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The Interplay Between Frailty and Alzheimer's Disease: Pathophysiological Mechanisms, Biomarker Landscapes, and Integrated Therapeutic Strategies

Meirou Liang[1,2], Jiajun Liu[3], Yuzhe Zhang[3], Hui Wang[1,2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Xi'an Hospital of Traditional Chinese Medicine, Xi'an 710021, Shaanxi, China
[3]Department of Neurosurgery, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi, China
**Correspondence Author*

Abstract: ***Background:*** ***Frailty and Alzheimer's disease (AD) represent two of the most prevalent and debilitating conditions associated with human aging. Frailty is a dynamic, multidimensional syndrome characterized by a loss of physiological reserve and homeostatic resilience across multiple organ systems. Emerging epidemiological and clinical evidence demonstrates that physical frailty substantially accelerates cognitive decline and increases the incidence of AD in cognitively intact older adults. Conversely, neuropathological burden lowers the threshold for manifest physical frailty.*** ***Key Findings:*** ***This review systematically examines the intricate crosstalk between frailty and AD. We detail shared molecular pathophysiological mechanisms, including chronic low-grade systemic inflammation ("inflammaging"), oxidative stress, cellular senescence, mitochondrial decay, and neuroendocrine axis dysregulation. Furthermore, we evaluate common diagnostic landscapes and biomarker signatures, focusing on cerebrospinal fluid (CSF)Aβ42dynamics, plasma markers, blood-based metabolomics—notably the selective depletion of the dietary antioxidant ergothioneine (ERG)—and subcortical-frontal network alterations manifested through motoric cognitive risk (MCR) phenotypes. Finally, we analyze therapeutic implications, contrasting the potential adverse impacts of conventional anti-dementia pharmacotherapies on physical frailty with emerging multimodal lifestyle, nutritional (e.g., ERG supplementation), and targeted metabolic interventions.*** ***Conclusions:*** ***Recognizing frailty and AD as interrelated manifestations of accelerated biological aging provides a critical paradigm shift. Developing standardized, high-sensitivity screening tools and dual-target therapeutic strategies will be essential for advancing precision geriatric care and mitigating the global burden of neurodegenerative and functional decline.***

Keywords: Frailty, Alzheimer's Disease, Neuroinflammation, Inflammaging, Oxidative Stress, Mitochondrial Dysfunction, Ergothioneine, Motoric Cognitive Risk, Biomarkers, Multimodal.

1. Introduction

The rapidly accelerating demographic shift toward an aging global population presents unprecedented challenges to clinical medicine and public health systems worldwide. Among age-related pathologies, neurodegenerative disorders and geriatric frailty represent the primary drivers of disability, dependence, institutionalization, and mortality in older adults. Alzheimer's disease (AD) [1], the most common neurodegenerative disorder accounting for 60% to 80% of all dementia cases, currently affects over 50 million individuals globally—a figure projected to triple by mid-century. Concurrently, physical frailty affects an estimated 4% to 59% of community-dwelling older adults, depending on the diagnostic criteria employed [2, 3].

Traditionally, physical frailty and cognitive disorders were investigated as separate geriatric syndromes within distinct medical specialties—geriatrics and neurology, respectively. However, a growing body of longitudinal epidemiological, pathological, and biomarker research has challenged this historical dichotomy. Frailty is no longer viewed solely as a physical or motor deficit; rather, it is recognized as a complex, heterogeneous state resulting from a multi-system decline in physiological reserve and stress resilience [4, 5]. This multi-system vulnerability closely mirrors the systemic and metabolic alterations observed throughout the AD clinical continuum, which spans from preclinical pathology and Mild Cognitive Impairment (MCI) to overt dementia [6, 7].

Importantly, cross-sectional and prospective studies indicate that the presence of physical frailty markedly modifies the relationship between neuropathology and clinical dementia. Individuals with significant physical frailty are substantially more likely to express clinical symptoms of dementia at lower thresholds of amyloid-beta (Aβ) plaques and neurofibrillary tangles than their non-frail peers [8, 9]. Furthermore, physical deficits such as reduced gait speed, muscle weakness, and unintentional weight loss often precede overt cognitive impairment, pointing to shared underlying pathophysiological cascades [3, 10].

