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Mini Review

Cognitive frailty: a brief review

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Abstract

Frailty syndrome and cognitive decline, conditions linked with aging, jeopardize health status and promote an individual's dependence on daily living activities. Various models include cognition in the assessment of frailty, but recently a new term has been proposed, called "Cognitive Frailty'', originally presented as a probable outcome of frailty, but later it has been proposed to be an early sign of the syndrome. Cognitive frailty encompasses both the physical and the cognitive domain, explored as a unique entity, and includes two subtypes, the reversible and the potentially reversible cognitive frailty. Most studies examine cognition as another domain of frailty, using different methods for the assessment of both frailty and the status of cognition. In the present article, various definitions of the frailty syndrome and cognitive frailty as well as screening tools are reviewed. The link between cognitive impairment and frailty, and the common pathophysiological mechanisms such as neuropathological, vascular and metabolic factors, inflammation, hormones and nutrition are explored. Finally, this review presents the effects of multi-domain and single domain interventions, conducted in physical and/or cognitively frail populations that may be applied to the prevention and management of cognitive frailty.

Keywords: Cognition, Cognitive Frailty, Frailty Syndrome

Introduction

The frailty syndrome has received numerous attention over the years due to its consequences to adverse health outcomes, and relationship to aging, as indicated by various studies. Frailty is different from comorbidity and disability, but extends to both and vise versa[1]. The health outcomes may be detrimental and include falls, disability, hospitalization, and early mortality. For example, in a cohort study that examined institutionalized people, it was found that it is 3.3 times more probable that frail older adults will be disabled or dead in a year follow up[2]. In community dwelling people, the results of a meta-analysis reflected the higher probability of falls in frail, primarily, and pre-frail, secondly, older adults[3]. In addition to the previous study the community based Health and Retirement Study (HRS) displayed that frail and cognitively impaired individuals are prone to develop future disability expressed as dependence on activities of daily living (ADL dependence)-and death[4]. Furthermore, the level of frailty jeopardizes the elderly in the concept of making them susceptible to falls, dependence, institutionalization and death[5].

Besides the occurrence of death, frailty and its consequences have a large impact on Quality of Life (QoL). This concept is in accordance with the results of a study that demonstrates that older frail persons perceive their QoL as substantially lower, in comparison with their pre-frail and non-frail counterparts[6]. There is a link between aging, frailty and cognitive decline. Frailty is ascribed to various hazardous factors, age being one of them[7]. Consequently, older people are more likely to become frail[5]. Age also was associated with a rapid rate of -physical frailty related-cognitive decline[8], and was determined a crucial factor in dementia because it contributes to the progression from Mild Cognitive Impairment (MCI) to the former[9]. Thus, it is the current trade to scrutinize MCI[10] in the light of frailty, something that may indicate the increasing prevalence of cognitive frailty during the aging process[11].

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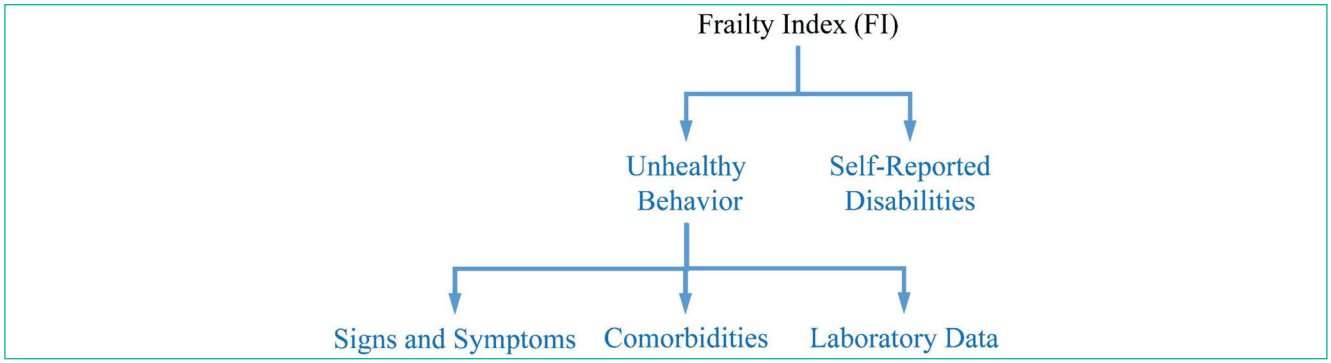

Figure 1. The Frailty Index (FI) algorithm.

