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Review

Epidemiological and clinical significance of cognitive frailty: A mini review

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ABSTRACT

Since the operational definition of "cognitive frailty" was first proposed in 2013 by the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics, several studies have been carried out using this cognitive frailty model. In this review, we examined the available clinical and epidemiological evidence for cognitive frailty. Despite its low prevalence (1.0–1.8%) in the community setting, cognitive frailty has been associated with a high risk of disability, poor quality of life, and death; while cognitive frailty appears to be associated with a high risk of dementia, there is no clear evidence for this association. Again, while the prevalence of cognitive frailty appears to have increased in the clinical setting, to date, very few studies evaluated the impact of cognitive frailty. While a new definition of cognitive frailty was proposed in 2015 to incorporate "reversible" and "potential reversible" subtypes, there is a paucity of epidemiological evidence to support this definition. In conclusion, there is no consensus on the definition of cognitive frailty for use in clinical and community settings or on which measures to be used for detecting cognitive impairment. Further study is required to formulate effective preventive strategies for disability in the elderly.

1. Introduction

With global rapid population aging, frailty has drawn attention in geriatric medicine. Frailty is a clinical state characterized by the increased vulnerability of an individual to stressors caused by cumulative decline in multiple physiological systems (Clegg et al., 2013; Rodriguez-Manas et al., 2013). Frailty is a multidimensional syndrome that encompasses physical, social, and cognitive dimensions (Clegg et al., 2013; Rodriguez-Manas et al., 2013). Conceptually, frailty is thus a pre-disability syndrome and a reversible condition.

To date, the frailty phenotype as proposed and validated by Fried et al. (2001) in the Cardiovascular Health Study (CHS) has been widely used, which focused primarily on the physical dimensions. The frailty phenotype model is operationalized by using a pre-defined set of five criteria exploring the presence/absence of signs or symptoms (weight loss, exhaustion, sedentary behavior, slow gait, low muscle strength). Individuals in whom 3 or more of these 5 criteria are present are considered to have physical frailty, and those in whom 1 or 2 are present are considered to have pre-physical frailty. Physical frailty has the capacity to predict the risk of negative health outcomes, such as falls, disability, fractures, hospitalization, institutionalization and mortality in the community-dwelling elderly (Clegg et al., 2013; Ensrud et al., 2009; Graham et al., 2009).

Dementia, as well as frailty, are common health problems in the elderly. Cognitive impairment is also considered a component of frailty, and the association between physical frailty and cognitive impairment or dementia has been investigated worldwide. To date, a number of cross-sectional and longitudinal studies demonstrated a significant link between physical frailty and cognitive impairment or dementia (Panza et al., 2015a; Panza et al., 2015b; Robertson et al., 2013).

Based on the extensive and numerous evidence available to support a significant association between physical frailty and cognition, the concept and operational definition of "cognitive frailty" was first proposed in 2013 by the international consensus group comprised of

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Table 1
The operational categories for older individuals without Alzheimer's disease or other forms of dementia according to their physical and cognitive status.

Physical status \ Cognitive status		Normal	Pre-clinical stage (Positive biomarkers and/or SCD)	MCI (CDR = 0.5)
Non-frailty		**Robust**	**Pre-MCI / SCD**	**MCI**
Pre-physical frailty	Weakness Slowness Low activity Exhaustion Weight loss	**Pre-physical frailty**	**Reversible cognitive frailty*1**	**Potentially reversible cognitive frailty*1**
			Motoric cognitive risk syndrome*2 (cognitive complaints + slowness)	
Physical frailty		**Physical frailty**		**Cognitive frailty*3 (IANA/IAGG)**

