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Review article

Cognitive frailty: A comprehensive clinical paradigm beyond cognitive decline

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ABSTRACT

Cognitive frailty is an emerging concept in research and clinical practice that incorporates both physical frailty and mild cognitive impairment (MCI) or subjective cognitive decline (SCD). Unlike traditional approaches that separate physical frailty and dementia, cognitive frailty treats these domains as interrelated and coexisting, with significant implications for clinical outcomes and predicting cognitive decline. Despite growing recognition of this interrelationship, a dualistic view of physical and cognitive processes persists. The paradigm of cognitive frailty holds promise as a biomarker- like amyloid plaques or neurofibrillary tangles- but with the advantage of identifying risk at a prefrail stage, before clinical signs of MCI or dementia emerge. This review examines the pathophysiological and clinical dimensions of cognitive frailty and promotes for its integration into routine assessments in memory clinics.

1. Introduction

Frailty is a multidimensional syndrome characterized by a decline in physiological reserves, increasing vulnerability to stressors and risk of adverse health outcomes, including falls, disability, hospitalization, and mortality (Fried et al., 2001; Clegg et al., 2013). Fried et al. (2001) conceptualized frailty through a phenotype model, defining it by criteria such as unintentional weight loss, muscle weakness, slow walking speed, exhaustion, and low physical activity, where the presence of three or more criteria indicates frailty. An alternative view, the cumulative deficit model, assesses frailty as an accumulation of deficits-including physical, psychological, and social components-that collectively indicate vulnerability (Rockwood and Mitnitski, 2007). More recent research has expanded frailty definitions to incorporate cognitive elements, recognizing that cognitive decline frequently coexists with physical frailty and can significantly influence outcomes. Cognitive frailty, has garnered attention as a reversible, early marker on the continuum to dementia (the progressive decline in cognitive function that impairs memory, thinking, and daily activities), allowing for potential preventive interventions (Kelaiditi et al., 2013). Understanding cognitive frailty as an early, reversible marker offers an opportunity to intervene at a prefrail stage, potentially delaying or even preventing the progression to dementia.

If physical phenotype of frailty is documented and recognized, cognitive frailty is a relatively new construct, with a relevant heterogeneity ranging from 1.0 % to 22.0 %, that is from 10.7 % to 22 % in clinical-based settings and from 1.0 to 4.4 % in population-based settings (Roppolo et al., 2017; Montero-Odasso et al., 2016; Solfrizzi et al., 2017). Individuals with cognitive frailty were likely at higher risk of developing functional disability but evidence remains limited for those with prefrailty and cognitive impairment (Tang et al., 2023; Sugimoto et al., 2020). Prevalence of frailty in dementia is between 50.8 % and 91.8 % in acute care setting, 24,3 %-98,9 % in community-dwelling individuals with dementia (Nader et al., 2023). Prevalence of combined frailty and mild cognitive impairment (MCI, defined as a mild decline in cognitive function that doesn't significantly impact daily life) is found 2.7 % among some community-dwelling older populations (Shimada et al., 2013; Song et al., 2024). In 2015, a systematic review

Abbreviations: MCI, Mild Cognitive Impairment; SCD, Subjective Cognitive Decline; CFS, Clinical Frailty Scale; CSHA, Canadian Study of Health and Aging; EFS, Edmonton Frail Scale; CGA, Comprehensive Geriatric Assessment; MCR, Motor Cognitive Risk; CDR, Clinical Dementia Rating; PRISMA, Program of Research on Integration of Services for the Maintenance of Autonomy; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; ADAS-Cog, Alzheimer's Disease Assessment Scale; CASI, Cognitive Abilities Screening Instrument; WMH, White Matter Hyperintensity; VR, Virtual Reality; TUG, Timed Up and Go; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.

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has proposed deficit accumulation model of frailty as associated to late-life cognitive impairment and decline and incident dementia (Panza et al., 2015). In another systematic review and meta-analysis, cognitive frailty was associated with higher risk of incident mortality, dementia, disability, hospitalization and poor quality of life (Chen et al., 2022). To date, despite well-documented adverse outcomes associated with MCI and dementia, research has predominantly focused on the cognitive and affective dimensions of these conditions, often overlooking the underlying physical fragility that frequently coexists. This oversight limits our understanding of the comprehensive risk factors contributing to patient vulnerability and hinders the development of targeted interventions. In this review, we examine cognitive frailty-a state where physical frailty intersects with cognitive impairment-as a multidimensional construct that challenges traditional, physically centered perspectives in geriatric and gerontological research. By investigating the combined impact of physical and cognitive domains, cognitive frailty emerges as a powerful framework for identifying high-risk, prefrail individuals who may benefit from proactive interventions before clinical frailty sets in. Recognizing cognitive frailty as a dynamic condition, particularly in cases of cognitive impairment unrelated to neurodegenerative disease, opens possibilities for reversing or stabilizing cognitive decline through timely and tailored interventions. This dual approach not only enhances our understanding of frailty trajectories but also enables the identification of modifiable risk profiles, ultimately informing preventative care strategies that could delay or even prevent the progression to advanced frailty (Buchman and Bennett, 2013).

2. Methodology

This narrative review synthesizes evidence from a broad range of clinical studies, theoretical frameworks, and empirical findings to examine the intersections between physical frailty and cognitive impairment. A systematic search was conducted across major databases, including PubMed, Scopus, and Web of Science, focusing on articles published within the last decade. Keywords included "cognitive frailty," "physical frailty," "mild cognitive impairment," "dementia," "geriatric syndrome," and "prevention of frailty." Only studies that considered both physical and cognitive dimensions were included to ensure a comprehensive, integrative approach. The review further emphasizes studies that explore intervention outcomes, biological markers, and subject trajectories, providing an evidence-based discussion of cognitive frailty as a precursor to clinical frailty. By mapping both risk and resilience factors, this review offers a novel understanding of cognitive frailty, underscoring its potential role as a critical biomarker for early, reversible interventions.

3. Frailty: beyond the notion of loss

3.1. Being frail: from theoretical definition to practical applications

"Fragility" refers to the quality of being easily broken, damaged, or disrupted when exposed to stress or external forces. It is commonly used in various fields, including material science, biology, medicine, and economics, to describe systems, objects, or individuals that lack resilience and are highly susceptible to failure. While glass is universally considered fragile, its degree of fragility varies significantly depending on its composition and structure. Some types of glass, such as tempered glass, maintain a degree of fragility yet exhibit remarkable resistance to impact, shattering only under extreme stress. In contrast, delicate glassware, like thin crystal, is so brittle that even minor impacts can cause it to break. Similarly, in the context of human frailty—particularly in geriatric medicine—individuals may differ in their vulnerability to stressors. Some older adults, despite being classified as frail, retain a certain resilience, while others are so vulnerable that even minimal physiological or environmental stressors can lead to severe adverse outcomes. When glass breaks, it undergoes irreversible structural damage—it does not return to its original state. When a frail individual experiences a severe stressor—such as a fall, infection, or hospitalization—their ability to recover is often incomplete, and they may not return to their previous level of function. Just as glass does not regain its original strength after breaking, a frail body may experience a permanent loss of physiological reserves, making future stressors even more challenging to withstand.

