSVD, as well as their temporal relationship to clinical symptoms, is essential for understanding this complex disease. DTI has provided major advances in quantifying these structural alterations [118, 119]. More recently, automated measures such as the peak width of skeletonized mean diffusivity (PSMD) have emerged as sensitive indices of diffusivity heterogeneity across white matter tracts [120, 121]. Notably, cross-sectional imaging and longitudinal cohort studies suggest that DTI detects subtle microstructural abnormalities in normal-appearing white matter (NAWM) well before conventional MRI reveals WMH, and these measures outperform lesion counts in explaining variance in cognitive performance [122-127]. Cross-sectional DTI studies further show that CSVD lesions, such as WMH, are surrounded by regions with altered diffusion properties that appear normal on conventional MRI, often referred to as the CSVD penumbra. Diffusion abnormalities within these penumbral regions correlate with total WMH burden and vary systematically with distance from the lesion core [128, 129]. These observations indicate that the clinical impact of CSVD reflects not only overt lesions but also remote microstructural injury, which may contribute to cognitive heterogeneity.

Functional imaging provides additional evidence for these remote effects. Several cross-sectional and longitudinal arterial spin labeling (ASL) studies report significant reductions in CBF within the cortices in individuals with CSVD-related cognitive impairment [130, 131]. The spatial distribution of CBF abnormalities appears to parallel the pattern of white matter damage [132, 133]. A systematic review identified 25 task-based functional MRI (fMRI) studies in CSVD, which consistently reported abnormal hyperactivation and hypoactivation across five cognitive domains: executive function, working memory, attention and processing speed, motor function, and affective processing [134]. Cross-sectional resting-state fMRI studies further show impairment of the frontoparietal network in CSVD [73, 135]. In addition, higher tract-specific white matter lesion burden associates with reduced functional connectivity in corresponding cortical regions [136]. Consistent with these findings, cross-sectional positron emission tomography (PET) studies reveal reduced perfusion and glucose metabolism in cortical areas remote from subcortical infarcts and WMH, supporting the presence of CSVD-related functional sequelae beyond visible subcortical MRI lesions [137, 138]. Together, these findings suggest that widespread disturbances in cerebral perfusion and functional connectivity represent key consequences of CSVD that may contribute to cognitive heterogeneity.

In addition to functional abnormalities, accumulating evidence indicates that CSVD also produces structural changes remote from the initial MRI-visible lesions [139, 140]. Several cross-sectional imaging and longitudinal cohort studies highlight a critical role for secondary neurodegeneration in shaping clinical outcomes [124, 141-148]. Subcortical infarcts and WMH burden can

trigger degeneration of connected cortical regions through damage to intervening white matter tracts. Compelling evidence comes from longitudinal cohort study of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a monogenic form of CSVD. In this population, incident lacunar infarcts lead to cortical thinning in regions structurally connected to the infarct, providing the first direct demonstration of CSVD-related secondary degeneration in remote cortex. Cortical thinning is most pronounced in areas with a high probability of connectivity through the lacune-affected white matter tract [149].

Growing evidence further indicates that heterogeneity in cognitive outcomes in CSVD may partly reflect differential vulnerability of neural oscillatory dynamics. Neural oscillation synchronization provides a fundamental neurophysiological basis for cognition. Precise phase alignment of oscillatory activity across distributed brain regions depends critically on intact white matter tracts that support temporally coordinated signal transmission. Damage to axons or myelin alters conduction velocity and timing, leading to oscillatory desynchronization and impaired cognitive integration. Under normal conditions, myelin plasticity can fine-tune conduction delays to preserve synchrony across networks [150-156]. Neuropathological and neurophysiological evidence suggests that CSVD-related white matter pathology compromises axonal conduction and disrupts the temporal precision of oscillatory synchrony [157]. Importantly, these pathological changes vary widely across individuals. Even when structural MRI shows similar lesion burdens, the extent of underlying microstructural damage can differ substantially, producing heterogeneous patterns of oscillatory disruption and divergent cognitive trajectories [158-160].

