

Review

Cognitive Frailty in Older Adults with Ischemic Stroke: Epidemiology, Mechanisms, and Multidimensional Management Strategies

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ABSTRACT: As global population aging accelerates, the number of older adults with ischemic stroke (IS) continues to rise. Cognitive frailty (CF), a geriatric syndrome, exhibits relatively high prevalence in this population and is associated with substantially elevated risks of disability, mortality, and poor prognosis. This review summarizes the epidemiological characteristics, underlying pathological mechanisms, and key influencing factors of CF in older patients with IS, and proposes a personalized prevention and management framework guided by digital and intelligent technologies through multidisciplinary collaboration. The aim is to provide a robust theoretical foundation and practical guidance for early identification and precise intervention targeting CF in older adults with IS. With the caveat that current evidence is constrained by regional concentration and heterogeneity in CF definitions and assessment tools, pending prospective validation through standardized protocols.

Keywords: Cognitive Frailty, Ischemic Stroke, Older Adults, Multidisciplinary Intervention

1. Introduction

As global population aging continues to accelerate, stroke has emerged as a major public health challenge worldwide. An estimated 12 million new stroke cases occur globally each year, with ischemic stroke (IS) accounting for approximately 70% – 80% and representing the predominant stroke subtype [1]. More than 50% of stroke survivors experience long-term impairments in physical functioning, such as difficulties with mobility and increased fall risk, and about 25% show further decline in physical function within the first year after stroke [2]. These deficits substantially reduce quality of life, while disability rates and associated healthcare

burdens continue to rise. In response, the World Health Organization has prioritized the prevention and control of major chronic diseases, including stroke and hypertension, as global health objectives, urging strengthened preventive strategies across countries. Recent studies indicate that cognitive frailty (CF) affects approximately 35%–40% of older patients with IS and is strongly linked to adverse outcomes such as hospitalization, falls, mortality, and functional decline [3]. Given the potential reversibility of CF, early identification and targeted intervention on its modifiable risk factors may delay or even reverse its progression and improve clinical outcomes. Nevertheless, research on CF remains in its early stages globally, particularly lacking

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standardized assessment criteria and large-scale epidemiological data across diverse regions and ethnic populations. This article reviews recent advances in understanding CF among older patients with IS from three perspectives, epidemiological characteristics, pathological mechanisms, and influencing factors, with the aim of providing theoretical support and practical guidance for clinical practice and scientific inquiry, ultimately contributing to the broader goal of healthy aging.

1.1 Search Strategy and Selection Criteria

A comprehensive literature search was conducted across five major electronic databases, PubMed/MEDLINE, Embase, Cochrane Library, CNKI (China National Knowledge Infrastructure), and Wanfang Data, from database inception through to May 2026. Search terms were constructed using a combination of Medical Subject Headings (MeSH) and free-text keywords, organized into three conceptual blocks: (1) Population: (“older adult*” OR “elderly” OR “aged” OR “senior*” OR “≥ 60 years”) AND (“ischemic stroke” OR “cerebral infarction” OR “brain infarct*”); (2) Index concept: (“cognitive frailty” OR “cognitive frail*” OR “frailty AND cognition” OR “physical frailty AND mild cognitive impairment”); (3) Outcomes/Context: (“epidemiology” OR “prevalence” OR “mechanism*” OR “pathogenesis” OR “risk factor*” OR “intervention” OR “management” OR “reversible”). Search syntax was adapted to align with the indexing rules and query formats of each individual database. Two independent reviewers first screened titles and abstracts for initial eligibility, followed by full-text assessment of potentially eligible articles. Any disagreements were resolved through discussion or, when necessary, consultation with a third reviewer.

Inclusion criteria were as follows: (1) peer-reviewed original research articles or consensus statements published in English or Chinese; (2) study populations consisting of adults aged ≥ 60 years with confirmed IS; (3) reporting of empirical data or expert-defined conceptual frameworks related to CF, consistent with the International Academy on Nutrition and Aging (IANA)/International Association of Gerontology and Geriatrics (IAGG) 2013 definition or subsequent updates; and (4) a focus on epidemiology, underlying mechanisms, modifiable risk factors, or non-pharmacological interventions. Exclusion criteria included: (1) case reports, editorials, or commentaries lacking primary data; (2) studies focused exclusively on dementia (e.g., Alzheimer’s disease), hemorrhagic stroke, or transient ischemic attack without separate analysis of an IS subgroup; and (3) animal-only studies or purely

preclinical mechanistic models lacking validation in human populations.