Despite these clear clinical overlaps, critical gaps remain in our understanding of how systemic frailty and central neurodegeneration interact at the cellular and molecular levels. This review aims to synthesize current knowledge regarding the interplay between frailty and AD. Specifically, we detail:

1) Operational definitions and epidemiological interconnections between frailty phenotypes and AD progression.

2) Shared molecular mechanisms, focusing on inflammaging, oxidative stress, mitochondrial bioenergetic failure, and neuroendocrine dysregulation.

3) Diagnostic biomarkers and clinical trajectories, including CSF/plasma signatures, whole-blood metabolomics (specifically ergothioneine), and motor-cognitive impairments.

4) Integrated therapeutic, nutritional, and non-pharmacological management strategies aimed at delaying both cognitive and physical decline.

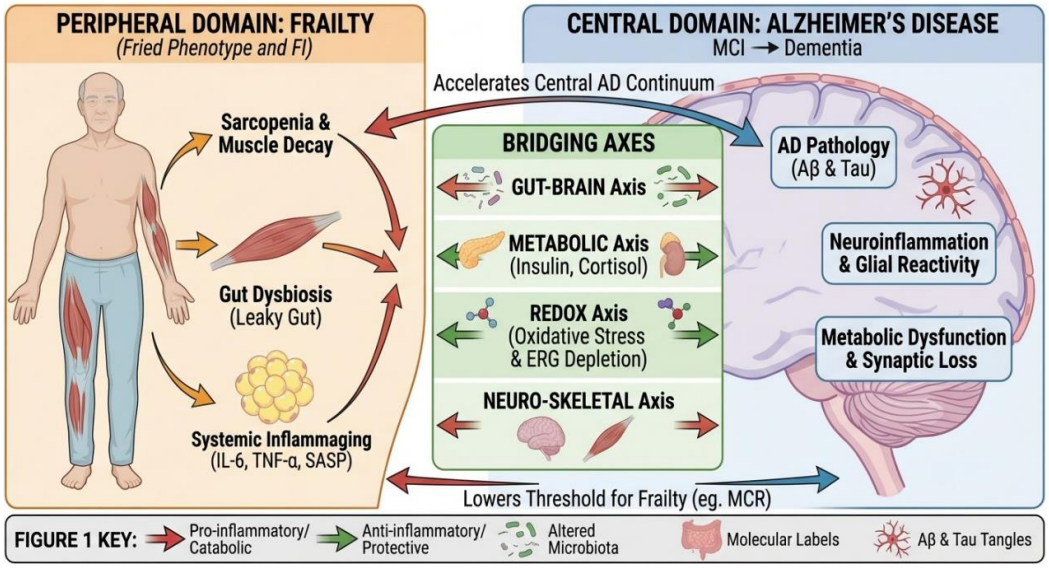

Figure 1: Bidirectional pathophysiological crosstalk between physical frailty and the Alzheimer's disease continuum

2. Operational Definitions, Conceptual Models, and Epidemiological Interconnections

2.1 Operational Models of Frailty

Establishing a standardized diagnostic definition for frailty has proven challenging due to its inherently complex, multi-organ etiology. To date, three principal theoretical and operational models dominate clinical and epidemiological research:

The Physical Frailty Phenotype (Fried Model): Developed by Fried and colleagues using data from the Cardiovascular Health Study, this model conceptualizes frailty as a distinct biological syndrome driven by energy dysregulation, neuroendocrine dysfunction, and sarcopenia [3]. It is operationally defined by the presence of three or more of the following five physical criteria:

1) Unintentional weight loss (≥10lbsor≥5%of body weight in the preceding year).

2) Self-reported exhaustion (identified via validated depression rating scales).

3) Muscle weakness (reduced handgrip strength measured via dynamometry, adjusted for sex and body mass index).

4) Slow gait speed (timed walking over a standard 15-foot distance).

5) Low physical activity level (kcal expended per week) Individuals meeting 1 or 2 criteria are categorized as "pre-frail," representing a vulnerable transitional state with a high potential for reversibility prior to onset of overt functional disability [3, 11].