Notes:
*1. The new definition of cognitive frailty includes two subtypes: "reversible" cognitive frailty and "potential reversible" cognitive frailty (Ruan et al., 2015). "Reversible" cognitive frailty is defined as simultaneous presence of both physical frailty or pre-frailty and pre-MCI and/or SCD. Pre-MCI is defined by biomarkers (amyloid β accumulation, markers of neurodegeneration or neuronal injury). SCD is defined by using a pre-MCI SCD research criteria (Jessen et al., 2014). "Potential reversible cognitive frailty" is defined as simultaneous presence of both physical frailty or pre-frailty and MCI. MCI is operationalized by a CDR score equal to 0.5.
*2. Motoric cognitive risk syndrome (MCR) (Verghese et al., 2013) is defined by both slow gait and subjective cognitive complaints. Slow gait is defined as walking speed one standard deviation or more below age- and sex-appropriate mean values established in the same cohort. Cognitive complaints are assessed by standardized questionnaires such as the 15-item Consortium to Establish a Registry for Alzheimer's Disease questionnaire and the standardized memory loss question on the Geriatric Depression Scale.
*3. Cognitive frailty proposed by the IANA and IAGG consensus group (Kelaiditi et al., 2013) is defined as simultaneous presence of both physical frailty and cognitive impairment. Cognitive impairment is operationalized by a CDR score equal to 0.5.
MCI, mild cognitive impairment; SCD, subjective cognitive decline; CDR, clinical dementia rating; MCR, motoric cognitive risk syndrome.

experts from the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) (Kelaiditi et al., 2013). Cognitive frailty was defined by the simultaneous presence of both physical frailty and cognitive impairment (clinical dementia rating [CDR] = 0.5) in older individuals without definite diagnosis of dementia (Table 1). Reversibility also characterized cognitive frailty, thus making cognitive frailty a useful target for secondary preventive measures against dependency in elderly people. However, there is a paucity of epidemiological evidence for cognitive frailty, including its prevalence and impact.

Following the first operational definition of cognitive frailty in 2013, several population-based studies were carried out using this cognitive frailty model. We searched the PubMed for papers published before August 2017 but no later than September 2013. The keyword used was "cognitive frailty" alone. Of the 46 articles (19 original articles, 16 review or special articles and 11 other articles) retrieved, only 12 original studies referred to the cognitive frailty model (Table 2). In this review, we reviewed these clinical and epidemiological studies and a few review or feature articles, which had been obtained for additional information on cognitive frailty. Finally, we evaluated the available clinical and epidemiological evidence to clarify the definition, prevalence and clinical significance of cognitive frailty and to propose future directions for research in cognitive frailty.

2. Cognitive frailty proposed by IANA and IAGG

2.1. Definition of cognitive frailty

In 2013, the international consensus group first proposed the operational definition of cognitive frailty as a heterogeneous clinical manifestation meeting the following criteria (Kelaiditi et al., 2013) (Table 1):

1) Presence of physical frailty and cognitive impairment (CDR = 0.5).
2) Exclusion of concurrent AD dementia or other forms of dementia.

Cognitive impairment is operationalized by incorporating it as equal to a CDR score of 0.5. As with the concept of physical frailty, cognitive frailty is also characterized by its potential for reversibility. Further, the consensus group went on to identify a condition of cognitive impairment due to physical factors, which led to conditions of cognitive impairment due to neurodegenerative disorders being excluded. However, to date, there is insufficient evidence to support this novel cognitive condition caused primarily by physical frailty, according to the review conducted by the consensus group (Kelaiditi et al., 2013). Moreover, in most clinical and research settings, it remains difficult to distinguish whether cognitive impairment is caused by neurodegenerative disease or physical factors. For cognitive impairment due to physical factors, it was thus deemed necessary that physical frailty be temporally present before the onset of cognitive impairment (Canevelli and Cesari, 2015). Further, biomarkers including magnetic resonance imaging (MRI) and positron emission tomography (PET) are deemed necessary to rule out

Table 2
Population-based and clinical studies on cognitive frailty.

