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REVIEW

Emerging biomarkers and screening for cognitive frailty

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Abstract Physical frailty and cognitive frailty are two important targets of secondary intervention in aging research to narrow the gap between life and health span. The objective of the present narrative review was to examine clinical and epidemiological studies investigating the recently proposed construct of cognitive frailty and its subtypes, with a focus on operational definitions, clinical criteria, and emerging biomarkers potentially useful for the screening of this novel entity. Both physical frailty and frailty indexes with a multidimensional nature were associated with late-life cognitive impairment/decline, incident dementia, Alzheimer's disease (AD), mild cognitive impairment, vascular dementia, non-AD dementias, and AD pathology proposing cognitive frailty as a clinical entity with cognitive impairment related to physical causes with a potential reversibility. The new clinical and research AD criteria established by the National Institute on Aging–Alzheimer's Association and the American Psychiatric Association could improve the differential diagnosis of cognitive impairment within the cognitive frailty construct. The emerging biomarkers of sarcopenia, physical frailty, and cognitive impairment will provide the basis to establish more reliable clinical and research criteria for cognitive frailty, using different operational definitions for frailty and cognitive impairment and useful clinical, biological, and imaging markers for this novel clinical construct.

Keywords Alzheimer's disease · Biomarkers · Cognitive screening · Dementia · Frailty · Mild cognitive impairment

Introduction

The major goal of aging research is not only to increase life span, but also to narrow the gap between life span and health span. Aging is a decrease in physiological reserves, which still can support acceptable functioning in the steady state, and cannot adapt to any additional, even physiological stress. Successful aging depends on the homeostatic reserves of different physiological systems. Frailty means an accelerated depletion of homeostatic reserves and increase in susceptibility to adverse health-related outcomes after minor stressor events. This heterogeneous clinical syndrome includes physical, cognitive, and psychosocial domains or phenotypes [1, 2]. Frailty is a critical intermediate status of the aging process that is at increased risk for negative health-related events, including falls, disability, hospitalizations, and mortality. The potential for reversibility of frailty and its different phenotypes suggests that these clinical constructs may be important secondary

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targets for the prevention of dependency and other negative outcomes in older age [2, 3].

In 2006, the term "cognitive frailty" was firstly used in a review article to indicate a particular state of cognitive vulnerability in mild cognitive impairment (MCI) and other similar clinical entities exposed to vascular risk with a subsequent increased progression to overt dementia, particularly vascular dementia (VaD) [4]. From an operational point of view, in 2013, an international consensus group from the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics defined cognitive frailty as an heterogeneous clinical syndrome that is found in older individuals, excluding those with Alzheimer's disease (AD) and other dementias, that is characterized by concurrent physical frailty and potentially reversible cognitive impairment [2, 5]. The identification of cognitive frailty individuals could permit the prompt implement of preventive interventions against adverse health-related outcomes. Physical frailty can be recognized by several simple screening tests. A broad consensus has been reached for the screening of physical pre-frailty or frailty in subjects older than 70 years [6]. However, there is no consensus to screen potentially reversible cognitive impairment in older population. The timeliness of the detection of cognitive impairment greatly influences the results of preventive interventions. It is also little known on what is the minimum work-up/advice that should be given to individuals with early cognitive impairment. The objective of the present narrative review article was to examine clinical and epidemiological studies investigating the recently proposed construct of cognitive frailty and its subtypes, with particular attention to operational definitions and clinical criteria. We also focused on some emerging biomarkers potentially useful for the screening of this novel entity.

Methods

In particular, we reviewed reports from the international literature published before December, 2016. We excluded papers based on frailty in specific patient populations (i.e., chronic kidney disease, HIV, and cancer). This narrative review article was based upon searches of the US National Library of Medicine (PubMed), Ovid MEDLINE, EMBASE, Google Scholar, Web of Science, and Scopus databases using terms to identify the risk exposure (frailty OR physical frailty OR frailty index) combined with terms to determine the outcomes of interest (Alzheimer's disease OR vascular dementia OR dementia OR mild cognitive impairment OR preclinical OR biomarkers OR criteria). A search filter was developed to include only human studies. There were no language restrictions on the search. After this extensive search, we selected the studies that were relevant to the aims of the present narrative review, charting the data, i.e., the information on and from the relevant studies, and reporting a narrative integration of the relevant evidence.