The relative power of electroencephalography (EEG) oscillations reflects interactions among local populations of excitatory and inhibitory neurons. High-frequency activity primarily depends on reciprocal corticocortical connections, whereas lower-frequency oscillations, such as delta waves, reflect regulatory interactions between cortical and subcortical structures that are normally suppressed during wakefulness [161-163]. Cross-sectional studies show that loss of faster oscillations and a relative increase in slow activity likely reflect weakening of inhibitory–excitatory feedback loops that govern thalamocortical interactions and may underlie functional changes detected by fMRI in WMH-related dementia [164]. Consistent with this framework, studies report reduced intrahemispheric frontoparietal EEG coherence across high-frequency bands, including alpha, beta, and gamma, in individuals with vascular mild cognitive impairment. These changes are associated with poorer executive function performance and greater structural brain damage [165, 166]. Vascular mild cognitive impairment is also associated with reduced information flow directionality, which normally proceeds from parietal to frontal regions, leading to impaired functional coupling of EEG rhythms in the theta, alpha, and beta frequency bands [167]. Notably, one cross-sectional study further report altered theta power and synchronization, disrupted theta–gamma coupling, and abnormal alpha activity even in asymptomatic individuals with moderate-to-severe WMH, suggesting that oscillatory dysfunction may precede overt cognitive impairment and potentially contribute to interindividual heterogeneity in cognitive trajectories [160]. Experimental studies in CADASIL mouse models further support a potential role for oscillatory dysfunction in CSVD-related cognitive impairment. Impaired hippocampal gamma oscillation patterns are observed alongside decreased neuronal fiber length and aberrant neuronal morphology [168].

In summary, converging evidence from DTI, ASL, fMRI, PET, and EEG demonstrates that CSVD exerts widespread effects beyond focal lesions. Structural network disruption, and remote structural and functional abnormalities beyond MRI-visible lesions, including microstructural injury in NAWM, reduced cortical perfusion, impaired functional connectivity, secondary neurodegeneration with cortical thinning, and neural oscillatory dysregulation, together constitute a cascade of network-mediated consequences that translate lesion burden into clinical heterogeneity. Targeting these downstream mechanisms may therefore represent a critical strategy for delaying cognitive decline in CSVD. However, although structural network disruption is supported by longitudinal cohort evidence, evidence for remote structural and functional abnormalities remains largely cross-sectional and associative. Further longitudinal and mechanistic studies are needed to clarify their temporal evolution and causal contribution to cognitive heterogeneity in CSVD.

4.3 Biological and pathological modifiers

4.3.1 Molecular biomarkers

An expanding body of research suggests that heterogeneity in cognitive outcomes in CSVD may partly reflect interindividual differences in molecular biomarkers beyond MRI-visible lesion burden. Molecular biomarkers increasingly indicate that protein- and peptide-based biomarkers related to endothelial dysfunction, BBB disruption, inflammation, oxidative stress, and neuroaxonal or glial injury, as well as circulating metabolites, lipid-related biomarkers, and ribonucleic acid (RNA)-mediated pathways may

contribute to differential susceptibility to cognitive decline. In arterial hypertension, a major driver of CSVD, a proposed mechanistic framework suggests that cognitive impairment may evolve through overlapping stages involving peripheral and meningeal immune activation, neurovascular unit dysfunction, glial inflammation, and subsequent disturbances in cerebral perfusion, perivascular clearance, synaptic plasticity, and neuronal function. Importantly, these processes may arise before overt structural lesions such as extensive WMH become apparent, raising the possibility that individuals with apparently comparable structural lesion burdens may differ substantially in underlying biological vulnerability [169].

Investigators have evaluated numerous proteins and peptides that reflect diverse pathological pathways; however, their associations with CSVD and cognitive impairment remain inconsistent, underscoring substantial underlying biological variability. Although findings remain heterogeneous, several biomarkers are supported by longitudinal cohort evidence. Baseline serum soluble intercellular adhesion molecule-1 (sICAM-1) levels are associated with subsequent cognitive decline, suggesting a link between endothelial inflammation and cognitive outcome over time [170]. Similarly, longitudinal and cross-sectional studies implicate placental growth factor (PlGF), with elevated plasma and CSF levels associated with greater vascular brain injury and poorer cognitive performance [171-173]. Longitudinal cohort studies also suggest a complex role for serum soluble tumor necrosis factor receptor-1 (sTNF-R1) during predementia stages of CSVD, with higher levels associated with more severe CSVD burden at baseline, while potentially showing protective associations against subsequent cognitive decline [174]. In addition, plasma and CSF neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) show potential for predicting cognitive decline and dementia risk [175-177].