The search retrieved 637 records from the five databases as of May 2026. After deduplication, 519 citations were screened by title and abstract by two independent reviewers against predefined criteria, with ineligible records excluded at successive stages. Studies retained after screening, together with references identified through citation tracking and expert consultation, informed this narrative review. In total, 47 studies were cited.

2. Overview of CF in Older Patients with IS

2.1 Concept of CF

In 2013, IANA and IAGG jointly proposed the first operational definition of CF as a clinical syndrome characterized by the co-occurrence of physical frailty and mild cognitive impairment (MCI), with Alzheimer’s disease and other dementias explicitly excluded [Clinical Dementia Rating (CDR) ≤ 0.5] [4]. This definition marked a conceptual shift from the traditional practice of treating physical frailty and cognitive impairment (CI) as separate entities, instead emphasizing their interdependence and concurrent presence. Subsequently, Ruan et al. [5] refined the CF framework in 2015 by introducing two distinct subtypes: reversible cognitive frailty (RCF) and potentially reversible cognitive frailty (PRCF). Under this updated operational model, both subtypes require the presence of pre-frailty or physical frailty but differ in their cognitive features: RCF is defined by subjective cognitive decline (SCD) and/or positive biomarkers in the absence of MCI, whereas PRCF involves MCI (CDR = 0.5) without evidence of Alzheimer’s disease or other dementias. This distinction carries important clinical implications, RCF represents an earlier, more readily reversible stage, while PRCF, though still potentially modifiable, reflects more established cognitive deficits [5, 6]. In 2023, the Science and Technology Management and Evaluation Committee of the Chinese Association of Rehabilitation Medicine further clarified that CF constitutes an independent dimension within the broader frailty syndrome [7]. Its core feature lies in the dynamic interplay between age-related physiological decline and CI. CF has emerged as a significant predictor of adverse health outcomes in older adults, including progression to dementia, falls, and functional disability, with associated risks exceeding the combined effects of physical frailty or CI alone [8].

More recently, an international Delphi consensus study [9] published in 2025 convened multidisciplinary and multisectoral experts to develop consensus statements on CF interventions. This landmark effort reaffirmed CF

as a potentially reversible syndrome and underscored the importance of targeting modifiable risk factors, symptoms, and underlying mechanisms linking physical frailty and CI as key intervention priorities.

2.2 Heterogeneity in CF Definitions and Conceptual Distinctions between CF, MCI and Post-Stroke Cognitive Impairment

Substantial heterogeneity exists in the operational definitions and assessment tools used to identify CF [10]. Various instruments have been employed for physical frailty assessment, including Fried's phenotype, FRAIL scale, Study of Osteoporotic Fractures (SOF) Index, and Edmonton Frail Scale. Furthermore, Gobbens et al. have developed the Tilburg Frailty Indicator (TFI), a self-reported questionnaire to assess frailty [4]. Concurrently, diverse cognitive screening tools such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), CDR, and comprehensive neuropsychological test batteries have been utilized [10]. The use of distinct assessment combinations and the lack of consensus on optimal tools for CF across studies likely contribute to the inclusion of populations with differing severity levels and clinical characteristics under the broad diagnostic category of "CF".

It is also important to distinguish CF from MCI and post-stroke cognitive impairment (PSCI). MCI is a clinical condition intermediate between normal cognitive aging and dementia, characterized by cognitive decline beyond what would be expected for one's age, without impairing daily living activities [11]. CF represents a broader age-related geriatric syndrome; MCI serves as the cognitive component within the CF construct.

Specifically, CF emphasizes the coexistence and synergistic interaction between physical frailty and MCI, rather than viewing cognitive decline in isolation [4]. In IS patients, pre-existing frailty may amplify PSCI severity [12]. PSCI is a common neurological complication in stroke patients, characterized by progressive cognitive decline ranging from MCI to vascular dementia, significantly affecting patients' quality of life and long-term prognosis [13]. Additionally, PSCI is explicitly classified within the spectrum of vascular cognitive impairment (VCI), and together with cerebrovascular disease-related CI, constitutes the clinical manifestations of VCI [14].