The clinical criteria of cognitive frailty

In 2013, the international consensus group with investigators of the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics convened in Toulouse, France established a first definition for cognitive frailty in older adults [5]. The proposed diagnostic criteria for this novel and heterogeneous clinical age-related condition included the simultaneous presence of physical frailty operationalized with the Cardiovascular Health Study phenotypic/biological model and cognitive impairment diagnosed with a Clinical Dementia Rating (CDR) scale of 0.5 (i.e., questionable dementia, a stage of the dementia continuum similar to MCI) without a concurrent diagnosis of AD or other dementias [5]. More recently, in an attempt to refine the framework for the definition and potential mechanisms of cognitive frailty, two subtypes for this clinical construct were proposed: "potentially reversible" cognitive frailty and "reversible" cognitive frailty [2]. The physical factors should be physical pre-frailty and frailty for both the subtypes. The cognitive impairment of potentially reversible cognitive frailty should be MCI (CDR = 0.5), as proposed by the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics consensus group [5], while the cognitive impairment of reversible cognitive frailty should be pre-MCI subjective cognitive decline (SCD), as recently formulated by the subjective cognitive decline initiative working group that proposed a basic conceptual framework for the study of the common concepts of SCD, pre-MCI SCD, and SCD in preclinical AD [7].

In clinical settings, clinicians have to identify the cognitive changes that may be clinically significant, and also they need to determine the causes of the cognitive impairment. Traditionally, AD has been diagnosed and its course followed based on clinical observations and cognitive testing, and confirmed postmortem by demonstrating amyloid plaques and neurofibrillary tangles in the brain. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) published by the American Psychiatric Association [8] provides diagnosis framework of both major neurocognitive disorder, corresponding to dementia, and mild neurocognitive disorder, partly corresponding to MCI, and also diagnostic criteria for the most common etiologic subtypes of the neurocognitive disorders [8]. However, the terms MCI and mild neurocognitive disorder are not interchangeable, because while the two are inter-related

concepts, there is only moderate agreement between the two constructs [9]. In mild neurocognitive disorder, individuals have modest impairment in one or more cognitive domains by objective cognitive assessment, but is still independent in everyday activities, albeit with greater effort. During this stage, cognitive reserve can potentially compensate and maintain cognition performance by decreased brain reserve, alternative neural networks. Obviously, the DSM-5 diagnosis of mild neurocognitive disorder may be suitable for the screening of cognitive impairment of individuals with cognitive frailty.

The most common cause of MCI is AD. The National Institute on Aging–Alzheimer's Association workgroups developed core clinical criteria to screen for individuals with MCI due to AD [10]. Memory complaints strongly predict incident AD in individuals with normal baseline cognition but not in subjects with impaired baseline cognition [11]. SCD can occur in cognitively normal individuals, which also is part of MCI diagnostic criteria. In MCI individuals, specific aspects of SCD severity and quality may be measured by Subjective Memory Decline Scale [12] and cognitive function instrument [13] developed by the Alzheimer's Disease Cooperative Study to detect early changes in cognitive and functional abilities in individuals without clinical impairment. The cognitive function instrument includes 14 questions that are asked of the participant and a study partner separately. These questions, involved in the full realm of subjective cognitive concerns in the elderly, include items regarding memory decline (e.g., compared to a year ago, memory has declined), appraisal of cognitive difficulties (e.g., misplacing belongings more often), and functional abilities (e.g., need more help remembering appointments) [13]. Responses were coded as 1 for yes, 0 for no, and 0.5 for maybe and were summed to create a total score [14]. During a follow-up of 48 months, both self- and partner-reported Cognitive Function Instrument change were associated with longitudinal cognitive decline. The combination of self- and partner-reported Cognitive Function Instrument change demonstrated a slight advantage over individual report at months 12, 36, and 48, suggesting that the combination was particularly powerful in detecting subtle cognitive decline [14]. In another study, self-report was more accurate than partner report at baseline and month 24, whereas partner report was numerically superior (but did not reach statistical significance) at months 36 and 48 [15]. One possible interpretation is that self-report is more reliably correlated with cognition earlier in the process of decline and partner report might become more useful later with the development of anosognosia due to cognitive impairment [15]. The rapid cognitive screen was a validated instrument to identify amnestic MCI and dementia with good sensitivity and specificity [16].