Frailty was initially introduced as a clinical term to identify dependent and institutionalized older adults (Woodhouse et al., 1988). A long-standing and widely accepted definition in geriatric medicine and gerontology describes frailty as a multidimensional, dynamic condition characterized by "a state of increased vulnerability, resulting from age-associated declines in reserve and function across multiple physiologic systems, such that the ability to cope with every day or acute stressors is compromised" (Fried et al., 2001). While frailty strongly correlates with aging, age alone is neither a necessary nor sufficient condition for diagnosing frailty in individuals over 65 years old. In fact, the term "frail" includes various domains, such as physical/lifestyle, psychological, sociodemographic, economic, educational, and jurisprudential factors (Sciacchitano et al., 2024).

Traditionally, frailty measurement relies primarily on physical criteria, with the most common operational definition being the Fried frailty phenotype. This model defines frailty as a clinical syndrome in which three or more of the following five criteria are present: unintentional weight loss ($\geq$10 lbs in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity (calories expended weekly) (Fried et al., 2001). Patients are classified as non-frail (0 points), intermediate (1–2 points), or frail ($\geq$3 points). Another perspective considers frailty as a loss of adaptability and complexity, leading to dysfunction across multiple organ systems (Lipsitz, 2002) or as a pre-disability condition (Cesari et al., 2017). Beyond the phenotype model, frailty is also conceptualized as an age-related accumulation of deficits (Mitnitski et al., 2001). The Frailty Index (FI) relies on a comprehensive geriatric assessment (FI-CGA), encompassing up to 80 items with a maximum of 15 diagnoses and 20 medications. For everyone, the frailty index is calculated as the number of deficits present divided by the total number of deficits (Jones et al., 2004; Rockwood and Mitnitski, 2011). The FI-CGA has been associated with increased mortality and institutionalization risk (Lee et al., 2020). Another multidimensional tool is the Clinical Frailty Scale (CFS), introduced in 2005 by the Canadian Study of Health and Aging (CSHA) for clinical use and individual health screening. The revised CFS (version 2.0) employs a 9-point scale, from "very fit" to "terminally ill" (Rockwood et al., 2005). The Edmonton Frail Scale (EFS) assesses frailty across nine domains—cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and functional performance—with scores ranging from 0 to 17. Frailty categories include 0–5 points (no frailty), 6–7 (vulnerability), 8–9 (mild frailty), 10–11 (moderate frailty), and 12 + (severe frailty) (Rolfson et al., 2006). The 5-item FRAIL Score includes five domains: fatigue, resistance, ambulation, illnesses, and weight loss (Aprahamian et al., 2017). Another tool, PRISMA-7 (Program of Research to Integrate Services for the Maintenance of Autonomy), assesses frailty with seven yes/no questions, where a score of $\geq$ 3 indicates frailty (Hébert et al., 2003).

Despite the availability of numerous tools and the recognized clinical importance of identifying frailty as a precursor to geriatric syndromes, evidence supporting routine assessment remains limited. This gap is particularly evident when it comes to incorporating the cognitive dimension of frailty, which further complicates clinical evaluation (Walston et al., 2018). Collectively, frailty in older adults is often framed as a condition of decline, vulnerability, and inevitable loss. However, shifting the perspective on frailty reveals its deeper significance—not merely as a deficit but as an adaptive state, a marker of resilience, and a call for a more person-centered approach in geriatric care.