2.3 Epidemiology of CF in Older Patients with IS

Studies have shown that the prevalence of CI and frailty among older patients with IS reaches 80.97% and 66.8%, respectively, and that these two conditions interact and form a vicious cycle [15, 16]. The prevalence of CF among hospitalized older patients with IS is 35.17% [3], while the prevalence in patients aged ≥ 80 years with IS increases to 43.75% [17]. Another study reported a CF prevalence of 27.90% among older patients with mild IS [18]. Approximately 50% of older patients who were frail before stroke experience acute-phase cognitive decline [12]. The Global Burden of Stroke analysis in 2019 [19] indicated that the coexistence of CF in patients with stroke may be heterogeneous due to racial and genomic differences; however, as related research remains in its early stages and lacks specific data, further evidence from multicenter, large-scale epidemiological studies is required.

Table 1. Summary of Quality Appraisal for Key Epidemiological Studies.

Study (Author, Year)	Quality Tool	Design	Quality Rating
Lin et al. [3] (2023)	AHRQ	Cross-sectional	High-quality (8/11)
Taylor-Rowan et al. [12] (2019)		Cross-sectional	High-quality (9/11)
Jokinen et al. [15] (2015)	NOS	Prospective cohort	High-quality (9/9)
Hu et al. [17] (2020)		Retrospective cohort	Moderate-quality (6/9)
Zhao et al. [18] (2023)		Nested case-control	High-quality (9/9)
Burton et al. [16] (2022)	AMSTAR-2	Systematic review & meta-analysis	High-quality (All critical domains were met)
Sukumaran et al. [19] (2024)	JBIC*	Ecological study	High-quality (8/8)

Notes: AHRQ: Agency for Healthcare Research and Quality, Total scores range from 0 to 11 points, with 8–11 indicating high quality, 4–7 moderate quality, and 0–3 low quality; NOS: Newcastle-Ottawa Scale, Total scores range from 0 to 9 stars, with ≥ 7 indicating high quality, 4–6 moderate quality, and ≤ 3 low quality; AMSTAR-2: A Measurement Tool to Assess systematic Reviews-2, Overall methodological quality was rated as high, moderate, low, or critically low based on the presence of flaws across 7 critical and 9 non-critical domains. JBI: Joanna Briggs Institute. *: JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies adapted for ecological study at population level. Studies were classified as high quality if 7–8 of 8 criteria were rated "Yes" moderate quality if 4–6 were "Yes" and low quality if ≤ 3 were "Yes"

To ensure methodological rigor, we conducted a quality assessment of the key epidemiological studies cited in this section using established domain-specific

tools. These tools include the Agency for Healthcare Research and Quality (AHRQ) checklist, the Newcastle-Ottawa Scale (NOS), A Measurement Tool to Assess

systematic Reviews-2 (AMSTAR-2), and the Joanna Briggs Institute (JBI) critical appraisal checklist, selected according to each study's design. Overall, six of seven studies were rated as high-quality and one as moderate-quality (Table 1). However, several methodological limitations should be acknowledged. First, two studies employed cross-sectional designs (Lin et al. [3]; Taylor-Rowan et al. [12]), which precludes causal inference. Second, the majority of the studies were single-center investigations of modest sample size, which limits statistical power and generalizability. Third, substantial heterogeneity in CF operational definitions and assessment instruments captures clinically distinct subpopulations, likely contributing to markedly varied prevalence estimates that preclude direct comparison. Fourth, primary studies were largely confined to single regional or ethnic settings, which limits external validity across diverse populations and sociocultural contexts.

3. Pathogenetic Mechanisms of CF in Older Patients with IS

While the pathogenesis of CF in older adults with IS remains incompletely elucidated, it is characterized by multi-system interaction, mainly including bilateral damage of neuroinflammatory cascade, cerebrovascular regulation dysfunction and chronic hypoperfusion, energy

metabolism crisis mediated by mitochondrial dysfunction, and neuroendocrine-immune network dysregulation (Fig. 1). These mechanistic constructs primarily derive from the extrapolation of evidence in general stroke, aging, frailty, and preclinical models. Since direct mechanistic evidence in older patients with IS and CF remains scarce, it merits prospective validation.