Other causes of MCI that could result in the decline in cognition include non-AD neurodegenerative disorders, such as Parkinsonism, Lewy body disease, frontotemporal lobar degeneration and prion disease; multiple vascular risk factors and/or the presence of extensive cerebrovascular disease; and depressive, traumatic, and medical comorbidities. The crucial differences between MCI and cognitive frailty are shown in Table 1. However, the final diagnosis of these conditions depends on cerebrospinal fluid (CSF) and/or neuroimaging biomarkers plus neuropsychological

Table 1 Summary of the crucial differences between mild cognitive impairment (MCI) and cognitive frailty

	MCI	Cognitive frailty
Subtypes	Amnestic MCI, MCI with a slight impairment of multiple cognitive domains, single non-memory cognitive domain	Reversible cognitive frailty and potentially reversible cognitive frailty
Etiology of cognitive impairment	MCI due to AD: amnestic MCI due to AD genetic factors and longitudinal decline in cognition MCI due to non-AD dementias	Physical or pre-physical frailty, including risk factors of AD or non-AD dementias
Clinical evaluation	–	Physical or pre-physical frailty
	MCI SCD by patient or informant or clinician	With or without Pre-MCI SCD by patient or informant or clinician
Cognitive evaluation	Objective evidence of impairment in one or more cognitive domains	Reversible cognitive frailty: pre-MCI SCD without objective evidence of cognitive impairment Potentially reversible cognitive frailty: objective evidence of impairment in one or more cognitive domains
Functional abilities	Independence	Independence
Prognosis	Dementia due to AD and non-AD dementias A few patients may regain normal cognition	Many patients may regain normal cognition in reversible cognitive frailty Many patients fail to regain normal cognition, with dementia due to AD and non-AD in potentially reversible cognitive frailty

AD Alzheimer's disease, *SCD* subjective cognitive decline

assessment. In fact, the pathophysiological process of AD has begun many years before the diagnosis of MCI due to AD. The National Institute on Aging–Alzheimer's Association workgroups also established diagnostic clinical criteria for dementia due to AD [17], and research criteria for preclinical stages of AD and MCI due to AD mainly based on biomarkers [10, 18]. Correspondingly, there should be widely accepted research criteria for cognitive frailty.

Epidemiological evidence of cognitive frailty

A recent and growing body of epidemiological evidence suggested that frailty may increase the risk of future cognitive decline and that cognitive impairment may increase the risk of frailty suggesting that cognition and frailty may interact in advancing aging [19], suggesting that frailty may represent a novel modifiable target in early dementia. In fact, in 2011, frailty models and their possible links with predementia and dementia syndromes were reviewed narratively [20], and this topic was updated in another narrative review article [19]. In 2015, the first systematic review on this intriguing topic, also to the light of the proposed cognitive frailty model, reviewed epidemiological evidence suggesting that frailty indexes based on a deficit accumulation model were associated in hospital- and population-based studies with late-life cognitive impairment and decline, incident dementia, and AD [21]. Epidemiological evidence strongly suggested that also physical frailty models may be associated with late-life cognitive impairment and decline, incident AD and MCI, VaD, non-AD dementias, and AD pathology in older persons with and without dementia, thus giving support to identify cognitive frailty as a new clinical condition [21]. Very recently, a meta-analysis suggested that the frailty was a significant predictor of AD, VaD, and all dementia among community-dwelling older people, with frail women at higher risk of incident AD than frail men [22].

More recently, data from the Italian Longitudinal Study of Aging did not support a predictive role of a potentially reversible cognitive frailty model (physical frailty plus MCI) for the development of incident dementia compared with physical frailty or MCI alone in a 3.5-year follow-up [23]. However, in the same study, older individuals with potentially reversible cognitive frailty and high level of inflammation showed a significant additional predictive effect only on the risk of disability, but not of all-cause mortality [23]. In the Italian Longitudinal Study of Aging, the prevalence of cognitive frailty was 1%, increasing with age and more represented in women than in men [23]. Very recent findings from another population-based study, the Singapore Longitudinal Ageing Studies, confirmed that the prevalence of a potentially reversible cognitive frailty model [co-existing physical frailty and cognitive impairment operationalized with a score <23 on the Chinese version of the Mini Mental Score Examination (MMSE)] was 1% [95% confidence interval (CI): 0.5–1.4], but was higher among participants aged 75 and older (5.0%, 95% CI: 1.8–8.1) [24]. Other Japanese findings from the National Center for Geriatrics and Gerontology–Study of Geriatric Syndromes database confirmed a prevalence rate of 1.2% of a potentially reversible cognitive frailty model (physical frailty and cognitive impairment operationalized with two or more impairments in the National Center for Geriatrics and Gerontology—Functional Assessment tool, a 4-domain cognitive tool, indicated by an age-adjusted score of at least 1.5 standard deviations below the reference threshold) [25]. However, the operationalization of different cognitive frailty models and the size of study sample may influence the prevalence of this novel clinical entity. In fact, in 594 Italian community-dwelling older adults, the prevalence rate of a potentially reversible cognitive frailty model (physical frailty and cognitive impairment operationalized with a score <25 on the MMSE) was 4.4% [26].