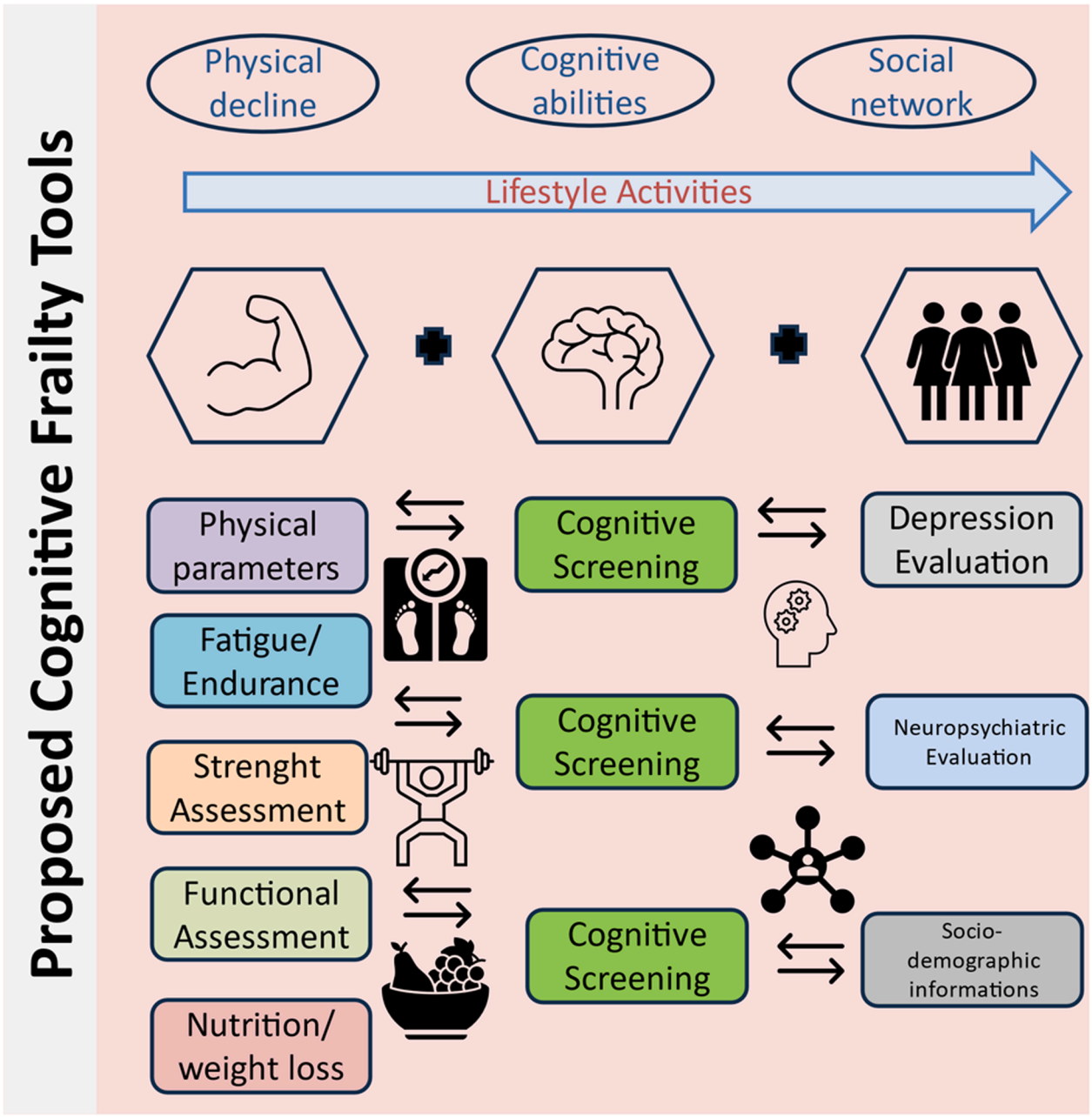

Fig. 1. Possible tools to measure cognitive frailty. This figure presents a framework for assessing cognitive frailty using multiple interconnected tools. It highlights the multidimensional nature of cognitive frailty, incorporating physical, cognitive, and social factors.

3.2. Cognitive frailty

Initially, cognitive frailty indicated a state of cognitive vulnerability in patients with MCI exposed to vascular risk factors, placing them at increased risk (Panza et al., 2006). In 2013, another panel consensus between the IANA (The International Academy on Nutrition and Aging) and the IAGG (the International Association of Gerontology and Geriatrics) placed the emphasis on the simultaneous presence of physical frailty and MCI (i.e., Clinical Dementia Rating, CDR score = 0.5) without a concurrent diagnosis of any forms of dementia, underlining an intermediate state of vulnerability (Kelaiditi et al., 2013). Another definition is based on the distinction between a potentially reversible form, which truly identifies the patient diagnosed with MCI, and a reversible form, which instead indicates those patients who complain of subjective cognitive decline (SCD) and/or positive biomarkers and neurodegeneration (Ruan et al., 2015). A categorization based on levels of severity is to distinguish level 1, physical pre-frailty + SCD; level 2, physical frailty + SCD; level 3, physical pre-frailty + MCI; and level 4, physical frailty + MCI (Nader et al., 2023). An operational definition of SCD that captures both cognitive and functional decline has been recently proposed (Edmonds et al., 2015), for earlier identification of cognitively normal older adults at risk for decline. In a systematic review, the SCD group was 2.15 times more likely to progress to MCI than the group without SCD (95 %CI 1.39—3.30; p = 0.005), especially using the NINCDS-ADRA (Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Criteria) criteria compared to DSM-V (Parfenov et al., 2020), with self-reported and above all informant-reported subjective cognitive complaints better predictors of progression to MCI and/or dementia (Perez-Blanco et al., 2022). Cross-sectional studies showed that frailty component and composite scores were related to SCD before the presence of overt dementia (Gifford et al., 2019), with subjective cognitive

decline positively associated with pre-frailty or frailty even after adjusting for potential confounding factors (Hsieh et al., 2018). Therefore, it becomes a clinical situation to pay particular attention to identify trajectories of frailty. The Motor Cognitive Risk Syndrome represents a clinical entity categorized by subjective cognitive complaints, assessed with the Consortium to Establish a Registry for Alzheimer's (CERAD) questionnaire (Rossetti et al., 2010). It typically involves non-amnestic decline and vascular aberrations such as frontal lacunar infarcts and white matter hyperintensity, as well as slow gait with associated postural, balance impairments and metabolic dysfunctions (Xiang et al., 2022; Verghese et al., 2012), without dementia or mobility disability (four diagnostic criteria). Physio-cognitive decline syndrome, in turn, is a term to distinguish the simultaneous presence of physical decline (physical weakness and/or slowness) and cognitive impairment in any domain (1.5 standard deviations below the mean for age-sex and education-matched norms) (Chen and Arai, 2020). When studies consider frailty, poor attention is dedicated to specific cognitive functions and domains (Canevelli et al., 2015). Measures of mobility/gait speed, strength, nutrition/weight loss, endurance/fatigue, and physical activity, neuropsychiatric testing and a cognitive assessment tool (Clinical Cognitive Assessment Tool defined as use of any of the following: Mini Mental State Examination MMSE, Montreal Cognitive Assessment MoCA, Clinical Dementia Rating CDR, Alzheimer's Disease Assessment Scale ADAS-Cog or Cognitive Abilities Screening Instrument CASI) seems to be the most common operational definition (Sargent and Brown, 2017; Larner, 2012; Larner, 2014). The Cognitive Frailty (CF) screening tool is a self-administered comprehensive screening tool consisting of socio-demographic information, morbidity, functional and depression assessment, as well as lifestyle activities, with 12 short items, used with good sensitivity and specificity for community-dwelling older adults (Malek Rivan et al., 2024). Another screening Cognitive Frailty Tool was based on definition of physical declines (only slowness and weakness to define physical pre-frailty, with slowness defined as 6-metre walk speed and weakness as handgrip strength$\leq$26 kg for men and $\leq$18 kg for women) and assessed cognitive function using MoCA or neuropsychological assessments to evaluate four cognitive domains: verbal memory (delay-free recall in the Chinese Version Verbal Learning Test), language function (Boston Naming Test, category (animal) Verbal Fluency Test), visuospatial function (Taylor Complex Figure Test), and executive function (Digit Backward Test, Clock Drawing Test). Scores below 1.5 standard deviations were considered indicative of cognitive frailty, with a maximum Cognitive Frailty Risk Score (CFR) of 4. The highest sensitivity was 81 % at CFR $\geq$ 4, and the highest specificity was 93 % at CFR $\geq$ 8. Six independent factors associated with cognitive frailty were age $\geq$ 75 years, female sex, central obesity, low calf circumference, memory complaints, and diabetes mellitus (Tseng et al., 2019). In some population-studies, a motor test, such as gait velocity, was combined with a cognitive test like the Montreal Cognitive Assessment to check individuals at risk for dementia, embracing in cognitive-frailty two different manifestations (Montero-Odasso et al., 2016). Among cognitive function tools, MMSE and MoCA have often been used, whereas CDR has been rarely utilized (Peng et al., 2024). Some evidence suggests that cognitive frailty may be distinct from cognitive impairment itself, with cognitive performance similar to that of individuals with mild cognitive impairment (MCI), but exhibiting larger temporal gray matter volume compared to those with the same MCI and Alzheimer's pathology. This may reflect a form of cognitive lifespan mediated by lifelong cognitive reserve, hearing impairment, and cardiovascular comorbidities (Kocagoncu et al., 2022). Fig. 1 describes the possible combinations of measurements to evaluate cognitive frailty. It represents a comprehensive approach to detecting cognitive frailty by integrating physical, cognitive, emotional, and social assessments. It underscores the need for a multidimensional evaluation to effectively identify individuals at risk and implement early interventions.