The Cumulative Deficit Model (Rockwood Frailty Index): Developed by Rockwood and colleagues, this model conceptualizes frailty as a continuous state of multidimensional vulnerability quantified by counting accumulated health deficits. These deficits encompass clinical signs, chronic disease diagnoses, lab abnormalities, cognitive impairments, and limitations in activities of daily living (ADLs). The Frailty Index (FI) is calculated as the ratio of deficits present relative to the total number evaluated (typically 30 to 70 items). Unlike the categorical physical phenotype, the FI provides a continuous score reflecting systematic physiological reserve exhaustion [12, 13].

Bio-Psycho-Social Models and Cognitive Frailty: Recognizing that physical constructs exclude mood and cognitive domains, integrated frameworks incorporate psychological, cognitive, and social determinants of vulnerability [5, 13]. In 2013, an international consensus group organized by the International Academy on Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) introduced the construct of "Cognitive Frailty". It is defined by the simultaneous presence of physical frailty (Fried phenotype) and cognitive impairment (Clinical Dementia Rating scale = 0.5) in older adults without concurrent vascular or primary neurodegenerative dementia [5].

2.2 Epidemiological and Longitudinal Crosstalk

A growing body of prospective cohort studies confirms a powerful bidirectional association between physical frailty and cognitive deterioration. In a landmark analysis of the Rush Memory and Aging Project (MAP), Boyle et al. demonstrated that physical frailty independently predicted a significantly higher incidence of mild cognitive impairment (MCI) and accelerated the rate of cognitive decline in community-dwelling older adults over a long-term follow-up period. Frail individuals displayed a more than two-fold increased risk of developing incident Alzheimer's disease (AD) compared to robust peers [8].

Reciprocally, neurodegenerative pathology exerts adverse impacts on systemic physical capacity. Essential cognitive domains, including executive function, spatial processing, and processing speed, rely heavily on subcortical-frontal network integrity [9, 14]. As neurodegeneration degrades these networks, motor coordination, postural balance, and dual-tasking performance deteriorate [9].

This motor-cognitive overlap has led to the formalization of Motoric Cognitive Risk (MCR) syndrome—a pre-dementia construct characterized by slow gait speed combined with subjective cognitive complaints in older adults who retain general functional autonomy and lack overt dementia. Epidemiological studies consistently show that individuals with MCR face a significantly elevated risk of progressing to vascular dementia and AD, positioning MCR as a vital clinical marker for early intervention [9, 15].

2.3 Frailty as a Neuropathological Modifier

In addition to serving as a concurrent risk factor, systemic frailty directly alters the clinical manifestation of AD neuropathology. In a cross-sectional clinical - pathopathological study examining post-mortem brain tissue from the Rush MAP cohort, Wallace et al. established that frailty functions as a crucial moderator in the relationship between central neuropathology and overt clinical dementia.

Specifically, among individuals with low levels of physical frailty (high biological reserve), a substantial burden ofAβplaques and tau neurofibrillary tangles was required to precipitate clinical dementia. Conversely, in highly frail individuals with elevated Frailty Index scores, even minimal to moderate levels of AD neuropathology were sufficient to induce symptomatic dementia. These findings indicate that systemic frailty depletes physiological and brain reserves, rendering central neural circuits far more susceptible to neurodegenerative damage. Moreover, physical frailty often triggers secondary psychological burdens—such as anxiety, depression, loss of independence, and social withdrawal—which exacerbate neuroendocrine dysfunction and further accelerate the neurodegenerative cascade [7, 13].

3. Shared Pathophysiological Mechanisms

The complex interplay between physical frailty and Alzheimer's disease (AD) is governed by systemic, multi-organ pathophysiological cascades. Rather than acting as parallel, independent age-related phenotypes, systemic physiological decline and central neurodegeneration share mutually reinforcing biological drivers. This section explores four core mechanistic axes: chronic systemic inflammation, oxidative stress with cell senescence, mitochondrial bioenergetic decay, and neuroendocrine-metabolic breakdown.

3.1 Neuroinflammation & Inflammaging

A hallmark of biological aging is "inflammaging"—a state of chronic, sterile, low-grade systemic inflammation characterized by elevated circulating levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF−α), and C-reactive protein (CRP). In physical frailty, peripheral inflammaging originates primarily from senescent skeletal muscle, visceral adipose tissue, and immune system senescence (immunosenescence) [16].