By contrast, most other candidate biomarkers remain supported primarily by cross-sectional studies. Elevated serum vascular cell adhesion molecule-1 (VCAM-1) [178], pyruvate kinase M2 (PKM2) [179], plasma lipoprotein-associated phospholipase A2 (Lp-PLA2), and superoxide dismutase (SOD) are associated with greater CSVD burden and poorer cognitive performance [180]. Additional cross-sectional studies implicate brain and CSF matrix metalloproteinases (MMPs) [181], CSF/blood albumin ratio [182], serum tumor necrosis factor-α (TNF-α), soluble receptor for advanced glycation end-products (s-RAGE) [183], plasma neutrophil extracellular traps (NETs) [184], circulating metabolites, particularly homocysteine [185, 186], and lipid-related biomarkers, including oxidized low-density lipoprotein (oxLDL) [187, 188], suggesting potential roles for BBB disruption, oxidative stress, vascular inflammation, and innate immune activation in cognitive impairment. However, these findings require longitudinal validation before their prognostic value can be established.

Emerging multi-omics approaches further support the biological heterogeneity of CSVD-related cognitive impairment. Large-scale proteomic studies identify protein signatures associated with CSVD burden and cognitive decline [189], whereas extracellular vesicle (EV) may provide an integrative platform reflecting endothelial dysfunction, inflammation, and coexisting neurodegeneration [190]. RNA-mediated pathways also attract increasing interest. Circulating microRNAs (miRNAs), including miR-130b-3p and miR-10b-3p, show promising diagnostic potential, although current evidence remains largely cross-sectional [191-193].

Collectively, these findings indicate that molecular signatures reflecting diverse biological pathways may serve not only as candidate biomarkers but also as potential contributors to cognitive heterogeneity in CSVD. Such molecular variability may partly explain why individuals with apparently comparable structural lesion burdens follow markedly different cognitive trajectories. However, current evidence remains heterogeneous and largely associative, and further longitudinal, mechanistic, and multi-omics studies are required to clarify the causal relevance and translational utility of these biomarkers.

4.3.2 Pathological heterogeneity and mixed pathology

The modest correlation between MRI-visible CSVD features and clinical symptoms can be partly attributed to heterogeneity in their underlying neuropathological substrates. Conventional T2-weighted MRI dichotomizes white matter into “WMH” and “normal”, yet WMH encompass a broad spectrum of pathology, ranging from mild myelin loss to severe axonal injury and gliosis. Similarly, lacunes and cerebral microbleeds, although identifiable on MRI, arise from diverse pathological mechanisms. Lacunes may result from acute thromboembolism, chronic hypoperfusion with progressive tissue rarefaction, or inflammatory injury. Microbleeds reflect distinct pathogenic processes, including hypertensive arteriopathy or CAA, and show variable relationships with WMH and lacunes.

Beyond conventional MRI, clinicopathological studies demonstrate that additional substrates such as subtle abnormalities within NAWM likely influence clinical outcomes but remain largely undetectable *in vivo*, becoming evident only with advanced imaging or postmortem analysis. This hidden heterogeneity may partly explain weak structure–cognition correlations, as similar MRI features can mask fundamentally different

tissue damage with distinct functional consequences. Moreover, clinicopathological studies in disease-specific contexts, such as CADASIL or hereditary CAA, demonstrate that identical MRI markers may reflect divergent pathological signatures, reinforcing the view that CSVD represents a spectrum of disorders rather than a single disease entity [158, 194]. Future studies integrating ultra-high-field MRI, diffusion-based microstructural mapping, molecular and pathological data will be critical for further clarifying CSVD heterogeneity and its contribution to cognitive decline.

CAA may further contribute to cognitive heterogeneity in CSVD by modifying the pathological significance of MRI-visible lesions. Although CAA and hypertensive arteriopathy may present with similar MRI markers, including WMH, CMB, and PVS, their underlying mechanisms differ substantially. Unlike hypertensive arteriopathy, CAA is characterized by amyloid-β deposition within cortical and leptomeningeal vessels, accompanied by impaired perivascular clearance, neuroinflammation, and diffuse microvascular injury [195]. Supporting divergent biological mechanisms, experimental studies show greater perivascular inflammation and inflammatory signaling in transgenic CAA models, whereas hypertensive models show more prominent perivascular dilation and metabolic dysfunction [196]. Clinical studies further suggest distinct cognitive profiles, with CAA showing relatively greater memory impairment compared with the predominantly executive dysfunction observed in hypertensive arteriopathy [197]. Although conventional MRI cannot fully distinguish these pathological substrates, imaging features such as posterior-predominant periventricular WMH may increase the likelihood of underlying CAA [198, 199]. Consequently, individuals with apparently similar MRI-visible lesion burdens may experience markedly different cognitive outcomes depending on the presence of concomitant amyloid-related vascular pathology.