3.3. Cognitive frailty: from early identification, trough molecular mechanisms to pathophysiological mechanisms

Cognitive frailty, traditionally perceived as a dual burden of physical frailty and cognitive decline, is often framed in geriatric medicine as a precursor to dependency and neurodegenerative diseases. However, shifting the perspective from loss to resource allows us to see cognitive frailty not merely as a risk factor, but as a window of opportunity for intervention, adaptation, and resilience. Unlike irreversible dementia, cognitive frailty represents a transitional and potentially modifiable state, where cognitive and physical reserves can still be modulated. This reframing invites a proactive approach that emphasizes neuroplasticity, compensatory mechanisms, and personalized strategies to maintain cognitive engagement and functional independence. Thus, rather than signifying inevitable deterioration, cognitive frailty highlights the power of adaptability—a call to action for early identification, intervention, holistic support, and an approach that values cognitive diversity in aging.

3.3.1. Early identification: biomarkers of cognitive frailty

At structural level, cognitive frailty appears to be linked to specific volumetric biomarkers, including white matter hyperintensity (WMH) observed through T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging (Sugimoto et al., 2019), structural losses in regions such as the thalamus and hippocampus (Wan et al., 2020), and disruptions in hippocampal-amygdala-cerebellar connectivity (Foo et al., 2016). These features are proposed as potential indicators of cognitive frailty and its progression (Facal et al., 2021; Park and Kim, 2023). From a genetic point of view a comprehensive review of 342 studies identified 456 protein and genetic single nucleotide polymorphisms (SNPs) associated with physical frailty and cognitive impairment, many of which are predictive of cardiovascular factors (e.g., diabetes, dyslipidemia, hypertension), neuroinflammatory proteins (e.g., IL-6, TNF-alpha, IL-18, and IL-1 beta), as well as nutritional, hematologic, renal, and hormonal biomarkers (Sargent et al., 2018, 2020). From a biological point of view, findings from the longitudinal "Invecchiare in Chianti" (InCHIANTI) cohort study further identified markers linked to cognitive frailty, including low levels of vitamin E (alpha-tocopherol), albumin, omega-6 and omega-3 fatty acids, low- and high-density lipoproteins (LDL and HDL), and specific metabolomic ceramides (Sargent et al., 2018). Again elevated cystatin C was also associated with an increased likelihood of conversion from MCI to Alzheimer's disease (AD) (Lopez et al., 2008; Sargent et al., 2020), while low levels of hormones such as dehydroepiandrosterone sulfate (DHEA), testosterone, urinary cortisol, total insulin-like growth factor, plasma insulin, and free thyroxine (FT4) were observed in cognitively frail individuals (Sargent et al., 2020). Further reviews on cardiovascular-related blood parameters in cognitively frail older adults highlight that glucose homeostasis and inflammatory markers, particularly TNF-α, leptin, HbA1c, insulin-like growth factor (IGF-1), glucose, insulin, and HOMA-IR, are consistently impacted (Ibrahim et al., 2023). Although the imbalance between pro- and anti-inflammatory mechanisms is well-documented in frailty and neurodegenerative disorders, studies that integrate both physical and cognitive frailty are still limited (Pan and Ma, 2024).

Epigenetic clocks, algorithms that predict aging-related phenotypes by combining methylation levels at specific CpG sites, are also potential indicators of cognitive frailty. These clocks align with the "geroscience hypothesis," which links frailty and multimorbidity to cellular aging processes (Kennedy et al., 2014; Bell et al., 2019). MiRNAs—small non-coding RNAs approximately 21–25 nucleotides in length that regulate gene expression by binding to complementary mRNAs (Hammond, 2015)—are emerging as promising biomarkers of both physical and cognitive frailty. Notably, miR-21 and miR-146a have been identified as inflammatory miRNAs associated with advanced oxidation protein products levels, which mediate the pro-inflammatory effects of oxidative stress on muscle frailty (Dimassi et al., 2018). Other miRNAs

play roles in amyloid-beta (Aβ) genesis, microglial activation, blood-brain barrier integrity, synaptic plasticity, and neurogenesis (Juzwik et al., 2019). Finally, research on gut microbiota underscores its potential role in the gut-brain axis and cognitive symptoms in animal models of dementia (AD). Through mechanisms involving vagal modulation, bacterial synthesis of neuroactive substances, and subsequent inflammation and amyloid deposition, gut microbiota may influence cognitive symptoms, though human studies are still ongoing (Ticinesi et al., 2018).

From a clinical point of view, considering the shared pathophysiologic mechanisms between cardiovascular disease, cognitive impairment, and frailty-such as hypertension, diabetes, obesity, sedentary behaviour, and smoking-the presence of cardiovascular disease is increasingly recognized as a crucial factor in uncovering underlying cognitive frailty (Ijaz et al., 2024). Although routine blood tests are used to detect physical frailty, no longitudinal studies have conclusively demonstrated their predictive value for cognitive frailty (Facal et al., 2021). Falls, instead, serve as sentinel events, given the association between cognitive frailty and fall risk in older adults (Wang et al., 2023). Gait parameters, including single-task and dual-task walking assessments with spatiotemporal characteristics, alongside simple physical performance measures like the Timed Up and Go (TUG) test, are increasingly recognized as useful indicators of cognitive frailty (Kerminen et al., 2024; Facal et al., 2021).

3.3.2. *Molecular mechanisms underlying cognitive deficits: an integrative perspective*

Cognitive deficits are the result of a complex interplay between cerebral and extracerebral factors, where molecular and cellular alterations play a crucial role in the progression of neurodegenerative and neuropsychiatric disorders (Azam et al., 2021, Ratan et al., 2023, Selvam and Ayyavoo, 2024). While well-established clinical mechanisms—such as vascular dysfunction, neuroinflammation, and synaptic failure—have been extensively studied for over a decade, recent advances in molecular biology have unveiled additional layers of complexity in cognitive decline (Moyse et al., 2022; Badji et al., 2023; Zhang et al., 2024). In particular, the role of immunomodulation in brain transmission, along with insights from omics technologies, spatial proteomics, and spatial transcriptomics, have revolutionized our understanding of the underlying pathophysiology (Dantzer, 2018; Fangma et al., 2023; Guo and Deng, 2024; Lee et al., 2024).

