# Cognitive Frailty

## Mechanisms, Tools to Measure, Prevention and Controversy

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**KEYWORDS**

• Cognition • Cognitive frailty • Frailty • Mechanisms • Prevention

**KEY POINTS**

- Frailty has been linked to cognitive impairment.
- Shared mechanisms might include both shared subcellular pathophysiology (eg, cardiovascular risk factors, nutrition, hormonal changes, inflammation, accumulation of neurotoxic β-amyloid in the brain, nigral neuronal loss, lifestyle, and mental health issues).
- Effective screening and diagnostic tools exploring identifying causes of frailty including cognitive status need to be developed.
- Multidomain interventions seem to be efficient in the prevention of cognitive frailty.
- Investigations and real randomized controlled trials are needed to improve appropriate treatment options for cognitive frailty.



## INTRODUCTION

The increase in life expectancy is a global phenomenon, affecting developed and underdeveloped countries. Aging is the progressive and overall physiologic decline of the reserves of an organism, which decreases the ability to generate adaptive responses and sustain homeostasis. Given the difficulty in reversing aging's disabling cascades, it is important to act preventively with specifically tailored interventions against prodromal signs of disease and disability when these processes are still amenable to effective modification. Frailty is a pathologic aging process that is

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reversible and occurs at an intermediate stage between age-related diseases and a poor prognosis, such as disability or death.[1–4] This syndrome is triggering considerable attention not only in clinics and research, but also among public health authorities.[1] Most of the available definitions have privileged the physical dimension of the frailty syndrome, mostly relying on symptoms and signs like weight loss, muscle weakness, slow gait speed, and sedentary behavior.[5] Nevertheless, a growing body of evidence suggests that other factors (eg, nutrition,[6] mental health,[7] and cognition[8]) may also influence the frailty status of the older individual. Based on different pathogeneses, frailty can be divided into physical frailty, cognitive frailty, and psychosocial frailty.[9,10] Cognitive frailty is increasingly recognized as a fundamental determinant of the individual's vulnerability and resilience to stressors.[11] Several investigators have also supported the idea that individuals who manifest both cognitive and motor deficits might have a greater burden of a shared underlying pathologic condition. They introduced a new idea that they refer to as *motoric cognitive risk* syndrome,[12–14] a concept closely connected with cognitive frailty. This report clarifies the framework for the definition and mechanisms of cognitive frailty and relevant screening tools. Furthermore, we explore the possible prevention of the cognitive frailty progression. Finally, we comment on the controversy that exists in the field.



## THE COGNITIVE FRAILTY APPROACH

### *The Proposed Definition of Cognitive Frailty*

In 2001, the term *cognitive frailty* was used by Paganini-Hill and colleagues[15] in a study on Clock Drawing Test (CDT) performance and its association with potential protective and risk factors for Alzheimer's disease (AD) in an older cohort. In 2006, cognitive frailty was proposed by Panza and colleagues[16] when these authors examined the risks of decreased cognitive functions modulated by vascular factors. Subsequent studies found that physical factors and cognition are crucial elements in predicting risk of death.[10,16,17] In 2013, a consensus on the definition of cognitive frailty was reached by an international consensus group (the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics).[18] The panel defined cognitive frailty as a syndrome in older adults with evidence of both physical frailty and cognitive impairment without a clinical diagnosis of AD or another dementia (Clinical Dementia Rating score [CDR] = 0.5).[18] This finding implies that cognitive frailty is a form of pathologic brain aging and a precursor to neurodegenerative processes. With this definition, physical frailty and cognition are associated; however, the causal links between physical frailty and cognitive impairment are not clear.

### *The History of the Link Between Frailty and Cognitive Impairment*

Based on the different domains and the multidimensional nature of frailty, this geriatric syndrome can be divided into physical frailty, cognitive frailty, and psychosocial frailty,[9,19] with this last definition suggesting that frailty may also affect quality of life and social connectivity.[20] In particular, in 2001, the term *cognitive frailty* was incidentally used by Paganini-Hill and colleagues.[15] In 2006, this clinical label was first used to indicate a particular state of cognitive vulnerability in mild cognitive impairment (MCI) and other similar clinical entities exposed to the risk modulated by vascular factors with a subsequent increased progression to dementia, particularly vascular dementia.[16] Thus, cognition plays an important role in the manifestation of the frailty syndrome. In this context, some investigators have proposed the addition of a cognitive assessment within the operational definitions of frailty. For example, Rockwood