This complexity is further amplified by the frequent coexistence of neurodegenerative and vascular brain pathology, most notably AD and CSVD, in aging populations. Mixed dementia, characterized by concurrent vascular and neurodegenerative pathological changes, is increasingly recognized as one of the most common forms of dementia rather than a distinct exception [200, 201]. Substantial evidence suggests that CSVD contributes to dementia partly through interaction with AD pathology, and coexisting neurodegenerative processes often act synergistically with CSVD to accelerate cognitive decline. CSVD and AD not only frequently co-occur in the aging brain, but may also interact biologically, with several vascular cognitive impairment risk factors also increasing the risk of AD [202]. Cross-sectional studies further show substantial overlap between CSVD and AD pathology. Patients with AD exhibit a high burden of CSVD markers, whereas approximately one-third of individuals with CSVD fall within the AD pathological continuum [203, 204]. Clinicopathological studies further indicate that mixed pathology is the rule rather than the exception in dementia. Large pathological cohorts consistently support frequent coexistence of Alzheimer-type and vascular pathology, with most individuals exhibiting multiple contributing lesions rather than isolated disease [205-209]. For example, cerebrovascular lesions commonly co-occur in patients with AD and exert additive or interactive effects on cognitive impairment [207]. Beyond coexistence, emerging evidence suggests reciprocal interactions between vascular and neurodegenerative mechanisms. In the presence of elevated amyloid-β or tau pathology, small vessel disease appears to confer greater microvascular tissue injury, supporting synergistic effects between neurodegenerative and vascular processes [210]. Genetic studies further support shared biological susceptibility, as AD-associated variants are also linked to all-cause and vascular dementia, implicating overlapping pathways involving neurodegeneration, vascular risk factors, and cerebral small vessel disease [211]. Together, these findings suggest that cognitive heterogeneity in CSVD cannot be fully explained by vascular lesion alone, but instead reflects complex interactions between vascular injury and coexisting neurodegenerative pathology.

4.4 Individual susceptibility factors

The pronounced heterogeneity in cognitive outcomes observed in CSVD cannot be explained by lesion burden alone and instead reflects substantial interindividual differences in vulnerability across the lifespan. This structural–cognitive heterogeneity likely arises, at least in part, from interactions between genetic and environmental factors that shape susceptibility to vascular injury and cognitive decline. Evidence from meta-analyses indicates that genetic predisposition, such as apolipoprotein E (APOE) polymorphisms, may amplify the effects of vascular pathology [212, 213]. In parallel, cross-sectional studies show that environmental exposures, including hypertension, diabetes, and hyperhomocysteinaemia, contribute through distinct biological pathways [186, 214-217]. These factors are thought to influence both the severity of CSVD lesions and their cognitive consequences, contributing to variable relationships between structural damage and functional impairment.

Accumulating evidence from multiple large longitudinal cohort studies demonstrate that early-life factors further modify CSVD risk later in life. Higher

birth weight is associated with fewer lacunes, fewer infarcts, and fewer moderate-to-severe enlarged perivascular spaces. Higher childhood intelligence quotient (IQ) correlates with lower WMH burden, fewer infarcts and lacunes, and reduced overall CSVD burden. In contrast, lower educational attainment is associated with a greater number of cerebral microbleeds and reduced total brain volume. Interestingly, lower childhood socioeconomic status has been linked to fewer lacunes [218]. Together, these findings suggest that early-life factors influence CSVD burden in older age, independent of adult vascular risk factors and socioeconomic status. These observations support the concept that susceptibility to small vessel disease may originate early in life, providing a mechanistic link between early exposures and later risk of stroke and dementia. Consequently, public health strategies that promote early childhood development may enhance lifelong brain health and contribute to the prevention of dementia and stroke in aging populations.