The immune system plays a fundamental role in brain homeostasis, regulating synaptic plasticity, neuronal survival, and neurotransmission (Morimoto and Nakajima, 2019; Matejuk et al., 2021) Emerging evidence suggests that an imbalance in neuroimmune interactions contributes to cognitive deficits by altering neurotransmitter dynamics and promoting neuroinflammation (Müller et al., 2025). Microglia, the resident immune cells of the brain, exhibit dual roles—protective under physiological conditions but deleterious when chronically activated (Colonna and Butovsky, 2017; Muzio et al., 2021; Gao et al., 2023). In neurodegenerative diseases such as Alzheimer's and Parkinson's, microglial overactivation leads to excessive production of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), which disrupt synaptic function and accelerate neuronal loss (Wang et al., 2023; Miao et al., 2023). Similarly, astrocytes, traditionally considered as supporting cells, actively participate in modulating synaptic transmission and blood-brain barrier integrity, thereby influencing cognitive performance (Ota et al., 2013; Müller et al., 2025). Telomere dysfunction, characterized by short or unstable telomeres, has been observed in microglia and peripheral immune cells. This dysfunction triggers the release of pro-inflammatory mediators, leading to brain damage and contributing to both aging and cognitive decline (Boccardi and Paolisso, 2014; Boccardi et al., 2015). Advancements in omics sciences (genomics, transcriptomics, proteomics, and metabolomics) have provided unprecedented insights into the molecular basis of cognitive disorders (Eteleeb et al., 2024). These high-throughput approaches allow the identification of gene networks, protein interactions, and metabolic pathways dysregulated in neurodegenerative conditions (Calabrese et al., 2022). Genome-wide association studies (GWAS) have identified several risk genes linked to cognitive disorders, including APOE4, TREM2, and CLU, which are implicated in lipid metabolism, amyloid clearance, and neuroinflammation (Karch and Goate, 2015; Wolfe et al., 2018; Lin et al., 2024; Krishnamurthy et al., 2025). Transcriptomic analyses further reveal changes in RNA expression profiles that correlate with disease progression, highlighting the dysregulation of neuronal and glial gene networks (Morabito et al., 2020; Gratuze et al., 2018; Quan et al., 2023). Mass spectrometry-based proteomics has identified protein signatures associated with synaptic dysfunction, tau pathology, and neuroinflammation, while metabolomics has uncovered alterations in glucose metabolism, oxidative stress, and mitochondrial dysfunction, all of which are critical contributors to cognitive impairment (Mendonça et al., 2019; Strefeler et al., 2023; Ryu et al., 2025). Traditional omics approaches provide valuable insights into molecular changes but lack spatial resolution, making it challenging to pinpoint disease-specific alterations at the cellular level (Bingham et al., 2020, İş et al., 2025). The emergence of spatial proteomics and spatial transcriptomics has overcome this limitation by enabling the high-resolution mapping of gene and protein expression within distinct brain regions (Chu et al., 2024). Recent developments in imaging mass spectrometry and multiplexed immunohistochemistry allow for the visualization of protein distribution in situ, facilitating the identification of disease-relevant molecular signatures in affected brain areas (Levenson et al., 2015; Hale and Cooper, 2020). For example, spatial proteomics studies in Alzheimer's disease have demonstrated region-specific accumulation of tau aggregates and inflammatory markers in the hippocampus and cortex, correlating with cognitive decline (Walker et al., 2024; Ma et al., 2024; Vilkaite et al., 2024; Pichet Binette et al., 2024). This cutting-edge technology enables the mapping of RNA expression patterns in intact tissue samples, revealing previously unrecognized cellular heterogeneity and disease-specific transcriptomic alterations (Li et al., 2024; Molla Desta and Birhanu, 2025). Studies in animal models have shown that cognitive decline is associated with dysregulation of neuronal activity genes, immune response pathways, and synaptic plasticity markers, providing novel therapeutic targets (Meftah and Gan, 2023; Zhong et al., 2024). The integration of immunomodulation, omics technologies, and spatial molecular profiling represents a paradigm shift in the study of cognitive deficits. These approaches not only enhance our mechanistic understanding but also pave the way for the development of precision medicine strategies targeting individualized molecular pathways.

3.3.3. *Potential pathophysiological mechanisms linking frailty and cognitive frailty*

The interaction between frailty and cognition in determining prognosis remains understudied (Ma and Chan, 2020). However, established concepts in frailty and vulnerability are increasingly applied to cognitive frailty. A common classification of risk factors includes psychosocial factors (such as socioeconomic status, mood disorders, and low education), biological factors (including genetic and epigenetic changes, oxidative stress, and proteostasis loss), and environmental factors (such as nutrition, sleep quality, and access to resources) (Nader et al., 2023). The hypothesis is that brain could have a core determinant not only for dementia but also for frailty syndrome, with a link between brain and muscle function (Lauretani et al., 2017). Sarcopenia, defined by reduced muscle mass and strength and recognized as a generalized skeletal muscle disease, is a potentially reversible condition (Kirk et al., 2024). Myokine secretion from muscle contraction during exercise, particularly the myokine irisin, which binds to neuronal receptors and stimulates brain-derived neurotrophic factor (BDNF) expression, may represent a key link between sarcopenia and cognitive decline (Chen et al., 2021; Lourenco et al., 2019; Arosio et al., 2023). Physical activity stimulates BDNF, vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF-1), which collectively promote cell growth and

Table 1
Key pathophysiological mechanisms and risk factors linking frailty and cognitive frailty.