Reference	Study design and population	Definition of cognitive frailty	Prevalence	Findings
Cross-sectional studies				
Shimada et al., 2016	Population-based study. 8864 subjects from the National Center for Geriatrics and Gerontology-Study of Geriatric Syndromes (NCGG-SGS) aged 65 years or older. Mean age, 73 years.	Frailty defined with the modified CHS criteria and MCI diagnosed by deficits on two or more cognitive domains (memory, attention, executive function and processing speed).	Frailty: 7.2% Cognitive impairment: 5.2% Cognitive frailty: 1.2%	Older adults with cognitive frailty had the highest risk for limited instrumental activities of daily living.
Delrieu et al., 2016	1617 subjects from Multidomain Alzheimer Disease Preventive Trial (MAPT) study aged 70 years or older who met at least 1 of the 3 following clinical criteria: (1) memory complaint; (2) limitation in one instrumental activity of daily living; and (3) slow gait speed. Mean age, 75 years.	Frailty defined as consistent with at least one CHS criterion and cognitive impairment defined as CDR = 0.5.	Frailty: 44.3% CDR = 0.5: 42.0% Cognitive frailty: 22.0%	Individuals with cognitive frailty had lower scores for executive and attention tests, compared to those with cognitive impairment but without physical frailty.
Roppolo et al., 2017	Population-based study. 594 subjects aged over 65 years or older. Mean age, 74 years.	Frailty defined with the modified CHS criteria and cognitive impairment defined as MMSE < 26.	Frailty: 13.8% Cognitive impairment: 15.3% Cognitive frailty: 4.4%	Older individuals with cognitive frailty showed a higher disability level than those without cognitive frailty.
Merchant et al., 2017	1051 community-dwelling older adults aged 65 years or older from Healthy Older People Everyday (HOPE) study. Mean age, 71 years.	Frailty defined with the 5-item FRAIL scale (fatigue, resistance, ambulation, illness, and loss of weight) and cognitive impairment defined as MMSE < 24.	Frailty: 6.2% Cognitive impairment: 15.9% Cognitive frailty: 1.8%	Older adults with cognitive frailty had weaker grip strength and longer timed up and go test time.
Fougere et al., 2017	1620 subjects admitted to the Toulouse frailty day hospital aged 70 years or older. Mean age, 82 years.	Frailty defined with the modified CHS criteria and cognitive impairment defined as CDR = 0.5.	Frailty: 44.7% Cognitive impairment: 52.5% Cognitive frailty: 26.7%	Physical frailty and slow gait were associated with cognitive impairment.
Longitudinal studies				
Montero-Odasso et al., 2016	252 subjects from the Gait and Brain Study aged 65 years or older. Mean age, 77 years. Mean follow-up, 18 months (range, 6–60 months).	Frailty defined as consistent with at least one CHS criterion and cognitive impairment defined as MoCA < 26 and CDR = 0.5.	Frailty: 13.9% Cognitive impairment: 55.6% Cognitive frailty: 10.7%	Cognitive frailty was associated with no significant risk for cognitive decline or progression to dementia. Slow gait (< 1 m/s) combined with cognitive impairment was associated with the highest risk for progression to dementia.
Jha et al., 2016	156 patients with advanced heart failure referred for heart transplantation. Mean age, 53 years.	Frailty defined based on 6 domains including physical 5 domains of the modified CHS criteria and cognitive impairment defined as MoCA < 26. Cognitive frailty was defined as 3 or more domains present.	Cognitive frailty: 39.7%	Cognitive frailty was shown to be a predictor of early mortality.
Feng et al., 2017a	Population based, cross-sectional and longitudinal study (3 years). 1575 subjects from the SLAS aged 55 years or older. Mean age, 66 years.	Frailty defined with the modified CHS criteria and cognitive impairment defined as MMSE < 24.	Frailty: 1.8% Cognitive impairment: 9.0% Cognitive frailty: 1.0%	Individuals with cognitive frailty were associated with a greater risk of incident neurocognitive disorder.
Feng et al., 2017b	Population-based, longitudinal study (3 years). 2375 subjects from the SLAS aged 55 years or older. Mean age, 66 years.	Frailty defined with the modified CHS criteria and cognitive impairment defined as MMSE < 26.	Pre-frailty with cognitive impairment: 8.9% Frailty with cognitive impairment 1.8%	Pre-frailty and frailty with cognitive impairment were associated with an increased incidence of functional disability, poor quality of life and mortality.
St John et al., 2017	Cohort study (5 years). 1751 community living older adults aged 65 years or more. Mean age, 78 years.	Frailty defined by the Frailty index (Frailty Index > 0.25) and cognitive impairment defined as MMSE < 26.	Frailty (FI > 0.25): 27.0% Cognitive impairment: 30.7% Frailty with cognitive impairment: 12.1%	Older adults with both frailty and cognitive impairment were associated with the highest mortality.
Solfrizzi et al., 2017a	Population-based, longitudinal study (3.5 years). 2373 subjects from the ILSA aged 65–84 years.	Frailty defined with the modified CHS criteria and diagnosis of MCI.	Frailty: 8.0% MCI: 3.5% Cognitive frailty: 1.0%	Potentially reversible cognitive frailty offered additional predictive value for the risk of disability.
Solfrizzi et al., 2017b	Population-based, longitudinal study (3.5 and 7 years). 2150 subjects from the ILSA aged 65–84 years. Mean age, 73 years.	Reversible cognitive frailty was defined as the presence of physical frailty and pre-MCI-SCD. Physical frailty was operationalized with CHS criteria. Pre-MCI-SCD was assessed according to positive response to the GDS-30: "Do you feel you have more problems with memory than most?"	Reversible cognitive frailty: 2.5%	Reversible cognitive frailty was a short- and long-term predictor of all-cause mortality and overall dementia, particularly VaD.