3.1 Bidirectional Detrimental Effects of Neuroinflammatory Cascades

After IS, excessive activation of microglia leads to the release of proinflammatory cytokines, such as tumor necrosis factor- α and interleukin-6, which are proposed to disrupt synaptic plasticity and neuronal regeneration in the hippocampus, potentially contributing to declines in executive function and memory [20]. In addition, inflammatory mediators have been shown to act on skeletal muscle through the circulatory system, activating the FOXO3-MuRF-1/Atrogin-1 axis-mediated protein degradation pathway and may thereby accelerate myofibrillar protein breakdown while inducing sarcopenia and reduced physical performance [21]. Together, these processes are suggested to constitute the inflammatory basis of concurrent cognitive and physical functional decline.

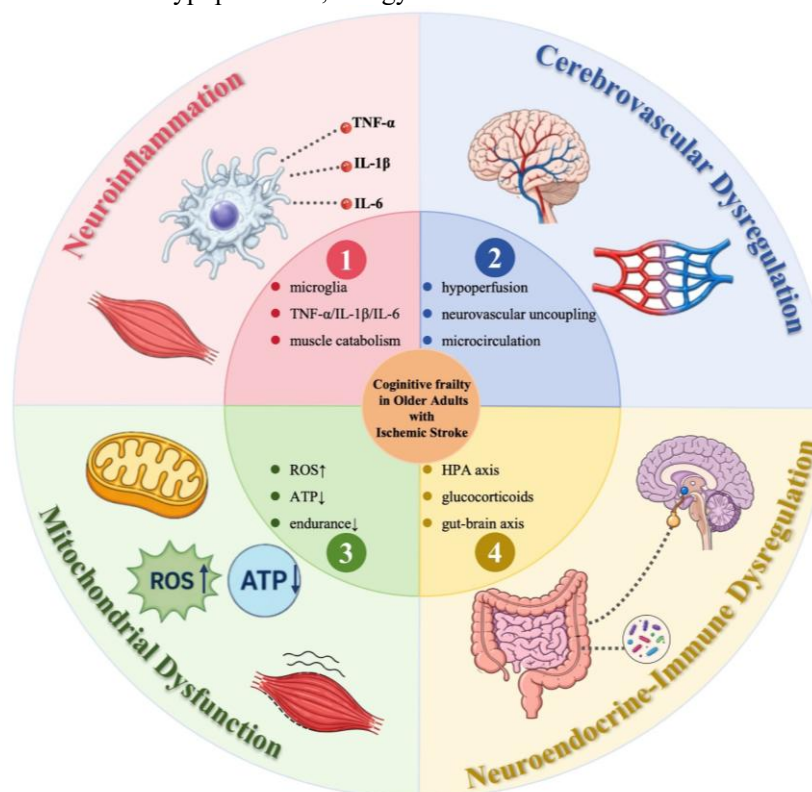


Figure 1. Multisystem Interacting Pathways in the Pathogenesis of Cognitive Frailty in Older Adults with Ischemic Stroke.

3.2 Cerebrovascular Regulatory Dysfunction and Chronic Hypoperfusion

Impairment of neurovascular coupling in infarcted regions, such as the thalamus and prefrontal cortex, as well as in remote brain areas leads to persistent cerebral hypoperfusion [22], which likely restricts neuronal energy supply and may disrupt default mode network connectivity, thereby impairing cognitive function [23]. Moreover, systemic microcirculatory dysfunction has been proposed to reduce oxygenation efficiency in muscle tissue, inducing decreased exercise tolerance and fatigue that may contribute to a dual vicious cycle of cognitive and physical functional deterioration [24].

3.3 Mitochondrial Dysfunction–Mediated Energy Metabolic Crisis

Following IS, neuronal mitochondrial oxidative phosphorylation capacity is reduced, with excessive accumulation of reactive oxygen species, which may lead to decreased ATP synthesis required for synaptic transmission and may contribute to impairment of cognitive functions such as working memory and learning ability [25]. Concurrently, peripheral skeletal muscle mitochondria exhibit complex I functional defects, which may result in diminished muscle contractile strength and reduced exercise capacity, potentially serving as a key metabolic hub linking cognitive decline and physical frailty [26].