In the Singapore Longitudinal Ageing Studies, continuous physical frailty score and MMSE score showed significant individual and joint associations with incident mild and major neurocognitive disorder, and potentially reversible cognitive frailty conferred additionally greater risk of incident neurocognitive disorder (mild plus major neurocognitive disorder) [24]. Very recently, findings from the Gait and Brain Study suggested that another model of potentially reversible cognitive frailty (physical frailty plus CDR of 0.5) increased incident rate but not risk for progression to dementia, although, in this sample, the combination of slow gait and cognitive impairment posed the highest risk for progression to dementia [27]. Frailty has been shown to be a dynamic process in older age, characterized by frequent transitions between frailty states over time [28]. In another Chinese study on a community-dwelling cohort of older adults, frailty transitions appear to be independent of progression in cognitive status in earliest stages of cognitive impairment, while mild-to-moderate AD subjects showed associations with age and cognitive deterioration [29], suggesting further evidence for cognitive frailty as a separate clinical entity.

Possible discrepancies in predicting cognitive-related outcomes may arise from different models of cognitive frailty in which cognitive impairment may be operationalized as MCI (potentially reversible cognitive frailty) or pre-MCI SCD (reversible cognitive frailty) and the physical factor may be operationalized as physical pre-frailty or frailty [2, 3]. At present, to the best of our knowledge, there is only one population-based study in which reversible cognitive frailty has been investigated as possible determinant of dementia and its subtypes and all-cause mortality

as well how mechanisms could be associated with reversibility. In fact, very recently, other findings coming from the Italian Longitudinal Study of Aging suggested that a model of reversible cognitive frailty was a short- and long-term predictor of all-cause mortality and overall dementia, particularly VaD [30]. In observational studies like the Italian Longitudinal Study of Aging, in extreme cases, could be of interest to verify that an interaction may reverse the relationship between the risk factor and the outcome. Therefore, it was hypothesized that the role of vascular factors and/or depressive symptoms as effect modifiers could modify the risk of dementia and all-cause mortality linked to the presence of reversible cognitive frailty. In particular, trying to support the reversibility of this new clinical construct, it was focused on the group of people without these risk factors as a proxy of optimal management of these factors. In the Italian Longitudinal Study of Aging, the absence of vascular risk factors and depressive symptoms did not modify the predictive role of reversible cognitive frailty on these outcomes [30]. Probably, the identification of reversibility due to several possible interventions could be more useful in designing randomized clinical trials, i.e., the multidomain preventive trials of cognitive decline and dementia, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability [31]. Finally, some longitudinal population-based studies investigated different cognitive frailty models linked to increased disability and all-cause mortality [32–34], although not using the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics criteria to identify potentially reversible cognitive frailty [5] or a slightly modified version of these criteria to diagnose reversible cognitive frailty [2, 3]. Very recently, two cross-sectional population-based studies found, in individuals with potentially reversible cognitive frailty, a higher risk of limitation in instrumental activities of daily living [24] and disability [25], giving further support to the longitudinal findings on the risk of disability in these subjects from the Italian Longitudinal Study of Aging [23].

Emerging biomarkers and the research criteria for cognitive frailty

According to the different types of cognitive impairment, cognitive frailty was suggested to divide into reversible and potentially reversible cognitive frailty [2, 3]. The reversible cognitive impairment may correspond to pre-MCI stage (CDR = 0) which may be preclinical AD or other pre-MCI due to non-AD with SCD. The potential reversible cognitive impairment may correspond to MCI (CDR = 0.5), a predementia state.

Biomarkers and research criteria of pre-MCI SCD and preclinical AD SCD

Prior to objective cognitive impairment, subjective cognitive complaints are early indicators of AD pathological changes, such as decreased gray matter volume [34–37], cerebral hypometabolism in parietotemporal and parahippocampal regions [38], and amyloid burden [39]. Many non-demented older adults with preclinical AD have substantial AD pathology and subtle cognitive dysfunction [40]. Although MCI is a predementia and not a preclinical state, SCD is also part of MCI diagnostic criteria. In MCI individuals, specific aspects of SCD severity and quality measured by Subjective Memory Decline Scale were associated with CSF biomarkers. Low-CSF β-amyloid (Aβ)42 together with either high tau or phosphorylated tau 181 levels, and more depressive symptoms was related to higher Subjective Memory Decline Scale scores [12].