Frailty domains	Frailty components
Physical:	Unintended weight loss, walking difficulties, grip strength, fatigue, balance, sight and hearing loss
Psychological:	Cognitive functions, depression symptoms, anxiety, activities of daily living
Social:	Living alone, social relations, supportive environment

Table 1. The Tilburg Frailty Index (TFI).

Domains of frailty

Regarding the question "what is frailty syndrome?" researchers haven't reached an accord pertaining to a common well accepted definition, thus there are several of them originated by the various frailty models respectively. In 2001, Fried et al. (2001) described frailty as a clinical syndrome, in which a person is vulnerable to acute stressors due to age related decline, both functional and in reserve, across multiple physiologic systems, resulting in an inability to maintain a stable homeostasis. She proposed a definition based on Frailty Phenotype, characterized by the presence of at least three out of five criteria: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity Conversely, the accumulation of one or two criteria identifies a pre-frail state that presents a high risk for frailty[1]. However this model does not take into account the psychological, cognitive, and social domain in the screening for frailty. On the contrary Rockwood et al. (2005) approached frailty from a multidimensional angle, applying both physical and cognitive origins to the frailty syndrome. Therefore a new definition of frailty was put forward based on a deficits accumulation such as unhealthy behaviour, signs and symptoms , laboratory data , comorbidity, and self-reported disabilities, whose screening tool is Frailty Index (FI), representing the total sum of deficits present on a person, that add up to 70. For example, when o person gathers 10 deficits out of 50 it results to a FI 10/50=0.20[12,13] (Figure 1).

On the other hand R.J. Gobbens et al. (2010) proposed the integral conceptual definition by which frailty was discerned as a dynamic state impacting on a human being who endures losses: a) concerning the physical, psychological including cognition, and social realm and b) are attributable to a range of variables, consequently leading to poor probabilities for adverse outcomes[14]. This model uses The Tilburg Frailty Index (TFI) a questionnaire that identifies frail older subjects, the severity of the syndrome and the specific frailty domain[15,16] Table 1).

Inevitably over the years many researchers have been involved in the study of frailty, therefore proposing definitions, measure tools and scales that differ between them.Despite the lack of agreement among the scientific community, a new entity appeared called cognitive frailty, that applied to both physical and cognitive decline, on account of the increasing interest and thought-provoking findings related to the cognitive defaults accompanying frailty.

Cognitive frailty

According to the International Academy on Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) (IANA/IAGG), an international consensus group, cognitive frailty indicates the concurrent clinical presence of both physical frailty and also of cognitive impairment. Specifically, this condition requires the co-existence of both physical frailty and cognitive impairment with a Clinical Dementia Rating (CDR) equal to 0.5 and the

Definitions of cognitive frailty	
Kelaiditi et al. (2013)[17]	a) Physical frailty + cognitive impairment b) Clinical Dementia Rating (CDR)=0.5 c) No dementia
Yu et al. (2018)[18]	Cognitive impairment + a pre-fraity status
Liu et al. (2018)[19]	Cognitive impairment (any domain) + dynapenia (slowness and/or weakness)

Table 2. Definitions of cognitive frailty.

exclusion of all types of dementia. Still, in a different situation cognitive frailty may signal a neurodegenerative process. A recognizable psychological element contributes to making the individual more vulnerable to stressors. The consensus group was exclusively interested in discussing cognitive decline and the existing evidence as a potential outcome of physical frailty and not the reverse, accounting to the already well known underlying neurodegenerative pathways[17].

Contrary to IANA/IAGG, cognitive frailty may be defined by the co-occurrence of cognitive impairment and a pre-fraity status rather than frailty[18]. In support to this study cognitive frailty was defined as the presence of both cognitive impairment in any domain and dynapenia expressed by slowness and/or weakness, both part of Fried's criteria for frailty that represent a decrease in muscle strength and physical ability[1] (Table 2).

There aren't many studies referring to the prevalence of cognitive frailty (CF), as frailty and cognitive impairment is only recently explored as a unique entity. The combined prevalence of frailty and MCI was found 2.7%[20], 9.8% in a later study[20] and Liu et al. (2018) presented a percentage of 13.3%[19]. Sex (women) were indicative of CF status and living in rural rather , than urban areas[11,21].

Stages of cognitive decline

The stages of cognitive decline are presented in Figure 2. Mild Cognitive Impairment (MCI) stands between normal cognition and clinically probable Alzheimer's disease. In 2003 a first key symposium was held by the International Working Group on Mild Cognitive Impairment and a consensus was reached in recommendations for the general MCI criteria including the following: a) absence of normal cognition as well as dementia, b) self/informant reported evidence of cognitive decay, and/or objective decline on cognitive tasks over time and c) the person preserves basic activities of daily living and is able to function at least adequately in complex tasks. MCI was further classified into three subtypes: amnestic, multiple domain, and single non-memory domain MCI[22].