Brain reserve describes interindividual differences in brain structure, whereas cognitive reserve refers to differences in how efficiently the brain processes tasks. Life experiences, including those in early development, shape both forms of reserve, and the two constructs are closely interrelated. Although these concepts continue to evolve, both are highly relevant to the clinical expression of CSVD. Evidence from multiple large longitudinal and cross-sectional studies suggests that higher cognitive reserve - commonly indexed by educational attainment and IQ - attenuates the impact of small vessel disease burden on cognition, influences motor function, and affects age at stroke onset [219-222]. Premorbid cognitive ability reflects cognitive reserve and associates with the burden of small vessel disease lesions later in life, helping to explain variability in the relationship between CSVD and cognitive performance. Prior cross-sectional studies further show this concept. Because participants are selected for normal cognition, individuals with underlying neurodegeneration likely possess particularly high cognitive reserve. This reserve manifests as higher baseline spectral power in frontal regions, reduced low-frequency oscillations, and increased functional connectivity [223, 224]. As amyloid burden increases, however, this reserve diminishes, which may explain why individuals with neurodegeneration and very high amyloid load show slowing of brain oscillations and reduced functional connectivity.

Another important contributor to the clinical manifestations of CSVD is resilience, defined as the capacity to maintain cognitive function in the presence of brain pathology. Brain resilience likely depends on the integrity of white matter structure and large-scale network connectivity, as global white matter network efficiency mediates the effects of small vessel disease lesions on cognition and progression to dementia [124]. The relationship between brain damage and cognitive impairment is therefore not straightforward. Some individuals with substantial pathological changes in brain tissue maintain normal cognitive performance, a phenomenon referred to as cognitive resilience. A network-based hypothesis has been proposed to explain cognitive resilience, suggesting that denser and more highly interconnected structural brain networks can buffer the cognitive impact of tissue damage. Their findings showed that lower gray and white matter volumes and greater WMH burden are associated with poorer cognitive performance, whereas higher network node degree - a marker of white matter connectivity - associates with better cognitive function. Importantly, increasing node degree significantly attenuated the relationship between markers of brain damage and cognitive performance, indicating that individuals with substantial pathology may preserve cognition when white matter connectivity remains robust. Consistent with this model, a large cross-sectional imaging study showed that individuals with a CSVD score of 3 exhibited accelerated cognitive aging equivalent to 9.3 years compared with those with a CSVD score of 0. However, within the high-burden group, each standard deviation increases in node degree reduced cognitive aging by approximately 7 years [225].

Together, these factors contribute to divergent clinical trajectories in CSVD. Some individuals develop mild cognitive impairment, often characterized by executive and memory deficits, whereas others progress to dementia with marked executive dysfunction and slowed information processing. This phenotypic variability underscores the critical role of interindividual susceptibility in shaping the structural–cognitive heterogeneity of CSVD (Fig. 2, Table 2).

From a prognostic perspective, current evidence suggests that multiple key drivers of cognitive heterogeneity in CSVD may provide clinically relevant information beyond conventional lesion burden alone. Longitudinal cohort and clinicopathological studies provide relatively stronger support for the prognostic relevance of structural network disruption, pathological heterogeneity and mixed pathology, and individual susceptibility factors in shaping cognitive trajectories in CSVD. Lesion topography, remote structural and functional abnormalities, and molecular biomarkers may provide complementary prognostic information, although current evidence remains more limited and heterogeneous. Together, these findings support a multimodal prognostic perspective integrating lesion-related, network-mediated, biological and pathological, and individual susceptibility factors to better predict cognitive outcomes in CSVD.