Factor	Description	Impact on Frailty	Impact on cognitive frailty
Psychosocial factors	Socioeconomic status, mood disorders, low education, social vulnerability, and loneliness influence frailty.	Increases vulnerability to stress and impacts physical resilience.	Worsens cognitive function and may lead to isolation, exacerbating cognitive decline.
Sarcopenia	Loss of muscle mass and strength, with myokine release (e.g., irisin) from exercise, which promotes BDNF, VEGF, and IGF−1, supporting neuronal health.	Reduces physical strength and resilience, contributing to frailty.	Enhances cognitive resilience through exercise-induced neurotrophic factors, reducing cognitive decline.
Telomere dysfunction	Short or unstable telomeres in microglia and immune cells, leading to chronic inflammation and brain damage.	Increases inflammation and accelerates physical aging.	Contributes to cognitive decline and aging through pro-inflammatory effects.
Insulin resistance	Increases inflammation, atherosclerosis, oxidative stress; insulin regulates bioenergetics and synaptic activity, promoting vascular health.	Leads to reduced muscle function, contributing to frailty.	Impairs cerebral energy metabolism and increases risk of cognitive impairment, especially in pre-diabetic and hypertensive older adults.
Metabolic syndrome	Combination of glucose intolerance, abdominal obesity, hypertension, hypertriglyceridemia, low HDL cholesterol, contributing to late-life cognitive decline.	Increases metabolic stress on body systems, exacerbating frailty.	Associated with cognitive impairment due to shared metabolic and vascular risks.
Depression	Associated with reduced neurotransmitter activity, undernutrition, decreased physical activity, sarcopenia, and increased cardiovascular risk.	Leads to physical inactivity, weight loss, and sarcopenia, contributing to frailty.	Depressive symptoms exacerbate cognitive decline and reduce motivation for social engagement, worsening cognitive frailty.
Nutritional deficiencies	Malnutrition, especially low levels of folate and carotenoids, increases frailty risk; cognitive frailty linked to a high prevalence of malnutrition.	Leads to sarcopenic obesity, weight loss, and general frailty.	Deficiencies impact cognitive function, and combined nutrient deficiencies may increase risk of cognitive decline.
Hormonal imbalance	Lower levels of testosterone and IGF−1 reduce muscle mass, affect synaptic plasticity, and contribute to physical and cognitive decline.	Reduced muscle maintenance and resilience in aging, increasing frailty.	Impairs cognitive function through reduced neuroprotection and synaptic integrity.
Engagement in activities	Lower physical and social activity increases risk factors for cognitive frailty, with unclear effects of factors like sleep quality, vitamin D, and body composition.	Lower physical and social activity exacerbates physical frailty.	Reduced cognitive engagement leads to cognitive decline, while unclear lifestyle factors might contribute variably.

BDNF: Brain-Derived Neurotrophic Factor; VEGF: Vascular Endothelial Growth Factor; IGF-1: Insulin-Like Growth Factor 1.

neuronal plasticity (Bibel and Barde, 2000; Delezie and Handschin, 2018). Lang et al. (2009) proposed that frailty operates as a cycle involving age-related changes in bone density and muscle function. Leptin has a role in regulating hippocampal neuron morphology and synaptic function (McGregor et al., 2014) and mediates the relationship between high body fat mass and low bone density, a predictor of frailty in older adults (Aguirre et al., 2014). Insulin resistance, assessed by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), increases inflammation, atherosclerosis, endothelial dysfunction, and oxidative stress. Insulin plays a critical role in regulating brain bioenergetics, enhancing synaptic activity and neurotransmitter turnover, and supporting vascular function through vasoreactivity, lipid metabolism, and proteostasis. These functions position insulin as a key regulator of neuronal survival, potentially mediated via insulin-like growth factor receptors (Kellar and Craft, 2020; Del Turco et al., 2013). In frail, pre-diabetic, and hypertensive older adults, insulin resistance has been associated with cognitive impairment (Mone et al., 2023). Insulin-like growth factor 1 (IGF-1) and its binding protein IGFBP2 are also implicated in age-related cognitive decline and physical frailty (Royal and Plamen, 2019). Testosterone, another hormone with neuroprotective effects, promotes synaptic plasticity to support cognition (Maggio et al., 2012) and helps maintain muscle mass during aging (Muller et al., 2003). The “metabolic-cognitive syndrome,” involving impaired glucose tolerance, abdominal obesity, hypertension, hypertriglyceridemia, and low HDL cholesterol, has been identified as a core risk factor for late-life cognitive decline (Panza et al., 2012). In older adults (aged 90 +), frailty is a more significant predictor of mortality than metabolic syndrome, even after adjusting for age (Hao et al., 2016; Hao et al., 2019).

Social factors are also important. A systematic review of 130 observational studies found bidirectional relationships between frailty, loneliness, and social factors like the social vulnerability index and social frailty. Social interactions appear to buffer the negative effects of frailty on cognitive function in older adults (Hanlon et al., 2024; Devita et al., 2024). Depression is another psychosocial factor closely linked to cognitive frailty, with studies identifying lower education, material wealth, and social support as significant risk factors (Ellwood et al., 2022). Lifestyle factors related to living conditions-such as access to healthcare, engagement in active aging activities, and home environment safety-may also mediate these associations (Navarro-Pardo et al., 2020). In a meta-analysis, high prevalence rates of cognitive frailty combined with depression were noted among older adults, despite inconsistencies in the definitions and assessments of cognitive frailty across studies (Zou et al., 2023). Depression in older adults contributes to frailty through mechanisms such as reduced neurotransmitter activity (e.g., noradrenaline and dopamine), leading to lower motivation and physical inactivity, and a cycle of chronic undernutrition, sarcopenia, and increased cardiovascular risk (Robertson et al., 2013). A systematic review highlighted age, activity level, and emotional state as independent risk factors for cognitive frailty, with unclear associations with gender, marital status, education, social participation, sleep problems, calf circumference, body fat, albumin, and vitamin D (Zhang et al., 2022). Malnutrition is also highly associated with cognitive frailty. A meta-analysis found that 23 % of older adults with cognitive frailty also experience malnutrition, with a significantly increased risk (3.77 times higher) of malnutrition among those with cognitive frailty compared to those without. Co-occurring nutrient deficiencies, including low levels of folate and carotenoids, are linked to poorer cognitive health, highlighting the importance of identifying “at-risk” groups early through nutritional assessment (Feng et al., 2024; O’Connor et al., 2023). Table 1 outlines critical biological, psychosocial, and lifestyle mechanisms linking frailty and cognitive frailty. Collectively, frailty and cognitive frailty share common biological and psychosocial risk factors, including sarcopenia, telomere dysfunction, insulin resistance, metabolic syndrome, hormonal imbalances, and nutritional deficiencies, all of which contribute to physical and cognitive decline. Psychosocial factors like depression, low education, social isolation, and inactivity further exacerbate both conditions by increasing vulnerability to stress and reducing resilience. Exercise, proper nutrition, and social engagement play a crucial role in mitigating these risks, highlighting the need for multidimensional interventions to prevent frailty and cognitive impairment in aging populations.