cognitive impairment due to neurodegenerative disease. These biomarkers are too expensive and time-consuming, however, for their application in all clinical and research settings. Moreover, in the elderly population, the coexistence of neurodegenerative and non-neurodegenerative disease is frequently observed. Indeed, data from the religious older study (ROS)/memory and aging project (MAP) cohorts demonstrated that over 85% of the elderly with mild cognitive impairment (MCI) had mixed pathologies including neurodegenerative disease (AD, Lewy body, TDP-43, hippocampal sclerosis pathology) and cerebral vascular disease (macroinfarcts, microinfarcts, moderate to severe atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy) (Kapasi et al., 2017), thus indicating the difficulties in differentiating cognitive frailty (cognitive impairment caused by cardiovascular risk factors) based solely on the pathogenesis of cognitive impairment.

As described above, there are several issues which could limit the applicability in clinical and research settings of the concept cognitive frailty as proposed by the international consensus group.

2.2. Prevalence of cognitive frailty

Epidemiological data on cognitive frailty are still limited, despite the several cross-sectional and longitudinal studies conducted to date (Table 2).

In the community setting, Shimada et al. (2013) first showed the combined prevalence of physical frailty according to the CHS criteria and MCI in a sample of 5104 Japanese community-dwelling elderly people. In this study, the prevalence of cognitive frailty was shown to be 2.7%. Moreover, following proposal of the first operational definition, they showed the prevalence of cognitive frailty to be 1.2% in a larger sample of 8864 Japanese elderly adults (Shimada et al., 2016). In the Singapore Longitudinal Ageing Studies (SLAS) that recruited 1575 community-living Chinese older adults, physical frailty and cognitive impairment were determined by the modified CHS criteria and as consistent with a score of 23 or less by the Chinese version of the MMSE, respectively. In this study, the prevalence of cognitive frailty was shown to be 1.0% but to increase with age (Feng et al., 2017a). They also investigated the prevalence of physical pre-frailty or physical frailty with impaired cognitive function (MMSE $<$ 26) in 2375 Chinese Singaporeans aged 55 and above without dementia from the SLAS, which led to the prevalence of physical frailty with cognitive impairment and physical pre-frailty with cognitive impairment being estimated to be 1.8% and 8.9%, respectively (Feng et al., 2017b). Furthermore, in 2373 elderly adults from the Italian Longitudinal Study on Aging (ILSA), cognitive frailty was defined as physical frailty and clinically diagnosed MCI, where the prevalence of cognitive frailty was found to be 1.0% (Solfrizzi et al., 2017a). Relative to these studies, a slightly higher prevalence of cognitive frailty was observed in a study conducted by Roppolo et al. (2017). They reported that, of the 594 Italian older adults surveyed, 4.4% subjects were cognitively frail (physical frailty plus MMSE $<$ 26).

In contrast to most of these studies in which physical frailty was defined by the modified CHS criteria, two studies used other criteria to determine physical frailty. Among 1051 elderly adults from the Healthy Older People Everyday (HOPE) study, the combined prevalence of physical frailty according to the FRAIL scale (fatigue, resistance, ambulation, illness, and loss of weight) and cognitive impairment (MMSE $<$ 24) was estimated. Though the subjects with cognitive impairment (MMSE $<$ 24) might have dementia or other neurodegenerative conditions, the prevalence of cognitive frailty was shown to be 1.8% (Merchant et al., 2017). Moreover, St John et al. (2017) investigated the significance of cognitive frailty as determined according to the Frailty Index (FI) proposed by Rockwood et al. (2005). In this study, the FI included 40 variables, and then the individual FI score was calculated as the ratio of actual to potential deficits (deficits present in an individual divided by 40). They categorized the FI as frailty ($\geq$0.25) and non-frailty ($<$ 0.25), with cognitive impairment defined as a score of 25 or less on the MMSE. Of the 1751 community-dwelling elderly subjects, those with frailty (FI $<$ 0.25) and cognitive impairment totaled 211 (12.1%). Since this study did not exclude participants with dementia or and neurological diseases, the prevalence of cognitive frailty may have been higher.