SCD means self-perception of decline of cognitive performance, but it could not be confirmed by objective cognitive testing. The subtle cognitive decline still demonstrates in part successful compensation to yield unimpaired cognitive performance by cognitive tests. SCD can appear in preclinical AD, pre-MCI, and MCI [7]. We suggest the use of pre-MCI SCD research criteria, in combination with suggested SCD features, as a preliminary screening tool for cognitive performance of individuals with reversible cognitive frailty. Preclinical AD SCD conceptual framework, in combination with biomarkers of preclinical AD and apolipoprotein E (APOE) ε4 allele, may be a useful screening tool to further differentiate whether a patient with pre-MCI SCD is in a preclinical phase of AD or in the subclinical stages of another neurodegenerative disease [7, 18]. The identification of individuals with reversible cognitive impairment without SCD will depend on the research criteria of preclinical AD proposed by the National Institute on Aging–Alzheimer's Association.

Biomarkers, preclinical AD, and reversible cognitive frailty research criteria

A cross-sectional analyses of dominantly inherited AD baseline data in relation to estimated years from expected symptom onset showed that the decline of CSF Aβ42 concentration was detected 25 years before expected symptom onset; the increases of Aβ deposition, concentrations of tau protein in the CSF, and brain atrophy were detected 15 years before symptom onset; and the increases of cerebral hypometabolism and impaired episodic memory were observed 10 years before symptom onset [41]. Global cognitive impairment, as measured by the MMSE and the CDR, was detected 5 years before onset, and patients met diagnostic criteria for dementia at an average of 3 years

after expected symptom onset [41]. Therefore, the research criteria of preclinical AD dependent on biomarkers can find the asymptomatic individual with AD pathological changes. Preclinical AD is divided into three stages according to markers of Aβ accumulation and neurodegeneration or neuronal injury [18, 42]. Two additional stages, no biomarker evidence of AD pathology and non-AD pathology, were proposed by Jack and colleagues in 2012 [43]. Thus, reversible cognitive impairment due to preclinical AD in individuals with cognitive frailty may correspond from stage 0 to stage 3 [42] (Table 2). Reversible cognitive impairment due to non-AD in individuals with cognitive frailty may correspond to stage 4, only showing biomarkers of neurodegeneration. The subject may have suspected non-AD pathology, including normal aging and other age-related neurodegenerative diseases (Table 2). The heterogeneity of underlying etiologies would mean that AD is only one of many possible etiologies and mechanisms of cognitive frailty. In fact, given that physical frailty may be a prodromal stage of VaD [44, 45], preclinical "vascular" cognitive frailty could be classified as such based on neuroimaging evidence of vascular lesions.

Preclinical AD is common in cognitively normal older people. A longitudinal study revealed that subjects with preclinical AD had an increased mortality and high 5-year progression rate to symptomatic AD (diagnosed with CDR = 0.5), 2% for normal subjects, 11% for stage 1, 26% for stage 2, 56% for stage 3, and 5% for suspected non-AD pathophysiology [46]. These results suggested that a small proportion of individuals classified as stage 0 may experience early AD not detected with current biomarkers. Aβ oligomers, for example Aβ*56, correlated with pathological tau proteins and postsynaptic proteins and proposed Aβ*56 may contribute to the very early stage in the pathogenesis of AD [47, 48]. However, we still need to develop more specific assays to measure the precise natures of oligomers via more sensitive amplification platforms. The identification of subjects with preclinical AD among cognitively normal older people is critical in secondary prevention trials. According to NIA–AA guidelines, asymptomatic amyloidosis is the stage 1 of preclinical AD [18, 42, 43, 47]. Among biomarkers, CSF Aβ42 decrease and Aβ accumulation on positron emission tomography (PET) amyloid imaging could reveal aberrant metabolism and accumulation of Aβ. A meta-analysis showed that the prevalence of cerebral amyloid pathology in subjects without dementia, evidenced by PET or CSF findings was associated with age, APOE genotype, and the presence of cognitive impairment [49]. There is a 20- to 30-year interval from the presence of amyloid positivity to onset of dementia. However, only Aβ deposition is not sufficient to diagnose an individual with preclinical AD, but Aβ deposition shows greater specificity than biomarkers of neurodegeneration, such as tau protein neurofibrillary tangles (NFTs). Non-demented preclinical AD cases showed different patterns of distribution of NFTs and Aβ plaques. In a unique series of cases whose premortem cognitive status had been assessed with the CDR, NFTs have been found in non-demented subjects, especially in hippocampal and parahippocampal areas and the average NFT concentration increased exponentially with age [50]. In healthy aging, the initial formation of NFTs and Aβ plaques appeared to be independent of each other [50]. Aβ plaques were absent in some brains up to age 88, and in other cases, the earliest Aβ plaque formation, in patches of diffuse plaques, occurred in the neocortex [50]. In this case series, an interaction between amyloid and neurofibrillary change also existed in another group of non-demented cases with preclinical AD, characterized by widely distributed neuritic and diffuse plaques throughout neocortex and limbic structures [50]. To reduce the screening costs, inexpensive and non-invasive measures, such as APOE genotype, could significantly reduce the number of population-based cognitively normal individuals needed to screen to enroll by 48% in subjects aged 70–79 and 33% in these aged 80–89 with amyloid positivity [51].