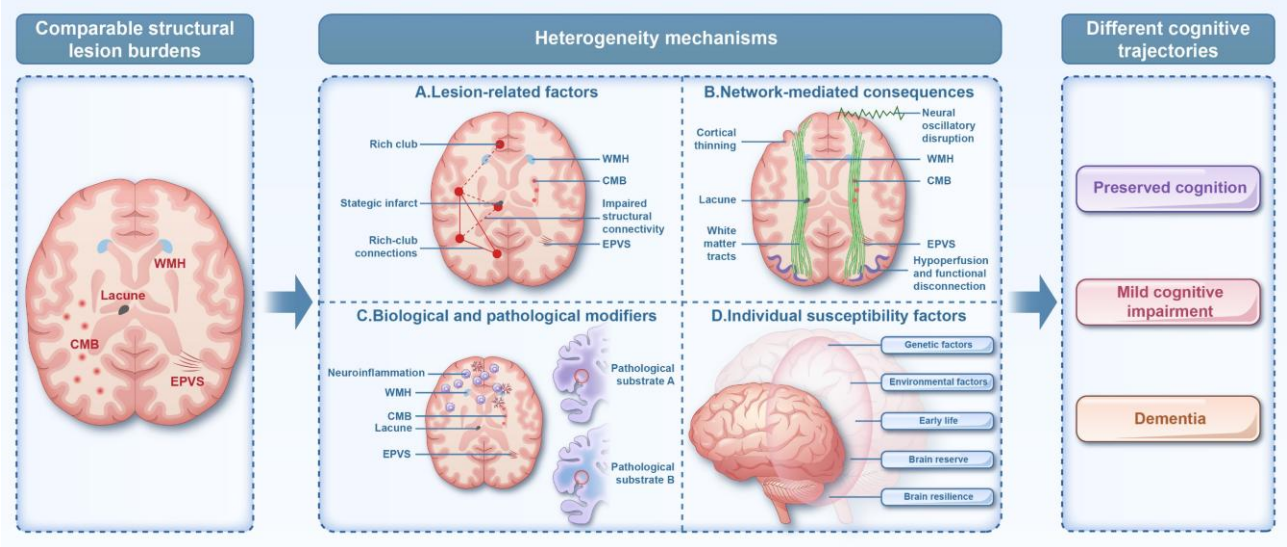

Figure 2. Integrated conceptual framework of the mechanisms underlying cognitive heterogeneity in CSVD. Individuals with apparently comparable structural lesion burdens may follow markedly different cognitive trajectories owing to the combined influence of lesion-related factors, network-mediated consequences, biological and pathological modifiers, and individual susceptibility factors. A. Lesion-related factors. Lesions involving strategic locations and/or highly connected rich-club hubs and their long-range connections may cause disproportionate disruption of structural connectivity, explaining cognitive deficits more effectively than total lesion volume. B. Network-mediated consequences. In addition to MRI-visible CSVD lesions, structural network disruption and remote structural and functional abnormalities, including microstructural injury in NAWM, reduced cortical perfusion, impaired functional connectivity, secondary neurodegeneration with cortical thinning, and neural oscillatory dysregulation, may collectively contribute to clinical heterogeneity. C. Biological and pathological modifiers. Biological modifiers accompanying CSVD lesions, particularly inflammatory processes, are highlighted as parallel, potentially self-reinforcing pathways that may exacerbate tissue injury and network dysfunction. Distinct underlying pathological substrates (illustrated as substrate A vs substrate B) may yield similar MRI features yet result in different cognitive trajectories, contributing to inter-individual variability (including the possibility of mixed pathologies). D. Individual susceptibility factors. Genetic factors, environmental exposures, and early-life influences shape brain reserve and brain resilience, thereby buffering or amplifying the cognitive impact of a given CSVD burden. Abbreviations: CMB, cerebral microbleed; CSVD, cerebral small vessel disease; EPVS, enlarged perivascular space; MRI, magnetic resonance imaging; NAWM, normal-appearing white matter; WMH, white matter hyperintensity.

5. Clinical translation: diagnosis and management of CSVD-related cognitive impairment

5.1 Multimodal clinical assessment and diagnostic evaluation

Diagnosing cognitive impairment related to CSVD remains challenging because symptoms are often subtle, nonspecific, and overlap with those of other neurodegenerative disorders. Accurate clinical evaluation therefore requires a multimodal diagnostic approach, although the translational readiness of available tools varies substantially.

In current clinical practice, conventional MRI remains the foundation for identifying core CSVD features. Standardized cognitive screening tools also remain essential for early detection and longitudinal monitoring, despite limited sensitivity to network-level dysfunction and subtle executive deficits. Advanced imaging approaches, used primarily in research settings or tertiary centers, provide deeper mechanistic insight into CSVD-related cognitive impairment. DTI provides deeper insight into microstructural white matter damage and its relationship to cognitive dysfunction. In parallel, functional neuroimaging demonstrate CSVD-related disruption of large-scale brain networks, improving diagnostic specificity in cases where structural markers alone fail to explain cognitive symptoms. Recent advances in ultra-high-field 7T MRI further enhance diagnostic sensitivity by enabling *in vivo* detection of cortical microinfarcts - lesions previously identifiable only at postmortem - thereby revealing clinically relevant but subtle pathology. However, cost, limited accessibility and lack of standardized implementation currently restrict the widespread clinical application of these techniques. Emerging computational approaches may further improve individualized diagnosis and prognostication. AI-based models that integrate multimodal imaging, clinical variables, and neuropsychological data show promise in improving diagnostic accuracy, refining individual risk stratification, and predicting cognitive trajectories. Nevertheless, these approaches remain investigational and require prospective validation, external replication,

and standardization before routine clinical implementation.