4. The impact of frailty on human cognition

4.1. *Influence of frailty on cognitive diagnosis and prognosis*

In a systematic review of longitudinal studies, frailty components,

particularly slowness and muscle weakness, were associated with poorer cognitive outcomes, including memory deficits, dementia onset, and increased mortality risk. Cross-sectional studies similarly indicate a direct relationship between frailty and cognitive impairment in older populations (Brigola et al., 2015). Another systematic review found an association between physical frailty and MCI, identifying slower gait speed, reduced grip strength, advanced age, a greater number of comorbidities, poorer cognition, and female sex as significant risk factors for frailty (Kiiti Borges et al., 2019). Interestingly, the UK Biobank, a large, prospective cohort study, demonstrated an association between frailty and increased dementia risk, independent of genetic predisposition. This suggests that frailty mediates the relationship between dementia, lifestyle factors, and genetic risk, particularly in individuals with low frailty scores (Ward et al., 2022). Within MCI subtypes (amnestic and non-amnestic MCI), higher frailty increased the risk of dementia, especially in non-amnestic MCI, suggesting that frailty may serve as a predictive element for cognitive decline (Ward et al., 2021). An observational retrospective study examining clinical records of outpatients with amnesic MCI (aMCI) found significant associations between age, male sex, Mini–Mental State Examination scores, and frailty index scores with the likelihood of MCI conversion to overt dementia (Trebbastoni et al., 2017). A cross-sectional study analyzing data from three American cohorts (National Alzheimer's Coordinating Center [NACC], Rush Memory and Aging Project [MAP], and Alzheimer's Disease Neuroimaging Initiative [ADNI]) showed an inverse relationship between Frailty Index (FI) scores and MMSE scores, suggesting that frailty severity modulates cognitive test outcomes (Canevelli et al., 2013). Additionally, frailty may influence the expression and progression of Alzheimer's Disease (AD) neuropathology through cumulative damage (Wallace et al., 2019). Again, frailty increases the likelihood of developing dementia, independent of neuropathological burden (e.g., neurofibrillary tangles and amyloid plaques) (Wallace et al., 2021). In the ADNI database, participants with abnormal biomarker values and higher FI scores had a greater prevalence of dementia compared to those with FI scores ≤ 0.20 (Canevelli et al., 2021). Despite a close link between frailty and AD biomarkers, evidence on this complex relationship remains limited due to internal and external influences (Wallace et al., 2018). Frailty index scores have also been observed to accelerate in the years leading up to dementia onset (4–9 years before), suggesting frailty may precede dementia itself (Ward et al., 2024). The Frailty Index and pre-frailty, as categorical variables, are independently associated with caregiver burden measured by the Dementia Behaviour Disturbance Scale (DBD) and the Zarit Burden Interview (ZBI) (Sugimoto et al., 2018). These findings suggest both direct and indirect associations between frailty and dementia, underscoring the multidimensional nature of AD and dementia, which extends beyond neuropathological hallmarks and biomarkers (Canevelli et al., 2022; Canevelli et al., 2024). In fully developed neurodegenerative disease, frailty influences the expression and severity of dementia outcomes (Kelaiditi et al., 2016). A meta-analysis and systematic review assessing the association between frailty, pre-frailty, MCI, and adverse outcomes in older adults found that frailty and MCI are both associated with higher mortality and disability risks (Chen et al., 2022). In a 90-year cohort study in Sichuan Province, China, combined frailty and cognitive impairment increased mortality risk more than either frailty or cognitive impairment alone (Hao et al., 2018). Similarly, in a nationally representative sample of community-dwelling older Americans, combining physical and cognitive vulnerability provided a more accurate risk profile for adverse outcomes (Aliberti et al., 2019).

However, frailty may also be reversible, as a longitudinal study showed that sustained frailty remission was associated with a lower risk of developing dementia, particularly in younger participants ($\leq$80 years) and men (Wang et al., 2024). The I-Lan Longitudinal Aging Study (ILAS), a population-based cohort, demonstrated that cognitive frailty can be mitigated with physical and cognitive training exercises (Lin et al., 2022). In the Italian Longitudinal Study on Aging, cognitive frailty showed significant predictive value, supporting the potential for reversibility with intervention (Solfrizzi et al., 2017). In a secondary analysis of a prospective cohort, older adults with cognitive frailty combined with other factors such as sedentary behavior, weakness, and exhaustion had higher mortality risks (Vargas-Torres-Young et al., 2022). These findings emphasize the importance of predictive models for frailty progression, like those used for other conditions like cardiovascular diseases, as increased frailty is not necessarily irreversible (Howlett et al., 2021). Thus, frailty influences the risk factors, clinical presentation, and outcomes associated with cognitive impairment along the continuum from brain integrity to MCI and dementia. For older adults with AD, considering frailty as part of a comprehensive, evidence-based treatment plan aligned with individual risk profiles is essential (Dyer et al., 2023). Furthermore, frailty serves as a risk factor for delirium, sharing phenotypic features such as modifiable and non-modifiable risk factors (aging, loneliness, sociodemographic factors, depression, sleep disturbances, chronic pain, medications, poor nutrition, chronic diseases), pathophysiological pathways (inflammation, vascular burden, microvascular changes, altered metabolism), clinical symptoms (motor, cognitive, affective, sleep-wake cycle disturbances), and outcomes (hospitalization, prolonged stay, new disability, institutionalization, and mortality) (Bellelli et al., 2017, 2024). Multimorbidity, defined as the presence of two or more chronic diseases, interacts with frailty to impact cognitive impairment expression and progression. A prospective cohort study of nearly half a million middle-aged and older individuals (UK Biobank cohort) found that frailty and pre-frailty were strongly associated with multimorbidity, characterized by long-term conditions and mortality risk (Hanlon et al., 2018). The Swedish National Study on Aging and Care showed that multimorbidity, particularly neuropsychiatric, sensory impairment, cancer, and cardiovascular patterns, has a significant impact on cognitive decline and life expectancy, with certain disease combinations associated with incident physical frailty (Tazzeo et al., 2021; Valletta et al., 2023; Patel et al., 2024). Thirteen diseases have been identified as notable multimorbidities in neurodegenerative conditions, including hypertension, lipid metabolism disorders, diabetes, chronic ischemic heart disease, and mental disorders (Amini et al., 2024). In a population-based study of over 600,000 individuals aged 65 +, dementia increased risks for mortality, emergency department visits, hospital admissions, and discharge to long-term care, especially with high multimorbidity (Tonelli et al., 2017). However, a causal association between frailty and multimorbidity remains unproven, as many frail individuals have comorbidities, but multimorbidity is not synonymous with frailty (Vetrano et al., 2019; Villacampa-Fernández et al., 2017). Older adults with frailty are at the highest risk for hospitalization (Chang et al., 2018), and cognitive frailty independently predicts adverse outcomes like falls, disability, and hospitalization (Zhang et al., 2022). Hospitalized older adults with both frailty and cognitive impairment at admission face an increased risk of new ADL dependency one-year post-discharge (Zeng et al., 2022). Cognitive impairment affects care needs during and after hospitalization, increasing risks of complications and poor outcomes and emphasizing the need for preventive strategies (Fogg et al., 2018). Hospital care should consider individual abilities, social connections, and support systems to ensure smooth transitions in care and maintain supportive relationships among patients, caregivers, families, and staff (Nicholson et al., 2017).