To date, only 4 studies have been performed in the clinical setting. In the Gait and Brain study (Montero-Odasso et al., 2016), 252 older adults aged 65 years or older were recruited from geriatric clinics and a retirement community to increase the probability of enrolling participants with frailty and cognitive impairment, with physical frailty defined by the modified CHS criteria and cognitive impairment defined as a Montreal Cognitive Assessment (MoCA) score below 26 and a CDR of 0.5. In this study, the prevalence of cognitive frailty was shown to be 10.7%. The Multidomain Alzheimer Disease Preventive Trial (MAPT) enrolled a total of 1617 frail elderly subjects aged 70 years or older who had met at least 1 of the 3 following clinical criteria: (i) memory complaint; (ii) limitation in one instrumental activity of daily living (IADL); and (iii) slow gait speed. Frail individuals were defined by the presence of at least one of the CHS criteria, and cognitive impairment defined as a CDR score of 0.5, which led to the prevalence of cognitive frailty being determined to be 22.0% (Delrieu et al., 2016). In a study of 1620 patients recruited in the Toulouse frailty day hospital with frailty defined by the modified CHS criteria and cognitive impairment defined as a CDR score of 0.5, the prevalence of cognitive frailty was shown to be 26.7% (Fougere et al., 2017). The highest prevalence of cognitive frailty was observed in a study focused on patients with advanced heart failure referred to a transplantation center. Among the 156 patients, the prevalence of cognitive frailty (the presence of 3 or more of the 6 domains including 5 physical domains of the CHS criteria and cognitive impairment [MoCA $<$ 26]) was shown to be 39.7% (Jha et al., 2016).

Based on these studies published after proposal of the first operational definition, the prevalence of cognitive frailty is estimated to be 1.0–12.1% among the community-dwelling elderly but as high as 10.7-39.7% in clinical settings. Of note, those studies that did not exclude the subjects with underlying neurodegenerative conditions showed a higher prevalence of cognitive frailty (Jha et al., 2016; Merchant et al., 2017; Roppolo et al., 2017; St John et al., 2017). On the other hand, among the studies focused on the elderly without dementia or other concomitant neurodegenerative conditions, the prevalence of cognitive frailty in community settings was strikingly lower (1.0–1.8%). Although the prevalence of cognitive frailty may be shown to be increased in clinical settings, the lower prevalence of cognitive frailty in the community-dwelling elderly suggests a limited clinical utility. The prevalence of cognitive frailty depends on the population studied and the diagnostic methods used, especially for evaluation of cognitive impairment. Most of these studies defined cognitive impairment by using global cognitive tests, such as MMSE, although the CDR was proposed in the original operational definition of cognitive frailty. Thus, no appropriate and robust instrument is available for detecting cognitive impairment as part of cognitive frailty.

2.3. Cognitive profile

To date, it has been reported that physical frailty is associated with various cognitive dysfunctions, such as global cognition, memory, processing speed, orientation, and verbal fluency (Robertson et al., 2013). Nevertheless, most studies have found a stronger and closer association between frailty and frontal-related dysfunction including attention and executive function (Robertson et al., 2013). Delrieu et al. (2016) investigated the neuropsychological profiles of cognitive frailty in 1617 subjects enrolled in the MAPT study and found that cognitively frail individuals had significant impairment in memory function in a visual analogue scale, CDR-sub boxes, trail making test-A, and digit symbol substitution test than those with cognitive impairment without physical frailty. These results indicate that individuals with cognitive frailty have lower executive and attention performance and that

cognitive frailty has a cognitive profile similar to physical frailty.

This decline in specific cognitive domains suggests that evaluation of executive function could be a useful tool to make a clinical distinction between cognitive impairment due to neurodegenerative disease and that due to physical factors, given that most patients with neurodegenerative disease frequently experience memory impairment (Canevelli and Cesari, 2015).