Table 2. Key drivers of cognitive heterogeneity in CSVD and corresponding levels of evidence.

Category	Key driver	Level of evidence
Lesion-related factors	Lesion topography involving strategically positioned network hubs or critical long-range white matter pathways	Findings supported by cross-sectional imaging studies
Network-mediated consequences	Structural network disruption, and remote structural and functional abnormalities beyond MRI-visible lesions, including microstructural injury in NAWM, reduced cortical perfusion, impaired functional connectivity, secondary neurodegeneration with cortical thinning, and neural oscillatory dysregulation	Structural network disruption supported by longitudinal cohort and cross-sectional imaging studies, whereas remote structural and functional abnormalities supported mainly by cross-sectional imaging studies, with some longitudinal cohort evidence and experimental animal models
Biological and pathological modifiers	Molecular biomarkers, including protein- and peptide-based biomarkers related to endothelial dysfunction, BBB disruption, inflammation, oxidative stress, and neuroaxonal or glial injury, as well as circulating metabolites, lipid-related biomarkers, and RNA-mediated pathways that may contribute to differential susceptibility to cognitive decline	Findings supported mainly by cross-sectional studies, with some longitudinal and experimental evidence
	Pathological heterogeneity and mixed pathology, including diverse neuropathological substrates underlying similar MRI-visible lesions and coexisting AD or CAA pathology	Findings supported by clinicopathological, genetic, imaging and experimental studies
Individual susceptibility factors	Individual susceptibility factors, including life-course influences (e.g., genetic predisposition, vascular risk exposure, and early-life factors) together with brain reserve and resilience that shape vulnerability to CSVD-related cognitive impairment	Findings supported by longitudinal and cross-sectional studies

Abbreviations: AD, Alzheimer's disease; BBB, blood–brain barrier; CAA, cerebral amyloid angiopathy; CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging; NAWM, normal-appearing white matter; RNA, ribonucleic acid.

Collectively, these developments underscore the need for integrative diagnostic strategies that combine structural, functional, and computational approaches to address the heterogeneity of CSVD-related cognitive impairment, and support a tiered and multimodal diagnostic framework for CSVD-related cognitive impairment, whereby conventional MRI and cognitive assessment remain the cornerstone of routine clinical evaluation, whereas advanced neuroimaging and computational approaches may provide additional mechanistic and prognostic value in specialized or research settings. (Fig. 3).

5.2 Precision management and emerging therapies

At present, no disease-specific therapies exist for CSVD-related cognitive impairment, and clinical management focuses on reducing vascular risk and preserving cognitive function.

In routine clinical practice, pharmacological treatment relies primarily on antihypertensive agents and antiplatelet therapy, while additional drugs, including statins, cilostazol, and emerging neuroprotective compounds, remain under active investigation. Non-pharmacological interventions, such as aerobic exercise, dietary optimization, and cognitive training, may enhance cognitive reserve and network efficiency, thereby reducing the functional consequences of structural brain injury and contributing to interindividual variability in cognitive outcomes. Advanced and emerging therapeutic strategies, largely investigated in research settings, increasingly target network dynamics and molecular mechanisms underlying CSVD-related cognitive heterogeneity. Non-invasive neuromodulation techniques, including transcranial alternating current stimulation (tACS), may enhance functional integration and partially restore disrupted connectivity caused by strategic lesions, although clinical evidence remains limited. At the molecular level, interventions that modulate neuroinflammation and RNA-mediated pathways, including microRNAs, may limit secondary neurodegeneration and function as both biomarkers and therapeutic targets. However, these approaches remain

investigational and require further mechanistic and clinical validation before routine implementation.

Given the pronounced structural and clinical heterogeneity of CSVD, individualized treatment approaches are essential. Integrating advanced neuroimaging modalities, such as 7T MRI and diffusion-based connectomics, with artificial intelligence–driven predictive models enables refined stratification based on lesion burden, network disruption, and anticipated cognitive trajectories. Together, a multimodal, precision-based strategy that combines vascular risk control, lifestyle interventions, network-targeted neuromodulation, and molecularly informed therapies offers the greatest potential to address CSVD heterogeneity and improve cognitive outcomes across the disease spectrum. However, substantial challenges related to validation, accessibility, and standardization must be addressed before these approaches can be routinely translated into clinical care (Fig. 3).