4.2. Approaches to the treatment of cognitive frailty

The potential reversibility of cognitive frailty depends on overall health status and modifiable factors, including polypharmacy, psychiatric conditions, metabolic deficiencies, sleep disturbances, and sensory deficits. Effective strategies include raising dementia awareness, accurate identification and documentation, providing staff with training for person-centered dementia care, and creating a supportive physical environment that aids decision-making and includes family support (Ma

and Chan, 2020; Nader et al., 2023). Early identification of cognitive frailty during clinical evaluations is essential. In a retrospective study in Italian Centers for Cognitive Decline and Dementia in the Lombardy Region, mild frailty was observed in 40 % of patients, while moderate-to-severe frailty affected approximately a quarter of the population. This study underscored that frailty status, even when cognitive function is preserved, serves as a critical indicator for identifying individuals who may benefit from Comprehensive Geriatric Assessment (CGA) to slow dementia progression and improve outcomes (Bellelli et al., 2023). Targeted interventions including deprescribing, structured exercise, and increased caloric intake demonstrated the importance of addressing multiple factors to potentially reverse cognitive frailty (Inskip et al., 2020). CGA in frailty clinics, covering assessments of functional ability, physical and psychological health, nutrition, cognitive status, and social support, offers valuable insights into the prevalence and determinants of cognitive frailty across diverse communities, with evidence suggesting improved outcomes when tailored to cultural and socioeconomic contexts (Welsh et al., 2014; Woo et al., 2005; Bhattarai et al., 2024a,b).

A new clinical approach is emerging that views frailty as a cumulative imbalance between damage and repair over an individual's life. This paradigm identifies sources of damage, resilience factors (e.g., vaccination), and reparative interventions, including prevention and rehabilitation (Howlett et al., 2021). In Ireland, a randomized controlled trial in primary care highlighted that exercise focused on strength and protein intake improved health outcomes for older adults and counteracted frailty, contrasting with drug-based treatments that often leave patients feeling that their condition is irreversible (Travers et al., 2023; Archibald et al., 2020). Despite the importance of addressing frailty, it is often underrepresented in clinical trials for dementia and MCI, leading to potential underestimations of frailty's severity and an incomplete definition that focuses solely on physical deficits (Wightman et al., 2023). An umbrella review including 27 studies on MCI and dementia revealed that physical activity/exercise improves cognitive and non-cognitive outcomes, although evidence strength was rated from very low to moderate, with many systematic reviews demonstrating high risk of bias (Demurtas et al., 2020). Another comprehensive review found limited conclusive evidence for biochemical markers in exercise interventions but noted promising results for specific cognitive and motor functions, although impacts on functional autonomy and psychosocial outcomes remain inconclusive (Furtado et al., 2023).

A literature review using the GRADE framework supported by expert discussion found that higher physical activity and exercise levels are associated with reduced dementia risk. This is mediated by modulation of neurotrophic factors, decreased inflammation, and improvements in socioemotional aspects like sleep, depression, and anxiety (Veronese et al., 2023). Studies involving walking, Otago exercises, resistance and balance training suggest that exercise interventions are beneficial for cognitive frailty in older adults, despite some methodological limitations (Li et al., 2022). As far as nutritional interventions, while individual macro- and micronutrients show cognitive benefits (Vauzour et al., 2017), such as those observed with the Mediterranean diet (Masana et al., 2017), strong evidence for nutrient supplementation alone in cognitive health remains limited. Instead, health promotion strategies emphasizing a balanced diet with synergistic interactions among dietary components have been recommended as part of a multidomain intervention approach (Monti et al., 2015; Dominguez, Barbagallo, 2017). Indeed, innovative approaches such as Virtual Reality (VR) cognitive training, combined with aerobic exercise, have shown potential in promoting cognitive function and reducing physical frailty (Peng et al., 2024; Kwan et al., 2024). Additionally, machine learning and artificial intelligence (AI) are increasingly applied to large datasets to better understand cognitive risk mechanisms and develop targeted interventions (Wang et al., 2022).

Table 2
Open research questions in cognitive frailty.

Category	Research Question / Hypothesis	Key Focus
Biomarker identification	What are the most reliable biomarkers for early detection of cognitive frailty, and how can they predict outcomes?	Multi-system biomarkers (inflammatory, hormonal, metabolic) for comprehensive profiling.
Mechanisms of reversibility	To what extent is cognitive frailty reversible, and what factors influence its progression or regression?	Identifying pathways for personalized interventions to reverse cognitive frailty.
Role of lifestyle interventions	How do physical activity, social engagement, and cognitive stimulation interact to influence cognitive frailty?	Refining intervention strategies based on population-specific needs.
Impact of technology and digital health	What is the role of AI, Virtual Reality, and remote monitoring in cognitive frailty management?	Enhancing accessibility and adherence to cognitive frailty prevention programs.
Social determinants of cognitive frailty	How do socioeconomic factors, resource access, and psychosocial dynamics affect cognitive frailty?	Developing targeted interventions for at-risk populations and shaping health policies.

AI: Artificial Intelligence

5. Conclusions

In conclusion, cognitive frailty represents a critical intersection of physical and cognitive decline, embodying the cumulative impact of aging, lifestyle, environmental, and biological factors on overall health. This integrative construct underscores the need for a multidimensional approach that goes beyond treating cognitive symptoms in isolation to address the entire spectrum of frailty. By identifying and targeting modifiable factors—such as physical inactivity, nutritional deficiencies, polypharmacy, and social isolation—researchers and clinicians can potentially slow or even reverse cognitive frailty progression. Recent advances in personalized interventions, such as tailored exercise regimens, dietary optimization, and cognitive training, combined with technological innovations like Virtual Reality and machine learning, bring new hope to treatment approaches. Nevertheless, many aspects of cognitive frailty remain poorly understood, requiring further investigation. Table 2 concisely organizes the key research gaps to guide future studies and practical applications in cognitive frailty management.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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