and colleagues[21–23] consider frailty as a cumulative index of health deficits, including cognitive impairment, and developed and validate the so-called Frailty Index. Cognitive impairment has been independently associated with several adverse outcomes (eg, falls, hospitalization, and mortality), even when specific conditions (eg, dementia and MCI) were considered.[24] Cross-sectional studies document high rates of cognitive impairment in frail compared with robust older persons, being observed in nearly 20% of frail individuals living in the community[25] (**Table 1**). Consistently, longitudinal studies repeatedly reported that physical frailty predicts the onset of future cognitive decline and incident dementia[8] (see **Table 1**). The reciprocal association (ie, cognitive impairment predicts future frailty) has also been observed.[26] In addition to these epidemiologic evidences, various studies suggest that there are multiple interrelated mechanisms that may mediate these associations, including chronic inflammation, nutritional patterns, vascular disease, depression, and endocrine deficiencies.[27]

### *The Relationship Between Frailty and Cognition*

Many pathologic processes contribute to cognitive impairment, leading to several possible avenues for dementia prevention. Age is consistently reported as the most important independent risk factor for cognitive impairment and dementia, and so it is likely that many of the age-associated processes that lead to frailty in older people are also responsible for brain aging and consequent cognitive decline. The place of cognitive impairment in a definition of frailty has been widely debated. The model by Fried and colleagues[5] describes a wasting syndrome with weight loss and negative energy balance as important elements and does not include cognitive function in its definition, whereas the model by Rockwood and colleagues[21–23] allows poor cognition to be included as one of the possible deficits. A review of frailty measures found that the most commonly included components in an operational definition of frailty were physical function, gait, strength, and cognition, with cognition being included in 50% of the definitions.[28,29] On the other hand, statistical analyses on these proposed components of frailty suggest that, although physical activity, mobility, energy, strength, and mood aggregate highly correlated, cognition does not correlate strongly with these other components and, therefore, may not be part of the frailty syndrome.[30,31] It seems not useful, therefore, to treat frailty and cognitive impairment as related but distinct concepts that frequently co-occur (**Fig. 1**).

## THE MECHANISMS OF COGNITIVE FRAILTY

Numerous studies found that multiple risk factors that cause cognitive impairment are also associated with the development and worsening of physical frailty in older individuals.[8,18,24] These risk factors include cardiovascular events (eg, diabetes, dyslipidemia, hypertension), nutritional deficiencies (eg, malnutrition, vitamin D deficiency), hormonal imbalance (eg, reduced testosterone, insulin resistance), inflammation, accumulation of neurotoxic β-amyloid (Aβ) in the brain, nigral neuronal loss, lifestyle, and mental health issues[8,18,24] (**Fig. 2**).

### *Cardiovascular Risk Factors*

Cardiovascular risk factors and common vascular diseases have been related to both frailty[32] and cognitive impairment.[16] In fact, several studies found that comorbidities like congestive heart failure, myocardial infarction, peripheral arterial diseases, diabetes mellitus, and hypertension increased the risk for frailty.[32,33] The association between physical frailty and increased risk of incident cognitive impairment may be linked to an underlying increased risk of stroke and cerebrovascular disease. In