2.4. Outcome of cognitive frailty

It has been shown that physical frailty has strong predictive validity for adverse health outcomes including falls, fracture, disability, hospitalization, institutionalization and death (Clegg et al., 2013; Ensrud et al., 2009; Graham et al., 2009). Moreover, adding cognitive impairment improves the predictive validity for these outcomes (Avila-Funes et al., 2009).

There are few studies investigating the association between cognitive frailty operationalized by the IANA/IAGG criteria and adverse health outcomes. In cross-sectional studies, Shimada et al. (2016) showed that cognitively frail individuals had the highest risk for IADL limitations in the National Center for Geriatrics and Gerontology-Study of Geriatric Syndromes. Roppolo et al. (2017) also demonstrated that older adults with cognitive frailty showed a higher disability level than those without. In longitudinal studies, Feng et al. (2017b) demonstrated that pre-frailty and frailty with cognitive impairment was associated with an increased incidence of functional disability, poor quality of life and mortality during 3-year follow-up. Solfrizzi et al. (2017a) also showed that cognitive frailty offered additional predictive value for the risk of disability during 3.5-year follow-up. Moreover, they also demonstrated that a model of reversible cognitive frailty, as defined by the simultaneous presence of subjective cognitive decline (SCD) and physical frailty, increased the risk of incident all-cause mortality over 3.5- and 7.0-year follow-up in the elderly without concurrent MCI, AD or other forms of dementia (Solfrizzi et al., 2017b). In a 5-year prospective study of frailty defined by the FI (FI > 0.25), frailty with cognitive impairment was shown to be associated with the highest mortality (St John et al., 2017).

Of the cognitive outcomes, including the incidence of dementia and cognitive decline, the incidence of dementia, in particular vascular dementia (VaD), was associated with physical frailty (Avila-Funes et al., 2012; Solfrizzi et al., 2013; Gray et al., 2013). However, at present, very few studies have investigated the progression of cognitive frailty towards dementia, with only three available for evaluation.

Feng et al. (2017a) investigated whether cognitive frailty may markedly increase the risk of developing neurocognitive disorders (NCD) in a 3-year follow-up study, with the incident cases of NCD defined as those who had cognitive impairment (MMSE ≤ 23), CDR ≥ 0.5 and met the criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for NCD at follow-up. Of the 1491 community-dwelling elderly without NCD at baseline, 118 (7.9%) had NCD at follow-up and cognitive frailty (frailty with cognitive impairment [MMSE < 23]) had the highest odds ratio (OR) for NCD (OR, 6.37; 95% confidence interval [CI], 1.74–23.28). Moreover, Solfrizzi et al. (2017b) examined the association of the reversible cognitive frailty model as defined by the simultaneous presence of physical frailty and SCD with the incidence of dementia in 2150 elderly adults without MCI, AD, or other forms of dementia from the ILSA. As a result, reversible cognitive frailty was shown to be a significant predictor of overall dementia, particularly VaD over a period of 3.5 years (overall dementia, hazard ratio [HR] 2.30, 95% CI 1.02–5.18; VaD, HR 6.67, 95% CI 2.12–20.99) and 7.0 years (overall dementia, HR 2.12, 95% CI 1.12–4.03; VaD, HR 4.76, 95% CI 1.12–4.03).

On the other hand, Montero-Odasso et al. (2016) showed that cognitive frailty was not a risk for dementia in the Gait and Brain study. In this study involving 256 community-dwelling older adults, cognitive frailty was defined by the simultaneous presence of physical frailty (modified CHS criteria) and cognitive impairment (MoCA < 26 and CDR = 0.5) and cognitive decline defined as a decrease of at least 2 points in the MoCA scores, and incident dementia defined using DSM-5 and CDR progressing to one or higher at follow-up. During the follow-up (mean, 18 months), 53 of the 252 participants experienced cognitive decline, and 27 participants progressed to dementia, and cognitive frailty presented no significant risk for cognitive decline or incident dementia. However, when each CHS frailty criterion was combined separately with cognitive status, slow gait (< 1.0 m/s) combined with cognitive impairment significantly predicted incident dementia. Combined slow gait and cognitive impairment was shown to be similar to another clinical construct known as Motoric Cognitive Risk syndrome (MCR) proposed by Verghese et al. (2013). MCR was characterized by both slow gait and the presence of subjective cognitive complaints, and MCR was shown to be associated with an increased risk of developing dementia, especially VaD (Verghese et al., 2013; Verghese et al., 2014a). Although the mechanisms of the association between physical frailty, especially slow gait, and incident dementia remain yet to be fully understood, this association may be explained by the presence of a common underlying pathophysiology. Moreover, the presence of brain pathologies, including cerebral small vessel disease, AD and other neurodegenerative disease, was associated with progression of physical frailty, or specifically a more rapid decline of gait speed in community-dwelling older adults (Buchman et al., 2013). These studies suggest that these brain pathologies including neurodegenerative pathology may manifest as cognitive frailty.

