

# 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  $\beta$ -amyloid in the brain, nigral neuronal loss, lifestyle, and mental health issues).
- Effective screening and diagnostic tools exploring and 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.<sup>1–4</sup> This syndrome is triggering considerable attention not only in clinics and research, but also among public health authorities.<sup>1</sup> 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.<sup>5</sup> Nevertheless, a growing body of evidence suggests that other factors (eg, nutrition,<sup>6</sup> mental health,<sup>7</sup> and cognition<sup>8</sup>) 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.<sup>9,10</sup> Cognitive frailty is increasingly recognized as a fundamental determinant of the individual's vulnerability and resilience to stressors.<sup>11</sup> 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,<sup>12–14</sup> a concept closely connected with cognitive frailty. This report refines 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*

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In 2001, the term *cognitive frailty* was used by Paganini-Hill and colleagues<sup>15</sup> 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<sup>16</sup> 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.<sup>10,16,17</sup> 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).<sup>18</sup> 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).<sup>18</sup> 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*

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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,<sup>10,19</sup> with this last definition suggesting that frailty may also affect quality of life and social connectivity.<sup>20</sup> In particular, in 2001, the term *cognitive frailty* was incidentally used by Paganini-Hill and colleagues.<sup>15</sup> 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.<sup>16</sup> 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

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