Peripheral inflammatory mediators compromise the integrity of the blood-brain barrier (BBB) [17]. Circulating IL-6 and TNF−α disrupt endothelial tight junction proteins (such as claudin-5 and occludin), promoting capillary leakage and pericyte degeneration. This breach permits peripheral cytokines and inflammatory monocytes to infiltrate the central nervous system (CNS) parenchyma, triggering microglial activation [18].

In the healthy brain, microglia maintain homeostasis through phagocytic clearance of metabolic waste and synaptic pruning. Under chronic inflammatory stress, microglia shift from a neuroprotective homeostatic/anti-inflammatory phenotype (M2-like) toward a chronically activated pro-inflammatory state (M1-like). Pro-inflammatory microglia unleash neurotoxic factors, includingIL−1β, IL-6, TNF−α, and reactive nitrogen species, which drive reactive astrogliosis (A1 astrocyte conversion). Reactive A1 astrocytes lose their capacity to support neuronal synaptic function and promote oligodendrocyte toxicity [19].

Simultaneously, peripheral muscle decay (sarcopenia) interacts with CNS damage via the Gut-Brain-Muscle Axis [20]. Age-associated gut dysbiosis alters intestinal barrier integrity ("leaky gut"), releasing lipopolysaccharide (LPS) into systemic circulation. LPS stimulation of Toll-like receptor 4 (TLR4) cascades exacerbates peripheral sarcopenia while simultaneously signaling through the vagus nerve and circumventricular organs to fuel microglial polarization and accelerate neurodegeneration [19, 20].

3.2 Oxidative Stress & Cellular Senescence

Uncontrolled oxidative stress serves as a crucial molecular bridge connecting physical decline to neurodegeneration. Mitochondrial leakage and enzymatic dysregulation yield excessive Reactive Oxygen Species (ROS), overwhelming endogenous antioxidant defenses [21]. Elevated ROS induces extensive lipid peroxidation, protein carbonylation, and oxidative DNA/RNA damage in both skeletal muscle fibers and cerebral neuronal networks [21, 22].

In AD, toxic amyloid-beta oligomers (Aβ1−42) bind to neuronal membranes and receptor complexes, stimulating NADPH oxidase (NOX) activity and spiking intracellular ROS generation [22, 23]. This central ROS release accelerates tau hyperphosphorylation through the activation of stress-sensitive kinases, such as glycogen synthase kinase-3 beta (GSK−3β) and p38 mitogen-activated protein kinase (p38 MAPK) [23]. Systemically, chronic oxidative stress disrupts muscle satellite cell regeneration, blunting muscle protein synthesis and promoting the functional loss characteristic of physical frailty [21, 22].

Persistently high ROS levels and DNA damage activate the p53−p21CIP1/WAF1and p16INK4a−retinoblastoma (Rb) pathways, triggering cellular senescence. Senescent cells

enter an irreversible cell cycle arrest while remaining metabolically active [24]. They secrete a toxic array of pro-inflammatory cytokines, chemokines, matrix metalloproteinases, and growth factors known collectively as the Senescence-Associated Secretory Phenotype (SASP). In skeletal muscle, SASP secretion accelerates matrix degradation and muscle fiber atrophy. Within the brain, senescent astrocytes and microglial cells accumulate, creating an inflammatory microenvironment that destabilizes synaptic integrity, damages neuronal spines, and impairs long-term potentiation (LTP) [25].

3.3 Mitochondrial Dysfunction, Autophagy & Bioenergetic Failure

Mitochondria are central regulators of energy homeostasis, cellular survival, and apoptosis [26]. Biological aging, physical frailty, and AD share marked mitochondrial decay and bioenergetic failure [27]. Genomic and epigenomic instability—manifested as somatic mitochondrial DNA (mtDNA) mutations, telomere attrition, and aberrant DNA methylation—disrupt the transcription of essential mitochondrial electron transport chain (ETC) subunits [28].

According to the Mitochondrial Cascade Hypothesis of AD, inherited or acquired mitochondrial defects precede amyloid accumulation and tau pathology. Impairments in ETC complexes (particularly Complexes I and IV) reduce ATP production, cause loss of mitochondrial membrane potential ($\Delta\Psi m$), and trigger opening of the mitochondrial permeability transition pore (mPTP). In the brain, this energy failure compromises ion-motive ATPases, disrupting neuronal membrane potentials and inducing excitotoxic synaptic loss. In peripheral skeletal muscle, ETC dysfunction reduces maximum oxidative capacity (VO2max), leading directly to muscle fatigue, slow walking speed, and low physical grip strength [26, 28].