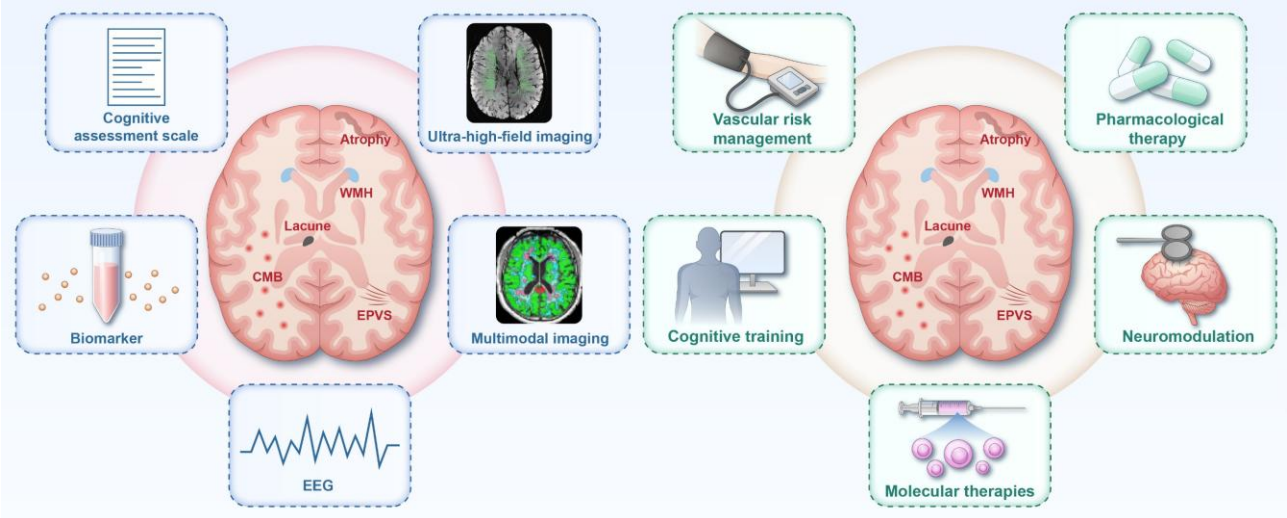

Figure 3. Multimodal assessment and therapeutic strategies for cognitive impairment in CSVD. The left panel summarizes a comprehensive assessment toolbox for CSVD-related cognitive impairment, integrating standardized cognitive and functional scales, fluid biomarkers, EEG, ultra-high-field neuroimaging [226], and multimodal neuroimaging approaches. These modalities enable phenotyping and longitudinal monitoring of CSVD burden and downstream brain injury and may serve as candidate surrogate markers and trial endpoints. The right panel outlines complementary therapeutic avenues targeting cognitive impairment in CSVD, including vascular risk factor management, pharmacological interventions, cognitive training, neuromodulation approaches, and emerging molecular therapies. Together, the schematic emphasizes a translational pathway from precision assessment and risk stratification to individualized treatment selection and outcome evaluation in CSVD-associated cognitive decline. Abbreviations: CMB, cerebral microbleed; CSVD, cerebral small vessel disease; EEG, electroencephalography; EPVS, enlarged perivascular space; WMH, white matter hyperintensity.

6. Conclusions

CSVD is a major cause of cognitive impairment in older adults, yet cognitive outcomes vary substantially even among individuals with apparently comparable structural lesion burdens. This heterogeneity suggests that conventional MRI-visible lesions capture only part of the disease process and that cognitive impairment in CSVD is better understood through the interaction of lesion-related factors, network-mediated consequences, biological and pathological modifiers, and individual susceptibility factors. Together, these mechanisms help explain how upstream structural injury translates into downstream functional dysfunction and divergent cognitive trajectories. By reframing CSVD-related cognitive impairment through a heterogeneity-oriented conceptual framework, this review highlights the importance of moving beyond a simple lesion-burden model toward more integrated approaches for diagnosis, prognosis, and therapeutic development. Continued research is needed to clarify the interactions among these mechanisms and to identify individualized strategies for preventing cognitive decline in CSVD.

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Author contributions

Wei Sun: conceptualized the review, conducted the literature review, designed the table and figures, and drafted the review. Aini He, Benke Zhao, Xuefan Yao and

Xiao Wu: drafted sections of the review. Haiqing Song: conceptualized the review, provided critical revision of the review. All authors have approved the submitted version.

Competing interests

The authors declare that they have no known competing interests.

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