Based on these studies, cognitive frailty is shown to be a risk for adverse health outcomes (disability, poor quality of life and death). While cognitive frailty appears to have a higher risk for dementia, especially VaD, of all cognitive outcomes (cognitive decline and dementia), there is no definite evidence available to support this.

3. New definition of cognitive frailty proposed by Ruan et al. (2015)

In an attempt to refine the framework for the definition of cognitive frailty, Ruan et al. (2015) proposed a new definition of cognitive frailty. The new operational definition includes two subtypes: “reversible” cognitive frailty and “potential reversible” cognitive frailty, each of which is defined based on the following criteria (Table 1):

Reversible cognitive frailty

1) Presence of physical frailty or pre-frailty and SCD and/or positive biomarkers; and
2) Absence of acute impairment, clinical diagnosis of neurodegenerative and other mental conditions.

Potentially reversible cognitive frailty

1) Presence of physical frailty or pre-frailty and cognitive impairment (CDR = 0.5); and
2) Absence of concurrent AD dementia or other dementia.

It is thus assumed that frailty is clearly different from normal aging and is part of a pathological aging process even in physical pre-frailty (Abellan van Kan et al., 2008). Therefore, pre-frailty has already become a target for primary prevention. Thus, it is deemed necessary that physical factors in the operational definition include both physical frailty and pre-frailty.

Cognitive impairment in “potential reversible” cognitive frailty has been operationalized by being regarded as consistent with a CDR score equal to 0.5 and the criteria proposed by the IANA/IAGG (Kelaiditi et al., 2013). Interestingly, “reversible” cognitive frailty is defined by the presence of SCD and/or positive biomarkers (amyloid β accumulation and neuronal injury), thus including pre-MCI and pre-clinical AD. SCD is a non-specific condition and may reflect the first symptom of

numerous conditions including preclinical AD and various types of pre-MCI, such as normal aging, personality traits, individual cultural background, non-AD mental or neurological disorders, and drug-abuse (Jessen et al., 2014). Identified by self-reports, SCD has practical advantages, such as ease of administration, ready availability for clinical application, low cost, safety and convenience. However, it is of note that individuals with reversible cognitive impairment, who may not have SCD, could only be identified by biomarkers (Ruan et al., 2015).

Recently, Solfrizzi et al. (2017b) investigated the association between reversible cognitive frailty and the incidence of dementia in the ILSA, with reversible cognitive frailty defined by the presence of physical frailty and pre-MCI-SCD, and physical frailty operationalized by the CHS criteria, and pre-MCI-SCD assessed according to the positive response to the item of the GDS-30: "Do you feel you have more problems with memory than most?" The study found the prevalence of reversible cognitive frailty to be 2.5%, and that reversible cognitive frailty was a short- (3.5 years) and long-term (7.0 years) predictor of all-cause mortality and overall dementia, particularly VaD. These results indicate that reversible cognitive frailty could be an optimal target for early intervention. However, there is at present insufficient epidemiological data on reversible cognitive frailty to support this.