**Table 1**
**Recent studies on the association between frailty and cognitive function**

| Study and Year | Type of RCT | Participants | Tools Used | Findings |
|---|---|---|---|---|
| Alencar et al,[106] 2013 | Longitudinal studies | N = 207<br>1 y | Physical frailty phenotype assessed with the CHS criteria.<br>Cognitive function and dementia evaluated with MMSE and CDR. | Frailty was associated with a subsequent decline in cognitive function when measured using the MMSE. No statistically significant differences among the different classifications of frailty were detected regarding the decline in cognitive function when assessed using the CDR. |
| Ferrer et al,[107] 2013 | Cross-sectional studies | N = 273 | Physical frailty phenotype operalizionated with the CHS criteria.<br>Cognitive function was evaluated with MMSE. | The overall prevalence of frailty and cognitive impairment and frailty and dementia combined was 55.4%, and 26.8%, respectively. |
| Forti et al,[108] 2014 | Longitudinal studies | N = 766<br>7 y | Physical frailty phenotype operalizionated with SOF index.<br>Cognitive function assessed with CDT. | The CDT may predict the mortality risk independently of the physical phenotype of frailty. |
| Gray et al,[109] 2013 | Longitudinal studies | N = 2619<br>6.5 y | Physical frailty phenotype operalizionated with the CHS criteria.<br>Diagnosis of dementia according to the DSM-IV, diagnosis of possible and probable AD according to NINCDS-ADRDA criteria. | Frailty was associated with higher risk of developing non-AD dementia but not AD. |
| Han et al,[110] 2014 | Cross-sectional studies | N = 10,388 | Physical frailty phenotype operalizionated with the CHS criteria.<br>Cognitive function was assessed using MMSE. | Frail subjects showed a higher percentage of cognitive impairment, with some gender differences. Cognitive impairment was associated with a higher likelihood of frailty in community-dwelling older men and women. |
| Kulmala et al,[111] 2014 | Cross-sectional studies | N = 6 | Physical frailty phenotype operalizionated with the CHS criteria.<br>Diagnosis of dementia, AD, and VaD according to the DSM-IV criteria and cognitive impairment evaluated with MMSE. | Frail persons were almost 8 times more likely to have cognitive impairment, 8 times more likely to have some kind of dementia, almost 6 times more likely to have VaD, and more than 4 times more likely to have AD than persons who were robust. |

| | | | | |
|---|---|---|---|---|
| Lee et al,[112] 2014 | Longitudinal studies | N = 3018<br>2 y | Frailty phenotype operalizionated with the CHS criteria.<br>Cognitive function was evaluated with MMSE. | Among prefrail participants, hospitalizations, older age, previous stroke, lower cognition, and osteoarthritis were risk factors associated with worsening to frail state or less improvement to robust state. |
| McGough et al,[113] 2013 | Cross-sectional studies | N = 201 | Physical frailty dimensions adapted from the CHS criteria.<br>Severity of cognitive impairment was measured with the ADAS-Cog. Cognitive functions were evaluated with TMT-A, TMT-B, WMS-R Logical Memory, and the delayed Word Recall subitem of the ADAS-Cog. | Lower performance on dimensions of physical frailty was associated with worse performance on the ADAS-Cog. In particular, slower usual gait speed was associated with elevated severity of cognitive impairment and worse performance within all dimensions of memory, attention, and executive function. |
| Montero-Odasso et al,[114] 2016 | Longitudinal studies | N = 252 | Frailty was defined using validated phenotypic criteria.<br>Cognition was assessed using the Montreal Cognitive Assessment.<br>Gait was assessed using an electronic walkway. | Frailty participants had a higher prevalence of cognitive impairment compared with those without frailty but not significant risk to incident dementia. Cognitive frailty increased incident rate but not risk for progression to dementia. The combination of slow gait and cognitive impairment posed the highest risk for progression to dementia. |
| Rolfson et al,[115] 2013 | Cross-sectional studies | N = 388 | Frailty was determined with the CHS criteria, the EFS, and a frailty index.<br>Cognitive function was assessed using MMSE and a test of visuomotor speed. | A relationship independent of the MMSE score was only demonstrated in the frailty index. |
| Runzer-Colmenares et al,[116] 2014 | Cross-sectional studies | N = 311 | Physical frailty phenotype operalizionated with the criteria.<br>Cognitive function was assessed with the CDT. | Frail subjects showed a higher percentage of cognitive impairment (41.9%), although cognitive function was not significantly associated with frailty. |
| Sampson et al,[117] 2013 | Longitudinal studies | N = 616<br>1 y | Waterlow Scale, a frailty marker, evaluating the risk of pressure sores.<br>Cognitive function assessed with MMSE, and | People with dementia had half the survival time of those without dementia. The effect of dementia on mortality was reduced after adjustment, particularly by the Waterlow score. |