3.4 Dysregulation of the Neuroendocrine–Immune Network

Excessive activation of the hypothalamic–pituitary–adrenal axis leads to sustained elevation of glucocorticoids, which directly damage hippocampal neurons and suppress expression of brain-derived neurotrophic factor, thereby potentially exacerbating CI. Simultaneously, cortisol may promote type II muscle fiber atrophy and insulin resistance through activation of the ubiquitin–proteasome system, thereby accelerating physical functional decline [27]. Metabolites such as trimethylamine N-oxide derived from gut microbiota dysbiosis have been suggested to further amplify inflammatory responses via the gut–brain axis, potentially contributing to a multisystem vicious cycle [28].

4. Influencing Factors of CF in Older Patients with IS

Based on recent domestic and international research advances, this review focuses on seven major influencing factors supported by convergent evidence, reproducibility across studies, and potential for clinical intervention.

Although age is non-modifiable, it is strongly associated with CF in older patients with IS and is therefore included as a background variable in the analysis.

4.1 Age

Advanced age is a well-established non-modifiable risk factor for CF in older patients with IS [29, 30]. As a potential shared mechanism underlying both IS and CF, aging markedly increases the risk of post-stroke CF by accelerating cerebrovascular injury, reducing brain reserve, and exacerbating comorbidity burden. Consequently, CF screening should be prioritized in very old stroke patients, and early intervention may improve prognosis.

4.2 Lifestyle

4.2.1 Smoking

Smoking has been shown to be independently associated with CI 18 months after IS or transient ischemic attack, likely through promotion of cerebral small vessel disease and brain atrophy [31], consistent with findings by Chen et al. [32]. Smoking is also closely linked to frailty development in older adults, with elderly smokers exhibiting a 2.07-fold higher risk of progressing to frailty compared with non-smokers [33]. Given that frailty status is significantly associated with post-stroke cognitive decline [31], smoking may indirectly contribute to CF. Although no study has yet established a direct link between smoking and CF in IS patients, this association merits further investigation.

4.2.2 Lack of Physical Activity

Insufficient moderate-to-vigorous physical activity (MVPA) accelerates CF progression, whereas activities such as brisk walking effectively increase MVPA levels [34]. Baseline frailty in stroke patients is significantly associated with PSCI [35], and regular physical activity reduces the risk of CF worsening over 24 months by 21% [36]. A domestic cross-sectional study further confirmed that regular exercise is protective against CF in older patients with IS [3]. Collectively, physical inactivity may exacerbate CF progression in this population through multiple interrelated pathways.

4.3 Multimorbidity

Multimorbidity is significantly associated with frailty in patients with stroke [37] and increases over eight years in both multimorbidity burden and frailty index are independently and dose-dependently linked to subsequent

decline in composite cognitive function [38]. Multimorbidity may also indirectly promote CF development by exacerbating depletion of physiological reserve and cerebral hypoperfusion in IS [22, 39]. Zhao et al. [29] reported that concomitant coronary heart disease and hypertension are independent risk factors for CF in older patients with mild IS. Similarly, Lin et al. [3] found that the number of coexisting chronic diseases is a risk factor for CF in older patients with IS, underscoring the importance of comprehensive clinical assessment and integrated intervention.

4.4 Nutritional Status

A longitudinal aging study in Singapore reported a very high prevalence of malnutrition among older adults with CF [40]. Studies conducted in China have confirmed that older patients with IS and a prognostic nutritional index ≤ 46.3 are more likely to develop CF [18]. Malnutrition is a recognized risk factor for CF in this population [3]. Nutritional interventions can significantly improve functional outcomes, for instance, by reducing stroke-associated pneumonia and depression through enhanced swallowing function and improved nutritional status [41]. As a modifiable factor, nutritional status plays a critical role in the management of CF in older patients with IS.