Table 2 The differentiation of diagnosis of cognitive impairment of reversible cognitive frailty according to biomarkers

Biomarkers	With pre-MCI SCD	Without pre-MCI SCD
No biomarker evidence of AD pathology	Normal aging or undetectable preclinical AD	Normal aging
Cerebral amyloidosis	Preclinical AD, early stage of dementia with Lewy bodies and/or VaD APOE ε4 allele and vascular lesions by neuroimaging is helpful	Normal aging, preclinical AD, early stage of dementia with Lewy bodies and/or VaD APOE ε4 allele and vascular lesions by neuroimaging is helpful
Amyloidosis plus evidence of neurodegeneration or neuronal injury	Preclinical AD	Normal aging or preclinical AD
With biomarkers of neurodegeneration without positive markers of amyloid accumulation	Normal aging or suspected non-AD dementias	Normal aging or suspected non-AD dementias

MCI mild cognitive impairment, *SCD* subjective cognitive decline, *AD* Alzheimer's disease, *VaD* vascular dementia, *APOE* apolipoprotein E

Biomarkers, MCI, and potentially reversible cognitive frailty research criteria

According to the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics criteria [5], the cognitive impairment of potentially reversible cognitive frailty corresponds to MCI (CDR = 0.5), a predementia state. Therefore, the research criteria of MCI due to AD should be one of the criteria of this subtype of cognitive frailty. The research criteria of MCI mainly include those from National Institute on Aging–Alzheimer's Association and the International Working Group for New Research Criteria for the Diagnosis of AD. These proposed criteria are useful to identify AD at the MCI stage [52]. Based on cognitive test performance and biomarkers, including both amyloid and neuronal injury markers, subjects can be divided into subjects with prodromal AD and without prodromal AD according to the International Working Group-1 and -2 criteria [53, 54]. Subjects also can be classified as in the high AD likelihood group, conflicting biomarker groups (isolated amyloid pathology or suspected non-AD pathophysiology), and low AD likelihood group according to the National Institute on Aging–Alzheimer's Association criteria [10]. For randomized clinical trials, selection of high AD likelihood subjects according to the National Institute on Aging–Alzheimer's Association criteria or corresponding to prodromal AD subjects for the International Working Group-2 criteria could be considered [52]. These criteria are benefit for uniform recruitment standards and comparability of different AD studies. In clinical setting, the diagnosis of MCI is usually considered as a means to screen subjects at high risk of progression to dementia due to AD or non-AD dementia at short term from 1 to 3 years [55]. Although a study with small sample showed that single marker models demonstrated a predictive accuracy of short-term MCI conversion comparable to that of any multipredictor model [56], the use of both amyloid and neuronal injury markers in the criteria of National Institute on Aging–Alzheimer's Association greatly improves the prediction of progression to AD and provides the most accurate prognosis [52]. In a study on patients with amnestic MCI, therefore at a predementia stage of AD, the neuropsychological measurements showed predominant delayed recall and semantic memory impairment, while [^{18}F] fluorodeoxyglucose (FDG)-PET measurement showed early metabolic defects in the temporoparietal associative cortex at baseline [57]. Over an 18-month follow-up period, only the FDG-PET predictor was specifically and accurately associated with subsequent global cognitive decline [57]. Thus, FDG-PET measurement appeared to be more accurate than neuropsychological assessments in predicting global cognitive deterioration in patients with MCI. In addition, the conflicting biomarker groups (isolated amyloid pathology or suspected non-AD pathophysiology), and low AD likelihood group according to the National Institute on Aging–Alzheimer's Association criteria also are important differential research criteria of potentially reversible cognitive frailty to screen non-AD cognitive impairment.

The challenges of the proposed research criteria for cognitive frailty

The pathophysiological sequence of AD

The current research criteria of preclinical AD are based on Aβ peptide aggregations as a key early event in the pathophysiological process of AD. In late-onset AD, Aβ storage may result from imbalanced or ineffective Aβ clearance rather than excess formation [18, 58]. Aβ oligomers, the major neurotoxic and synaptotoxic species, together with soluble fragments become large fibrils, which further aggregate to form insoluble deposits, including small diffuse Aβ plaques and dense core plaques in extracellular space [59, 60]. Aβ accumulation initiates a pathological cascade. NFTs are the downstream neuropathophysiological hallmarks, which result from the hyperphosphorylation of the microtubule-associated protein tau. The formation of tau oligomers and the subsequent conversion into insoluble filaments and finally NFTs, is a critical step in AD pathology [61]. The formation of intracellular NFTs, toxic Aβ oligomers, and Aβ plaques result in destabilization of axons, impairment of axonal transport, axonal degeneration, neuron dysfunction, and finally neuronal death.