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**Table 1**
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| Study and Year | Type of RCT | Participants | Tools Used | Findings |
|---|---|---|---|---|
| | | | diagnosis of dementia according to the DSM-IV criteria. | |
| Schoufour et al,[118] 2014 | Cross-sectional studies | N = 1050 | Frailty was defined with a frailty index.<br>Intellectual quotient scores, Vineland scores, and social emotional development were used to determine the level of cognitive disability. | The least frail group was characterized by the absence of mobility and physical fitness limitations, relative independence, fewer specific medical problems, and fewer signs of depression/dementia. |
| Shimada et al,[119] 2013 | Cross-sectional studies | N = 5104 | Physical frailty phenotype operalizionated slightly modifying the CHS criteria.<br>MCI diagnosed according to international consensus criteria. | The overall prevalence of frailty, MCI, and frailty and MCI combined was 11.3%, 18.8%, and 2.7%, respectively. A significant relationship between frailty and MCI was also found. |
| Solfrizzi et al,[36] 2013 | Longitudinal studies | N = 2581<br>3.5 y | Physical frailty phenotype operalizionated slightly modifying the CHS criteria.<br>Diagnosis of dementia according to the DSM-III-R, NINCDS-ADRDA and ICD-10 criteria. | Frailty syndrome was associated with a significantly increased risk of overall dementia and, in particular, VaD, whereas the risk of AD or other types of dementia did not significantly change in frail individuals compared with subjects without frailty syndrome. |
| Sourial et al,[120] 2013 | Longitudinal studies | N = 3447<br>6 y | Seven frailty markers (cognition, energy, mobility, mood, nutrition, physical activity, and strength) | The "best model" in each cohort was found to be a model including between 5 and 7 frailty markers including cognition, mobility, nutrition, physical activity, and strength. |

*Abbreviations:* ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CHS, cardiovascular health study; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders-III revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; EFS, Edmonton frail scale; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; SOF, study of osteoporotic fractures; VaD, vascular dementia; WMS-R, Wechsler memory scale revised.
*Data from* Refs.[36,106–120]

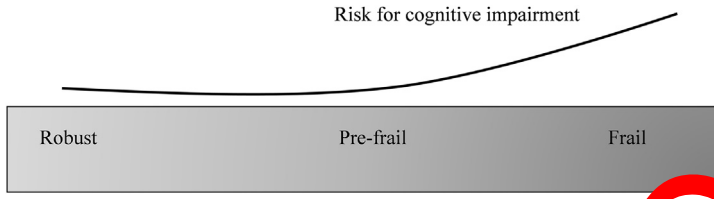


**Fig. 1.** Association between frailty and cognitive impairment.

fact, findings from the Cardiovascular Health Survey suggested that physical frailty was clearly related to subclinical vascular biomarkers and higher degree of infarctlike lesions in the brain.[34] Moreover, longitudinal population-based studies also suggested physical frailty as a prodromal stage of vascular dementia.[35,36] Finally, sarcopenia, an age-related decline in skeletal muscle mass and muscle function and a reliable marker of frailty, may be accelerated by comorbid conditions including vascular diseases such as congestive heart failure and peripheral arterial diseases.[37] Sarcopenia could worsen prognosis of neurodegenerative diseases including AD and a link also exists between sarcopenia and cognitive decline.[38]

### *Nutrition*

Nutrition may also play a role in the link between cognition and frailty because of the biological and behavioral effects of diet.[39] Sarcopenia is thought to be strongly associated with development of frailty and cognitive impairment, perhaps owing to oxidative stress.[38,40] Adherence to a Mediterranean diet, high in antioxidants, has been linked to lower frailty and better cognitive function.[40,41] In a recent randomized controlled trial (RCT) with a 6.5-year follow-up, nutritional intervention with a Mediterranean diet enhanced with extra-virgin olive oil or mixed nuts seemed to improve