A grey zone exists between normal status and MCI that may be indicating a pre-MCI state[23,24], called Subjective Cognitive Decline (SCD). Usually cognitive impairment comes from a gradual development of a neurodegenerative disease until it comes to the point where a deficit is detected by a

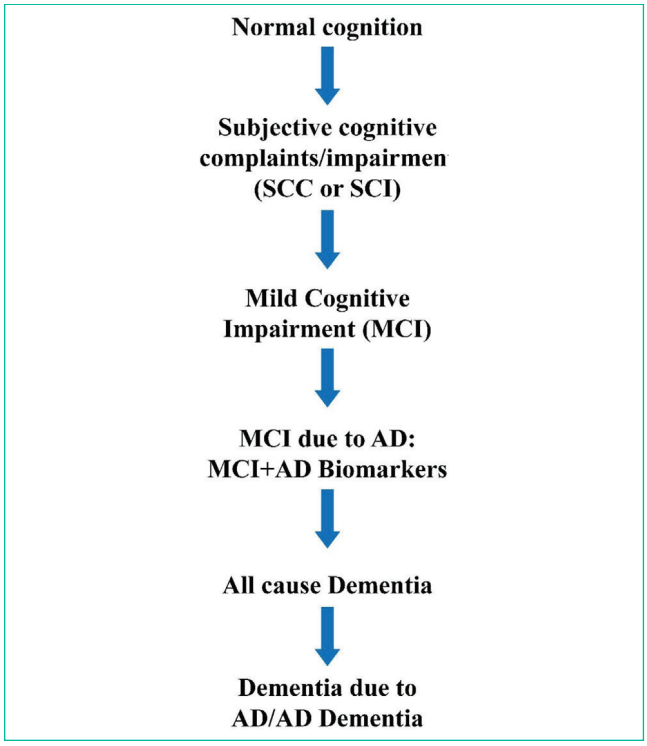

Figure 2. The stages of cognitive impairment.

standardized neuropsychological test[25]. According to Jak et al. (2009) MCI typically requires >1 standard deviation (SD) deficit in any cognitive domain or test[26-28] as opposed to stricter criteria of at least 1.5 SD on specific tests, usually memory tests[29,30].

The working group of the Subjective Cognitive Decline Initiative (SCD-I) proposed the term "Subjective Cognitive Decline" (SCD) to define a self-experienced persistent -over a >6 months period- decline in a previously intact cognitive ability that cannot be detected on standardized neuropsychological tests and is not related to an acute event[31-35]. According to them the criteria for MCI are: a) Clinical Dementia Rating (CDR) ≥0.5 or a Global Deterioration Scale stage 3 or more, or a neuropsychological profile

indicating MCI; b)Deficit of >1.5 SD on a single test currently used in studies to define MCI (e.g., an episodic memory test); or c)Deficit of >1.0 SD on two tests within one cognitive domain or of three single tests in three different domains. Furthermore, in order to put the term SCD to practical use with regard to activities of daily living, basic and instrumental (ADL,IADL), the group suggested that SCD manifests as a perception of decrease in the mastery of performing a task, while MCI may mean a subtle functional decline without clear impairment[36].

Screening for cognitive impairment

The gold standard for identifying cognitive decline is a full neuropsychological assessment, ergo cognitive status is usually evaluated by brief assessment tools including a series of tasks completed by the patient, scored as correct or incorrect, and by rating scales for the identification and staging of cognitive decline based on information acquired during a review[37].

A successful neuropsychological screening test for cognitive impairment is statistically robust (high sensitivity, specificity and high predictive value), easy, and quick to administer. It doesn't favour memory disorders over other cognitive domains, but should be able to discriminate all dementia types in unselected populations and cover six core domains: attention/working memory, new verbal learning and recall, expressive language, visual construction, executive function and abstract reasoning. Screens could be administered directly to patients, or be partly or fully informant rated[38].

However the screening for SCD holds major difficulties because most of the available assessment tools focus on the memory domain contrary to the concept that SCD assessment must not be limited to memory when dealing with non-AD dementias or not typical forms of AD[39]. The most widely known screening tool measuring cognition is the Mini-Mental State Examination (MMSE), firstly published in 1975 which includes attention/working memory, new verbal learning and recall, expressive language and visual construction tasks[40]. One of MMSE's limitations is its inadequacy to identify mild cognitive impairment[41].