Under physiological conditions, damaged mitochondria are selectively cleared through mitophagy, an autophagic pathway mediated by PINK1 (PTEN-induced kinase 1) and Parkin. In both frail and AD tissues, mitophagic flux and general macroautophagy are significantly suppressed. Accumulation of dysfunctional, uncleared mitochondria results in continuous ROS leakage and cytoplasmic release of mtDNA fragments. Intracellular mtDNA acts as a damage-associated molecular pattern (DAMP), binding cGAS-STING (cyclic GMP-AMP synthase - stimulator of interferon genes) sensors and triggering innate immune signaling, which reinforces systemic inflammaging and central neuroinflammation [29].

3.4 Neuroendocrine Axis & Metabolic Dysregulation

Systemic resilience depends on precise neuroendocrine regulation [30]. A key driver of both physical frailty and cognitive deterioration is chronic hyperactivation and dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Age-related loss of hippocampal glucocorticoid receptor-mediated negative feedback causes sustained elevations in circulating cortisol levels. Glucocorticoid toxicity damages hippocampal CA1 neurons, blunting neurogenesis and impairing memory consolidation [30, 31]. Systemically, chronic cortisol elevation drives muscle catabolism, suppresses osteoblast activity, increases visceral adiposity, and accelerates physical frailty.

Simultaneously, systemic and central metabolic signaling pathways undergo progressive dysregulation [31, 32]:

Insulin Resistance: Central insulin signaling regulates synaptic plasticity, dendritic spine density, and neuroprotective responses. Peripheral insulin resistance (often accompanying frailty) impairs brain insulin transport across the BBB, causing “brain insulin resistance” [31]. This state inactivates Akt signaling, leading to uninhibited GSK−3βactivity, increasedAβ accumulation, and enhanced tau phosphorylation [32].

IGF-1 Signaling Suppression: Insulin-like Growth Factor 1 (IGF-1) promotes muscle protein synthesis and neuronal survival. Downregulation or blunted sensitivity of the IGF-1 axis accelerates sarcopenia in the periphery while depriving cortical neurons of essential trophic support, promoting apoptosis [30, 32].

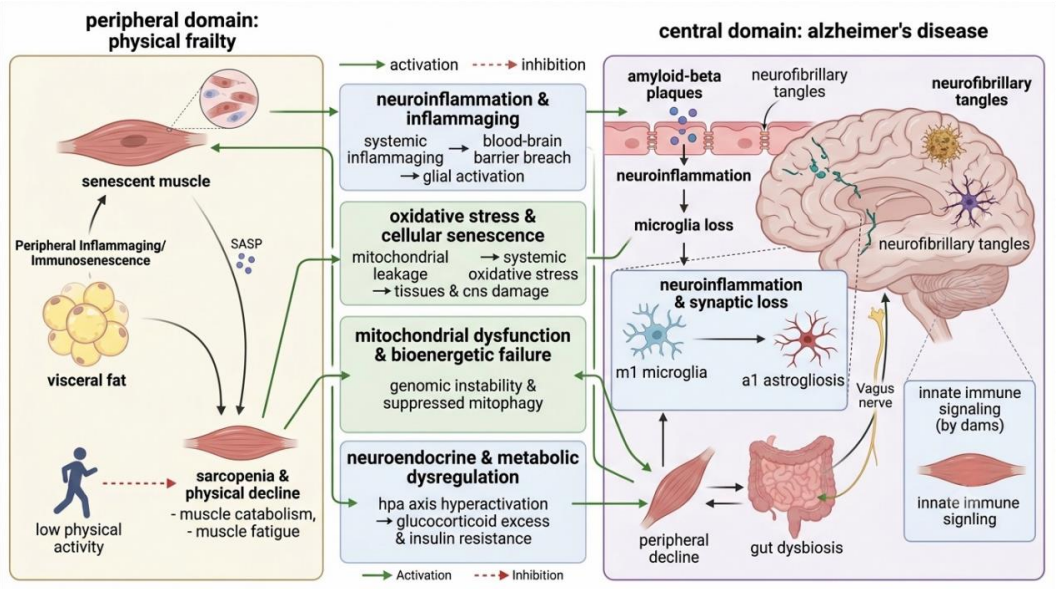

Figure 2: Molecular and cellular mechanisms underlying systemic crosstalk between physical frailty and Alzheimer’s disease

4. Diagnostic Landscapes & Biomarker Associations

Accurate clinical identification of individuals at the intersection of physical frailty and Alzheimer's disease (AD) requires a combination of neurochemical biomarkers, metabolomic profiling, and motor-cognitive functional evaluations. This section synthesizes fluid biofluid markers, whole-blood metabolomics, and functional trajectories that map onto shared subcortical-frontal neural network degeneration.