4. Motoric cognitive risk syndrome

There is increasing evidence that poor gait performance is strongly associated with the incidence of cognitive decline and dementia, especially non-AD dementia (Beauchet et al., 2016; Buracchio et al., 2010; Mielke et al., 2013; Verghese et al., 2007). MCR was proposed by Verghese et al. (2013) as a predementia syndrome which meets the following criteria (Table 1):

1) Presence of both slow gait and subjective cognitive complaints; and
2) Absence of concurrent dementia or mobility disability

Slow gait is defined as walking speed 1.0 standard deviation or more below age- and gender-based means. Cognitive complaints do not require formal cognitive testing and are obtained based on responses to items on standardized questionnaires. In a recent multinational study, the worldwide prevalence of MCR was estimated at 9.7% based on a sample of 26082 older adults from 17 countries (Verghese et al., 2014b). Moreover, the overall age- and gender-adjusted incidence of MCR was estimated as 51–80 per 1000 person-years (Verghese et al., 2014b). The prevalence of MCR is shown to increase with age, and MCR is shown to be associated with Parkinson's disease (PD), stroke, cerebral small vessel disease, depressive symptoms, inactivity and obesity (Verghese et al., 2014b). It is also reported that MCR is associated with an increased risk of developing dementia, especially VaD (Verghese et al., 2013; Verghese et al., 2014a). These cumulative lines of evidence indicate that MCR could also be a target for intervention to prevent cognitive decline.

5. Conclusion and future direction

Following proposal of the first operational definition of cognitive frailty in 2013, several population-based studies using this cognitive frailty model provided epidemiological evidence for this concept. In the community setting, the prevalence of cognitive frailty was shown to be 1.0–1.8% and to be increasing in the clinical setting. Cognitive frailty is shown to have a higher risk for adverse health outcomes including disability, poor quality of life, dementia and death.

However, a number of conceptual and methodological issues remain to be addressed. There is still insufficient evidence to support the new concept proposed by the consensus group. Additionally, it remains difficult to determine whether cognitive impairment is caused by neurodegenerative disease or cardiovascular risk factors in clinical and research settings. Moreover, most elderly adults with MCI are shown to have mixed pathologies (Kapasi et al., 2017).

Furthermore, cognitive frailty has been characterized by its potential for reversibility and represents a target for disability prevention, but the low prevalence of cognitive frailty suggests limited clinical utility of this concept and thus a need for modification of the criteria. A new definition of "reversible" cognitive frailty, which includes older adults with physical pre-frailty and SCD, is expected to resolve this issue (Ruan et al., 2015). In this context, cognitive frailty lacks an appropriate instrument for its detection, especially for evaluation of cognitive impairment, and calls for an evaluation procedure, which is easily and readily available for use in community and clinical settings. Moreover, although most studies used the frailty phenotype to define cognitive frailty, operational definitions of frailty should also be discussed. While multiple operational definitions of frailty have been proposed to date, the frailty phenotype and the FI are widely used. These two operational definitions share common characteristics, but are conceptually different and should rather be considered as complementary to each other (Cesari et al., 2014). Based on the concept that frailty is a pre-disability syndrome, the frailty phenotype clearly differentiates between frailty and disability. Thus, the use of the frailty phenotype is preferred as a screening tool for frailty in the first estimation (Cesari et al., 2014). Conversely, based on the concept that frailty results from accumulation of deficits, the FI takes into account impairment of ADL, comorbidities and geriatric syndromes and can be generated after a comprehensive geriatric assessment (Cesari et al., 2014). Despite this difference in concept, a recent systematic review suggested that both the frailty phenotype and the FI were associated with late-life cognitive impairment and incident dementia (Panza et al., 2015b). These results indicate that the FI could also be an appropriate instrument to determine the vulnerability of dementia and the dependence of the elderly. Further investigation is also needed into cognitive frailty models as operationalized by the FI (Panza et al., 2015b).

The underlying mechanisms of cognitive frailty also remain unclear. The close association between physical frailty and cognitive impairment suggests the presence of an underlying mechanism common to these conditions, which may include cardiovascular risk factors, chronic inflammation, nutritional problems, cerebral small vascular disease and AD or other neurodegenerative pathology (Panza et al., 2015a; Panza et al., 2015b). Identifying common modifiable factors between cognitive frailty, physical dysfunction and cognitive impairment may help develop effective strategies for preventing progression of disability and dementia among older adults.

In conclusion, there is as yet no consensus on the definition of cognitive frailty as applicable in clinical and community settings. Again, a consensus remains yet to be reached on which measures to be used for detecting cognitive impairment. Further study is required on cognitive frailty to develop successful preventive strategies for progression of dementia and dependency in older adults.

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