4.5 History of Cerebrovascular Disease

A prospective cohort study by Chen et al. [32] showed that patients with a prior stroke have a 2.932-fold higher risk of developing CI than those without such a history. Both a single prior cerebrovascular event and two or more events are risk factors for CF in older patients with mild IS [18]. Recurrent cerebrovascular events not only disrupt normal amyloid clearance in the brain, leading to white matter damage and cognitive decline, but also provoke fear of recurrence and leave residual physical impairment. These consequences often result in reduced physical activity and inadequate nutritional intake, ultimately contributing to the development of CF.

4.6 White Matter Lesions

Studies conducted in China have shown that moderate to severe white matter lesions (WML) are a risk factor for CF in older patients with mild IS [18], consistent with findings by Sugimoto et al. [42]. WML are linked to cerebral small vessel disease, contributing to ischemic injury and an elevated risk of both stroke and cognitive decline [43]. A longitudinal study at Radboud University Medical Center found that, 11 years after IS, reduced integrity of remote white matter was associated with poorer long-term cognitive performance [44]. By

disrupting white matter microstructural integrity, exacerbating neurovascular injury, and impairing functional connectivity within brain networks, WML represent a key pathological substrate for CF development in older patients with IS.

4.7 Psychosocial Factors

4.7.1 Depressive Symptoms

Studies conducted in China have confirmed that depressive symptoms are a risk factor for CF in older patients with IS [3], although this contrasts with results reported by Zhao et al. [18], a discrepancy likely attributable to methodological differences. Multiple studies support a significant association between depressive symptoms and CF. Among older patients with IS, the co-occurrence of physical frailty and depressive symptoms is associated with higher mortality than physical frailty alone [35, 45]. Moreover, depressive symptoms and physical frailty appear to act synergistically in accelerating cognitive decline: patients with both conditions show a 93% increased risk of CI 18 months after IS [31].

4.7.2 Sleep Disorders

Epidemiological data indicate that approximately 50% of stroke patients experience at least one type of sleep disorder [46]. Domestic research has identified sleep duration ≤ 6 hours as a risk factor for CF in older patients with mild IS [18], a finding corroborated by Lin et al. [3]. Clinical evidence suggests that treating sleep disorders, such as with continuous positive airway pressure therapy, may reduce the risk of post-stroke cognitive decline by 37% through mitigation of hypoxic events [47]. Accordingly, sleep disorder management should be considered an important target for CF prevention and control in older patients with IS.

5. Conclusion

The prevalence of CF in older patients with IS remains high and involves multisystem interactive mechanisms, including neuroinflammation, cerebrovascular regulatory dysfunction, mitochondrial dysfunction, and dysregulation of the neuroendocrine-immune network. Key clinical risk factors include advanced age, physical inactivity, multimorbidity, malnutrition, WML, depressive symptoms, and sleep disorders. However, current research has notable limitations: (1) The definition and assessment tools for CF have not been standardized, leading to substantial heterogeneity across studies; (2) Epidemiological data lack cross-ethnic and cross-regional

representativeness. Several central claims in this review, including reported prevalence rates and associations between multiple influencing factors and CF, are based largely on a limited number of regional studies conducted in China. These studies vary in sample sources, assessment instruments, and ethnic composition, and their findings should be generalized to other racial groups, healthcare systems, and sociocultural contexts with caution. Moreover, analyses of influencing factors remain fragmented, with a particular shortage of large-sample, prospective longitudinal cohort studies capable of elucidating the dynamic evolution and long-term outcomes of CF; (3) Randomized controlled trials specifically targeting older patients with IS and CF are

currently lacking. Although single-domain interventions, such as physical activity for general CF, nutritional support in post-stroke dysphagia, and sleep disorder management after stroke, have been extensively tested in related populations, high-quality trials are needed to systematically evaluate both single-component and multidimensional integrated strategies for CF in older adults with IS. In addition, “RCF” as a potential critical clinical window, remains in an exploratory phase regarding its identification criteria, transformation pathways, and optimal timing of intervention, underscoring the need for both theoretical advances and empirical validation.