4.1 Cerebrospinal Fluid (CSF) & Plasma AD Biomarkers

The transition along the AD continuum is characterized by classical fluid biomarker alterations, notably decreased levels of amyloid-beta 42(Aβ42) or reduced Aβ42/Aβ40ratios, accompanied by elevations in phosphorylated tau (p-Tau181 and p-Tau217) and Neurofilament Light Chain (NfL) [33]. In longitudinal studies, lower baseline CSF Aβ42 concentrations independently predict accelerated rates of domain-specific cognitive decline—particularly in executive control, attention, and processing speed [33, 34].

In frail populations, these neuropathological fluid signatures display distinct clinical dynamics. Systemic frailty interacts synergistically with elevated plasma NfL (a sensitive biomarker of axonal degeneration) and p-Tau217, accelerating cognitive deterioration even in individuals with moderate amyloid burden. Furthermore, circulating plasmaAβ42/Aβ40 reductions combined with elevated NfL closely correlate with peripheral muscle mass loss, suggesting that axonal loss and sarcopenia share continuous neuro-skeletal degenerative pathways [34, 35].

4.2 Metabolomic Profiling: Ergothioneine (ERG) and Beyond

Metabolomics provides crucial insights into systemic bioenergetic deficits in aging. Ergothioneine (ERG) is a water-soluble, food-derived amino acid derivative with potent antioxidant and cytoprotective properties [36]. Vertebrates cannot synthesize ERG endogenously and rely on dietary intake, accumulating ERG in high-stress tissues via a specific organic cation transporter, OCTN1 (encoded by SLC22A4) [37].

Non-targeted whole-blood metabolomic analyses have identified ERG as a selective biomarker distinguishing healthy aging from frailty and neurodegeneration [38, 39]. Research by Teruya et al. demonstrated that blood ERG levels are markedly depleted in individuals diagnosed with physical frailty and dementia, whereas levels remain relatively preserved in isolated sarcopenia. Depletion of ERG impairs free-radical scavenging, increasing susceptibility to systemic oxidative injury [37, 39]. Beyond ERG, untargeted metabolomics in frail AD cohorts reveals systemic alterations in long-chain acylcarnitines, essential amino acids (such as branched-chain amino acids, BCAAs), and membrane phospholipids, reflecting disrupted mitochondrial lipid β−oxidation and systemic protein catabolism [38, 39].

4.3 Motor-Cognitive Trajectories and Functional Deficits

Physical frailty measures—specifically reduced handgrip strength and slow walking speed—are closely tied to central nervous system pathology. Motor performance and executive function rely heavily on shared neural substrates, particularly prefrontal-subcortical circuits and frontoparietal control networks [10].

Longitudinal assessments demonstrate that physical weakness and gait slowing often precede detectable memory impairment. Dual-task motor testing (e.g., assessing walking speed while simultaneously performing verbal or arithmetic tasks) unmasks subclinical executive dysfunction and heightened fall risk. Structural and functional neuroimaging confirms that deficits in executive control and reduced grip strength correlate with frontal lobe atrophy, white matter hyperintensities, and disrupted subcortical connectivity. Thus, objective physical frailty metrics serve as direct clinical proxies for prefrontal network deterioration in early neurodegenerative states [40].

5. Therapeutic Interventions, Prevention Strategies, and Clinical Management

Managing older adults presenting with both physical frailty and Alzheimer's disease (AD) requires a unified clinical framework that optimizes disease-modifying therapies while avoiding treatments that exacerbate systemic vulnerability.