However, in AD patients, the neurodegeneration, synaptic loss, and cognitive performance were more strongly associated with the formation and extent of NFTs than Aβ plaque deposition [62]. Neuropathological processes other than β-amyloidosis must underlie declines in brain structure and memory function in middle age. The cross-sectional data from a large sample of cognitively normal individuals aged 30–95 year showed that memory worsened from age 30 years through 90s [63]. Brain structure (adjusted hippocampal volume) worsened gradually from age 30 years to the mid-60s and more steeply beyond that age. The median amyloid PET began to increase until after 70 years. These results are consistent with a model of late-onset AD in which β-amyloidosis arises in later life on a background of preexisting structural and cognitive decline that is associated with aging and not with Aβ deposits [63]. Recently, a modified pathophysiological model hypothesized that Aβ and tau may be initiated independently in late-onset AD, and an incident Aβopathy accelerates an antecedent tauopathy [64]. Thus, Aβ may not be the earliest pathology and more antecedent neurodegenerative changes,

such as the accumulation of tau, may already be in place and result in loss of synapses, AD associated atrophy, and more diffusely reduce glucose level uptake and metabolism [65]. If it is true, very early intervention to block Aβ storage, not preventing also the secondary pathologies from beginning, may be not an optimal target.

Biomarkers implicated in physical frailty and AD

The common consequences of aging have an impact on age-related conditions such as physical frailty and cognitive decline. The common aging mechanisms, such as nutrition-sensing signals, p53 activation, and subsequent telomere deletion and DNA damage, result in the physiological reserve declines of different organs (Fig. 1). The long-term chronic stressor overload further accelerates the physiological reserve declines. The different vulnerability of multiple organs, or different structures in same organ, such as brain, results in function-related homeostatic failure, and different phenotypes/diseases, physical frailty, or cognitive frailty [1, 2]. Thus, cognitive frailty should include concurrent physical frailty and reversible cognitive impairment (pre-MCI stage) [2], or physical frailty prior to cognitive impairment. In fact, frailty and AD generally share similar risk biological parameters, including inflammatory parameters, for example, interleukin-6, C-reactive protein, anemia, lipid, neuroendocrine, and nutritional parameters [66]. Sarcopenia which is an age-related loss of muscle mass and function, is the most common cause of physical frailty. Biomarkers of physical frailty, particularly sarcopenia, should predict early cognitive decline. A few studies showed that muscle function, assessed with handgrip strength or gait speed, was positively associated with cognition [67–70]. Furthermore, another clinical construct similar to cognitive frailty was proposed, i.e., a Motoric Cognitive Risk syndrome in non-demented older subjects with MCI and slow gait, with an increased risk to develop dementia, especially VaD [71]. Motoric Cognitive Risk syndrome was associated with a doubled risk of developing incident cognitive impairment in 4812 participants without dementia, even after adjusting for vascular disease and baseline cognitive status [72]. Stroke, Parkinson's disease, depressive symptoms, sedentariness, and obesity predicted risk of incident Motoric Cognitive Risk syndrome [73]. In healthy older men, larger neck muscle cross-sectional area measured by MRI scans was related to less whole-brain atrophy [74]. The emerging fluid biomarkers of sarcopenia, the positive and negative regulators, such as follistatin, irisin, myostatin, and growth and differentiation factor-15 [75] may also play an important role in cognition.

Conclusion

Among cognitive frailty models, the proposed definition of reversible cognitive frailty could be an interesting further step toward the identification of a reversible target for this new clinical entity (Table 3). However, at present, there is only one population-based study in which reversible cognitive frailty has been investigated as possible determinant of dementia and its subtypes [30], and how mechanisms could be associated with reversibility should be further