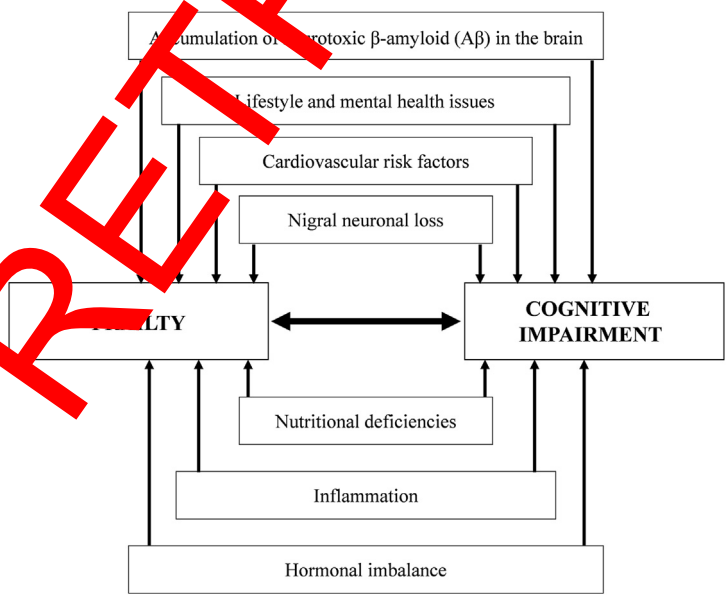


**Fig. 2.** Mechanisms underlying the observed link between frailty and cognitive impairment.

global cognition after adjustment for possible confounders.[42] Moreover, in a cross-sectional population-based study, higher adherence to a Mediterranean diet was inversely linked to prevalence of frailty.[43] Taken together, these findings may suggest a long-term effect of a Mediterranean diet both on frailty and cognitive function in older age even if other studies showed effects more nuanced.[44,45]

### *Hormonal Changes*

Reviews suggest that reduced testosterone and other androgen hormones may be involved in the development of frailty and cognitive decline.[46,47] Testosterone is thought to have protective effects on cognition through its promotion of synaptic plasticity in the hippocampus and its regulation of the accumulation of Aβ protein.[46] Furthermore, age-related depletion of testosterone is thought to be associated with declining muscle mass, an important factor in the development of frailty.[47] It is thus possible that reduced testosterone may be a mediator in the relationship or common underlying factor to both frailty and cognitive decline.

### *Inflammation*

The mechanisms of inflammation in cognitive impairment have already been described.[48,49] Increased serum concentrations of interleukin (IL)-8 are associated with poor performance in memory and speed domains and in motor function.[50] IL-6 and C-reactive protein are also prospectively associated with cognitive decline in older subjects.[51] On the other hand, immune system changes and inflammation are also associated with frailty. Data considering the effect of inflammation on frailty suggest that the inflammatory process is triggered by some cytokines, especially IL-6, tumor necrosis factor-α and other inflammatory proteins are associated in the older subject with increased risk of morbidity and mortality, and cohort studies indicate tumor necrosis factor-α and IL-6 levels as markers of frailty.[52–55] Consequently, the inflammatory process seems to have a role in the development of both frailty and cognitive impairment.[40]

### *Accumulation of Neurotoxic Amyloid in the Brain*

Aβ pathology in the brain causes slowing of gait speed, by a direct neurotoxic effect, by accelerating tau deposition or by other mechanisms. According to the prevailing amyloid cascade hypothesis, Aβ leads to the formation of tau tangles, which are primarily responsible for local synaptic dysfunction, neurodegeneration, and neuronal loss.[56,57] Consistent with this view, Aβ-induced tau tangles but not amyloid per se would be expected to have local neurotoxic effects with implications for the regulation of motor and sensorimotor circuits. However, there are reports of in vitro and animal studies that Aβ, independent of tau tangles, disrupts synaptic function in the immediate vicinity of Aβ plaques altering the organization of related neural networks,[58–60] supporting the notion that Aβ toxicity can also cause neuronal dysfunction. A study found a significant association between gait speed, marker of the frailty phenotype, and brain Aβ (measured with amyloid PET) in the posterior and anterior putamen, the occipital cortex, precuneus, and anterior cingulate, independent of age, ApoE genotype, and disease stage.[61] Another study speculated that accumulation of AD pathology in brain regions that subserve cognition could affect components of frailty by impairing neural systems involved in the planning and monitoring of even simple movements.[62]

### *Nigral Neuronal Loss*

The substantia nigra represents a structural component of neural reserve that contributes to brain reserve capacity.[63] In a meta-analysis, neuronal density in the locus

ceruleus, dorsal raphe nucleus, and substantia nigra was reduced in AD.[64] A study found that not only AD conditions but also several cerebrovascular conditions and nigral neuronal loss, a common finding in Parkinson disease, were associated with the rate of progression of physical frailty in community-dwelling older adults. These associations were robust and unchanged after controlling for baseline chronic health conditions and disability, excluding cases of Parkinson disease, and did not vary by dementia status.[65]