5.1 Pharmacological Management & Pitfalls

Conventional AD pharmacotherapies, including acetylcholinesterase inhibitors (AChEIs; e.g., donepezil, rivastigmine) and NMDA receptor antagonists (memantine), can present clinical challenges in frail patients. AChEI-induced cholinergic gastrointestinal side effects — such as nausea, chronic diarrhea, and anorexia—often trigger rapid unintentional weight loss and muscle wasting, worsening physical frailty. Furthermore, increased vagal tone from AChEIs may cause symptomatic bradycardia and syncope, elevating fall risk [30].

Consequently, therapeutic interest has shifted toward repurposing metabolic and senolytic agents that target shared underlying pathways [41]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs, such as liraglutide) and metformin lower neuroinflammation, improve brain microvascular perfusion, enhance mitochondrial bioenergetics, and reduce systemic insulin resistance. Phase 2/3 clinical trials demonstrate that GLP-1 RAs preserve cerebral glucose metabolism and attenuate cortical atrophy, highlighting their potential as disease-modifying options that address both metabolic dysfunction and cognitive decline [42].

5.2 Nutritional & Antioxidant Strategies

Targeted nutritional interventions offer safe avenues for mitigating systemic oxidative stress and metabolic imbalance. Ergothioneine (ERG)—a diet-derived, thiol-based antioxidant transported via OCTN1—exerts neuroprotective effects by clearing reactive oxygen species (ROS), activating the Nrf2 pathway, and suppressing pro-inflammatory cytokines (IL-6, TNF−α) [36]. Preclinical and translational studies show that

ERG supplementation protects hippocampal neurogenesis, preserves mitochondrial membrane integrity, and reverses spatial memory deficits [43].

At the dietary pattern level, adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet—rich in berries, green leafy vegetables, nuts, and olive oil—is associated with reduced risks of both physical frailty and AD progression. High intakes of polyphenols, omega-3 fatty acids, and essential micronutrients attenuate systemic inflammaging and support synaptic membrane homeostasis [44].

5.3 Non-Pharmacological Multimodal Interventions & Dual Clinical Assessment

Isolated monotherapies rarely reverse complex geriatric syndromes. The FINGER Model (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) established that a 2-year multidomain intervention — combining multi-component physical exercise (aerobic and progressive resistance training), cognitive training, vascular risk management, and nutritional guidance — significantly improves cognitive performance and physical resilience in at-risk older adults [45]. Multi-component exercise stimulates brain-derived neurotrophic factor (BDNF) synthesis, enhances synaptic plasticity, and counteracts sarcopenia [46].

To facilitate early diagnosis, clinical practices are adopting unified dual-screening protocols. Combining physical frailty metrics (e.g., electronic handgrip dynamometry and dual-task gait speed testing) with cognitive screening (e.g., MoCA) and blood-based biomarkers (plasma p-Tau217 and NfL) enables early stratification of high-risk "Cognitive Frailty" cohorts [47].

6. Current Challenges, Future Perspectives, and Conclusions

6.1 Methodological Limitations & Emerging Horizons

A major challenge in translating research into clinical practice is the heterogeneity of frailty metrics used across clinical trials (ranging from Fried's physical phenotype to Rockwood's continuous index), which complicates cross-study comparisons [30]. Additionally, standard clinical assessments often lack the sensitivity required to capture subtle, early-stage motor-cognitive fluctuations [47].

Emerging research technologies promise to overcome these limitations: Single-Cell Multi-Omics: ① Single-nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics are unravelling precise microglial and astrocytic senescent subpopulations across human cortical layers [36, 42].

② Microbiome Profiling: High-resolution metagenomics helps map gut microbiota shifts driving systemic inflammaging along the gut-brain-muscle axis [44].

③ Digital Health Markers: Wearable gait sensors and artificial intelligence algorithms can continuously quantify subclinical micro-gait parameters (such as stride time variability and double-support time) during daily life, serving as non-invasive digital biomarkers for cognitive frailty [47].

6.2 Concluding Remarks

Physical frailty and Alzheimer's disease represent intertwined manifestations of systemic biological aging [30, 45]. Viewing neurodegeneration through a broader systemic lens highlights the importance of moving beyond single-target therapies. Integrating blood-based biofluid biomarkers, digital motor tracking, metabolic therapeutics, and multimodal lifestyle interventions offers a promising path toward advancing precision geriatric medicine and preserving functional autonomy in aging populations [45, 47].

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