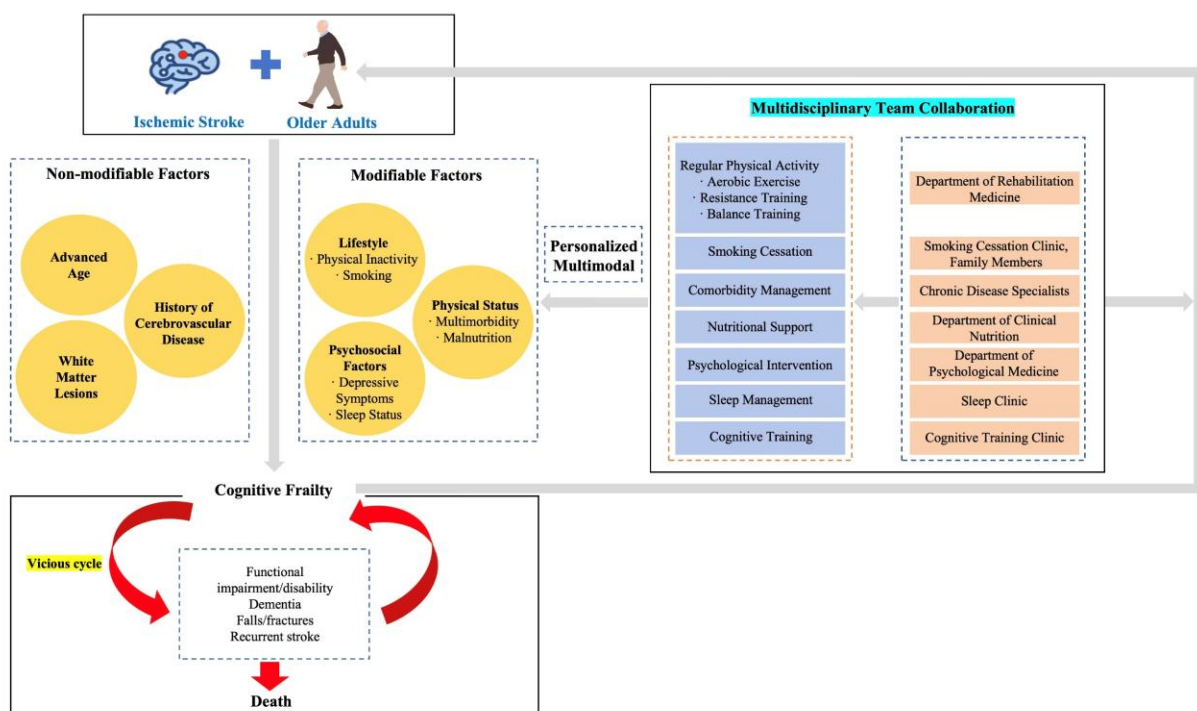


Figure 2. Multidimensional Framework and Multidisciplinary Management Strategy for Cognitive Frailty in Older Adults with Ischemic Stroke.

To address these challenges, a personalized, multidisciplinary prevention and control framework is urgently needed. Figure 2 illustrates a proposed multidimensional framework and interdisciplinary management strategy for CF in older adults with IS, integrating seven modifiable domains, cognition, nutrition, physical activity, smoking cessation, comorbidity management, psychological health, and sleep, through digital health technologies that enable remote monitoring, real-time feedback, and closed-loop management. This framework represents an evidence-informed, hypothesis-generating conceptual model requiring validation through prospective cohort studies and randomized controlled trials, rather than an

established standard of care. Priority should therefore be given to advancing multicenter, prospective cohort studies to establish consensus on standardized CF screening and assessment protocols, and to incorporating objective indicators such as biomarkers and neuroimaging parameters to deepen understanding of CF's core pathological mechanisms. Subsequent steps should evaluate the efficacy of personalized, multimodal intervention strategies grounded in digital health technologies in this population. Such an approach would facilitate a shift in CF prevention and control, from static risk prediction toward precise, dynamic intervention, ultimately supporting healthy aging in older patients with IS.

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Data Availability

This manuscript is a review article. All data supporting this work are derived from publicly available sources and have been appropriately cited.

Competing interests

The authors declare no financial, commercial, or personal conflicts of interest.

Authors' contributions

Yang Li: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. Xiaoxing Lai: Investigation, Writing – review & editing. Wanchen Song: Writing – review & editing. Kexin Zhang: Writing – review & editing. Donglei Shi: Supervision, Project administration, Writing – review & editing. Zhiyuan Zhang: Funding acquisition, Methodology, Writing – review & editing.

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