### *Lifestyle and Mental Health Issues*

Depression is both a risk factor for and a consequence of frailty.[66,67] Depression is also known to affect cognitive function.[68]This finding suggests that the mechanism underlying the link between frailty and cognition may be owing to psychological factors such as mood. Recently, a study found that participants with vascular depression at baseline were significantly more likely to have frailty.[67] Fifty-five percent of participants with vascular depression became frail within 4 years compared with 30% of participants with a high cerebrovascular burden alone and 25% of participants with neither. This finding suggests that in addition to the aforementioned link with vascular events, the interaction between the vascular burden and mood effects of depression is an important consideration in understanding frailty. In parallel, several studies suggested that lifestyle factors have a significant impact on how well people age. For example, Fratiglioni and colleagues[69] reported that 3 lifestyle factors can play a significant role in slowing the rate of cognitive decline and preventing dementia: a socially integrated network, cognitive leisure activity, and regular physical activity. In this review and others,[70,71] it is argued that out of these lifestyle factors physical activity has the most support as protective against the deleterious effects of age on health and cognition.

## THE TOOLS TO MEASURE COGNITIVE FRAILTY

To design effective interventions for cognitive frailty, effective screening and diagnostic tools allowing the exploration and identification of the causes underlying frailty, including cognitive status, need to be developed. This tool gives us the opportunity to better detect the possible future health trajectories that a frail person with cognitive impairment will follow. Consequently, this differentiation allows the design of better personalized preventive or therapeutic interventions.

Possible biomarkers, clinical markers, and imaging techniques are used to characterize and eventually predict distinct age trajectories. To identify cognitive frailty, the panel suggested that all the frail subjects should perform a comprehensive cognitive assessment exploring memory performance and other cognitive functions (ie, executive functions). The objective was to exclude the diagnosis of AD. The International Psychogeriatric Association survey found 20 brief cognitive instruments that respondents used in clinical practice chosen for "effectiveness," "ease of administration," and "familiarity."[72] The Mini-Mental State Examination (MMSE)[73] was the most common, followed by the CDT.[74] Other cognitive tests and instruments to identify cognitive frailty could be suggested: Frontal Assessment Battery,[75] the 5 words test,[76] Free and Cued Selective Reminding Test,[77] Trail Making Test (TMT) Parts A and B,[78] Wechsler Adult Intelligence Scale revised, and coding and verbal fluencies as diagnosis tests.[79] The Mattis Dementia Rating Scale[80] could also be proposed. Biomarkers of preclinical AD include the following: markers of Aβ accumulation, such as the level of amyloid-β42 in cerebrospinal fluid, and PET amyloid imaging; markers of neurodegeneration or neuronal injury, including the level of tau and phosphorylated tau protein in cerebrospinal fluid; $^{18}$F-fluorodeoxyglucose PET functional imaging or

functional MRI; and nerve degeneration or damage, such as that found by the MRI–based detection of hippocampus atrophy or cortical thinning. The assessment of nigral neuronal loss and white matter lesions could be also useful in his context. Based on various combinations of Aβ aggregation, nerve degeneration, and the subtle reduction of cognitive function, preclinical AD can be divided into 4 stages.[81] In addition, homozygous ApoE ε4 is a useful biomarker for late-onset familial and sporadic AD patients.

In parallel, usual physical frailty markers (such as weight loss and gait speed) should be assessed in persons exhibiting a cognitive decline. Based on the mechanisms of frailty, including those of phenotypic defect accumulation and the aggregation of multifunctional domains, various frailty screening techniques have been indicated.[28,82,83] Among these, Fried's phenotypic physiology based screening is being preferentially used for frailty research,[5] whereas scales for frailty resulting from defect accumulation are more suitable for health management such as predicting whether an elderly individual requires hospitalization.[22] Some markers may be able to capture well the risk of both future physical and cognitive decline, such as inflammatory biomarkers (C-reactive protein, IL-6).[53,84–86] However, biomarkers predictive of both types of decline may not be particularly useful in differentiating whether a person is at higher risk of a future physical rather than a cognitive decline and vice versa.