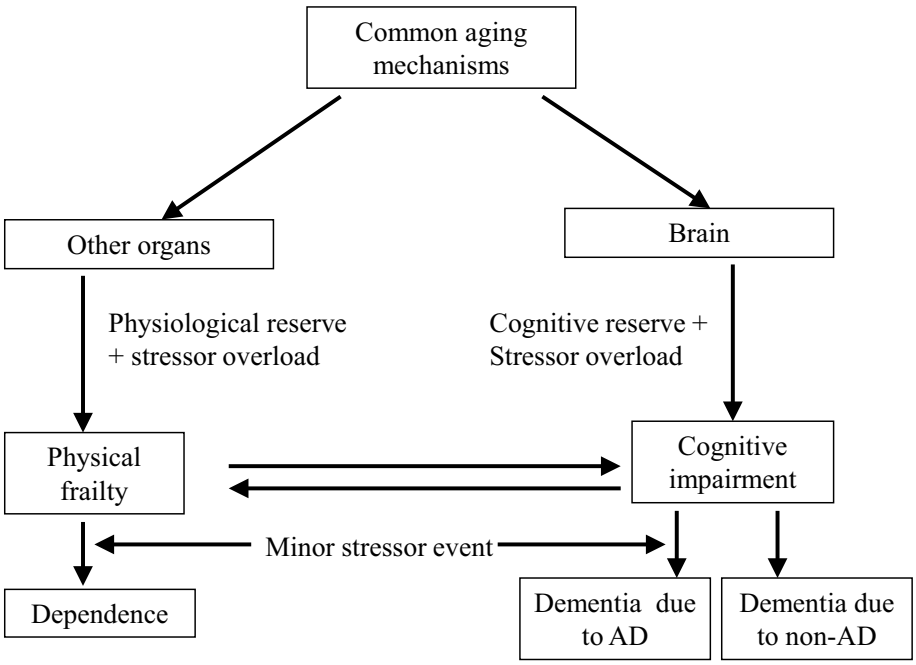

Fig. 1 Overview of the principal underlying mechanisms linking aging, physical frailty, and cognitive impairment. The common aging mechanisms such as stressor overload, chronic inflammation, and DNA damage may result in a decrease of physiological reserve in brain and other organs and, in turn, in the development of physical frailty and cognitive impairment. Under a minor stressor event, the interaction between physical frailty and cognitive impairment finally may cause adverse outcomes, including dependence, dementia due to Alzheimer's disease (AD) and non-AD

Table 3 Key points on cognitive frailty construct and emerging biomarkers for this proposed clinical entity

Both physical frailty and frailty indexes with a multidimensional nature were associated with late-life cognitive impairment/decline, incident dementia, AD, mild cognitive impairment, vascular dementia, other non-AD dementias, and AD pathology
Cognitive frailty has been proposed as a clinical entity with cognitive impairment related to physical causes, with a potential reversibility, and as an important target of secondary intervention
The new clinical and research criteria of AD established by the National Institute on Aging–Alzheimer's Association and the American Psychiatric Association will improve the differential diagnosis of cognitive impairment within the proposed cognitive frailty construct
The emerging biomarkers of sarcopenia, physical frailty, and cognitive impairment will provide the basis to establish more reliable clinical and research criteria of cognitive frailty
The present consensual criteria for cognitive frailty should be redefined using different operational definitions of frailty and cognitive impairment and useful clinical, biological, and imaging markers of cognitive frailty

AD Alzheimer's disease

investigated. Emerging biomarkers greatly improved the clinical diagnostic and clinical research criteria of AD and they will contribute to screen cognitive frailty. Physical frailty and cognitive impairment may share the common early aging biomarkers. The combination of the common aging biomarkers and special biomarkers of cognitive impairment will improve the specificity and sensitivity of different cognitive frailty models. Further well-designed population-based studies are needed to validate different cognitive frailty models for the risk of developing dementia and its subtypes. In fact, an expert consensus panel of the International Academy of Nutrition and Aging and its Global Aging Research Network agreed that persons with cognitive decline should be screened for physical frailty and vice versa [76], although the International Academy of Nutrition and Aging /Global Aging Research Network panelists agreed that more studies on the interaction of the two entities and their pathophysiology are needed [76]. A reversible cognitive damage as defined in this model of reversible cognitive frailty could be an optimal target for a secondary prevention of cognitive impairment. Further randomized clinical trials are needed to support possible efficacious strategies of intervention, although findings from very recent preventive trials suggested that physical exercise training in combination with protein supplementation [77] or alone [78] improved also cognitive outcomes in frail and pre-frail states, opening new viable routes for the prevention of cognitive decline. The new awareness of the need for prevention of frailty and cognitive decline is confirmed by the focus of the European Innovation Partnership on Active and Healthy Ageing, and particularly, the Cognitive Decline group in Action Group 3 on the prevention, early diagnosis, and management of frailty and of functional decline, both physical and cognitive, in older people. For that reason, the Action Group 3 included strategies to screen for physical, cognitive, psychological, and functional states related to development of frailty and, for prevention, some programs focused on physical activity and nutrition as lifestyle measures [79]. In the near future, the present consensus criteria for cognitive frailty should be redefined with the use of different operational definitions of frailty and cognitive impairment and useful clinical, biological, and imaging markers of cognitive frailty.

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Compliance with ethical standards

Conflict of interest None declared.

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