## THE PREVENTION OF COGNITIVE FRAILTY

For the older subjects, primary preventive intervention includes the promotion of physical activities, cognitive stimulation, exercise and a healthy diet (a Mediterranean diet), the cessation of smoking, promoting emotional recovery, engaging in an active and socially integrated lifestyle, an ideal amount of daily sleep, the maintenance of a proper body weight, and metabolic control (including the control of dyslipidemia, diabetes, and blood pressure).[28,87] At this stage, secondary prevention strategies for cognitive impairment and physical frailty are suggested. For the older subjects with potential cognitive frailty, secondary prevention is required, which comprises a geriatric assessment determining the cause of cognitive frailty and an evidence-based, medicinal, individualized multimodal intervention. Other measures, such as drug treatment for chronic diseases, fall prevention, and exercise and nutrition support, which target physical, nutritional, cognitive, and psychological domains, may delay the progression and secondary occurrence of cognitive frailty related adverse outcomes.[1,18,28,87] In fact, a multidomain intervention seems to be efficient in the prevention of cognitive frailty.

Although evidence on interventions in frailty coupled with cognitive decline is limited, a small number of studies point to the cognitive benefits of physical activity. In 2010, a review found that physical activity protected against both sarcopenia and cognitive decline in experimental training trials and in observational studies.[88] A study for frailty and cognitive decline found that an aerobic exercise and strength training program for frail older adults improved scores in functional capacity and physical endurance, cognition, and quality of life.[89] The significant improvements in cognition were caused by increased scores in measures of working memory, processing speed, and executive function.

## COGNITIVE FRAILTY CONTROVERSY

The concept of cognitive frailty has been proposed for framing the growing and consistent evidence linking physical and cognitive decline in older persons within recognizable and discriminative standards. However, a new clinical entity should be clearly defined from the previous entities defining cognitive impairment in older

persons. Thus, it is also difficult to distinguish the difference between cognitive frailty and cognitive reserve. *Cognitive reserve* refers to the capacity of a given individual to resist cognitive impairment or decline. Educational level and prior cognitive abilities are important determinants of cognitive reserve.[90–92] Cognitive reserve has been linked with resilience of brain function and structure in the presence of disease, injury, or other factors that alter physiologic functioning.[93]

A major controversial point regarding the definition of cognitive frailty is reversible cognitive impairment (CDR = 0.5), which can be confusing. It was proposed that a CDR value of 0.5 was equivalent to the MCI stage.[94,95] Some MCI patients have symptoms that are reversible and can recover to regain normal cognitive function. The cognitive functions of other patients may even be stable and not change throughout the remainder of their lives. However, more MCI patients exhibit an irreversible, progressive reduction in cognition.[96–98]

Several studies addressed the relationship between frailty and cognition. Delrieu and colleagues[99] attempted to characterize the "cognitive frailty" entity in a cohort of 1617 subjects enrolled in Multidomain Alzheimer Disease Preventive Trial (MAPT). Their cognitive frailty sample represented 22% of the population. However, there are no RCTs found in the field "cognitive frailty," underlining the scarcity of available evidence.[100] In fact, RCTs could provide useful information concerning the possibility of positively affecting the frailty syndrome by acting on cognition and improving cognition by targeting the physical components of frailty. These studies may provide key information to help characterize cognitive frailty and its underlying mechanisms and its reversibility. Furthermore, several RCTs were recently conducted to investigate the efficacy of physical interventions in improving cognitive functioning in healthy elderly individuals,[101,102] and other RCTs evaluated the effectiveness of multidomain interventions in preventing cognitive decline in older adults at risk of dementia.[103,104] However, no study has specifically targeted populations of cognitive frail older persons. Thus, there is currently a lack of sensitive and specific methods to detect cognitive frailty at the clinical level. Some investigators stress the importance of establishing a useful clinical entity because of its possible reversibility.[105] It is clear that longitudinal studies that incorporate cognition, physical frailty, and psychological constructs such as depression are needed.



## SUMMARY

Because of the population, the burden of aging-related conditions such as dementia and frailty is increasing. Available data corroborate the clear association between frailty and cognitive impairment via common underlying mechanisms including vascular and hormonal changes, nutrient deficiencies, and inflammation. The benefits of understanding the relationship between cognition and frailty are 2-fold. First, frail individuals are likely to be at high risk of cognitive impairment and vice versa. Second, understanding the link between frailty and cognition may lead to new interventions for the prevention and management of both conditions. Thus, cognitive frailty represents a window of opportunity for the prevention of adverse outcomes owing to aging, but important points remain to be clarified. In this context, further investigations and real longitudinal RCTs are needed to identify the common underlying mechanisms to improve appropriate treatment options for both conditions.

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