In order to overcome the MMSE's limitations, other screening tools have been proposed such as the Cognitive Abilities Screening Instrument (CASI) which is a 40-item 100-point test[42] and The Modified Mini-Mental State Examination (3MS). Both examine all 6-core domains. The 3MS is basically an expanded MMSE test with an extended scoring procedure toward achieving better discrimination ability among individuals[43], specifically the discrimination of MCI from intact cognition[44].

On the other hand, a meta-analysis suggested that the new version of Addenbrooke's Cognitive Examination (ACE), the ACE-R, which focuses on all core domains minus reasoning/ judgment, was suitable for both primary and secondary/ tertiary care settings being slightly superior to the MMSE[45].

The Abbreviated Mental Test Score (AMTS) is a 3–4 min 10-items test focused on orientation, registration, recall and concentration, but with low positive predictive value[46]. It is useful in primary care where it was found superior to the MMSE for case finding, but inferior for screening[47,48].

The Clock drawing test entails the drawing of a clock face that shows the time requested[49], and has become a part of numerous cognitive screening batteries[50] e.g. Mini-Cog. Initially it was used for screening for dementia, but later for detecting more subtle disorders connected to executive function[51]. The Mini-Cog integrates the clock-drawing test, and a word recall task into a 3 min test. It has shown approximate sensitivity and specificity to MMSE , and is suitable for screening in primary care[52], or settings with a higher prevalence of dementia[47,48]. The General Practitioner assessment of Cognition (GPCOG) is an efficient tool for dementia screening in primary care settings consisting of two sections: the patient and the informant section. The first section includes a nine item cognitive test, whereas the second includes eight history related questions[53-56]. The Montreal Cognitive Assessment (MOCA), is a 10-minute cognitive test developed for the detection of MCI[57], and a useful tool in screening for dementia due to vascular impairment[46]. The DemTect Scale is a neuropsychological screening test for MCI and early dementia including the following tasks : repeating a word list, number transcoding, word fluency, digit span and delayed world list recall[58]. As mentioned, in addition to the neuropsychological tests there are also staging systems of cognitive decline in which a specific, structured interview is not a prerequisite for their procedure[37]. The Clinical Dementia Rating scale is a five-point scale assessing 6 categories of cognitive and daily function usually affected in the dementia of the Alzheimer type: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Depending on the final score the subjects are classified as: no dementia(CDR:0), questionable (CDR:0.5), mild (CDR:1), moderate (CDR:2),and severe (CDR:3) dementia[59]. The Global Deterioration Scale (GDS), as CDR, is also used for the assessment and classification of a subject's cognitive function[46], largely interested in memory dysfunction and daily living disabilities[60].

Evidence for the relationship between cognitive impairment and physical frailty

Despite the lack of a gold standard screening tool for frailty, there are various studies across the world that explore the role of cognitive disorders within the frailty domain, presenting an heterogeneity in the methods measuring both frailty and cognitive assessment[61]:

a) Cross-sectional studies. In community dwelling French people, aged 65-95, frailty status was associated with more subjective cognitive complains and depressive symptoms than pre frailty and normal status[62-64]. Cognitive impairment was also detected in 39% of frail,

22% of pre-frail and 16% of robust population aged 65+ in a poor area of Sao Paolo[65-67]. MMSE screening identified frail older adults with significantly lower performance in Time Orientation and Immediate Memory[68, 69]. In Spain, community dwelling adults aged 75+ who were classified as frail and robust, were found to have cognitive impairment at a percentage of 20% and 5.3%[70]. In Japan, older women aged 65+ classified as frail, were prone to cognitive decline, as measured by MMSE, in a study searching the relationship between frailty and related factors[71]. In a clinical setting, 65+ year old participants, admitted to the Toulouse frailty day hospital, were examined for frailty and cognitive disorder[72-76]. Physical frailty was found in 51% of the cognitively impaired patients versus 38% of the patients with normal cognition, with gait speed being more related to cognitive impairment[73-76]. In Korea, older adults with frailty, living in a rural community, were more likely to have poorer cognitive functioning[77], as well as in China, where frail participants performed worse on global cognition in all cognitive domains than their robust and pre frail counterparts[10]. Additionally, Frailty Syndrome correlated with reduced cognitive ability in two Brazilian cities[78], pre frailty with worse memory and processing speed performance[79], while Subjective Cognitive decline may soundly indicate frailty in the otherwise unimpaired elders[80]. In all studies the cognitive failing interacted with frailty among other factors like age, sex, lower education, comorbidity and depressive symptoms.

b) Longitudinal studies. MMSE screening identified frail older adults with significantly lower performances in Time Orientation and Immediate Memory[68,69]. A study assessing elders with frailty that accelerates concluded to them having a higher risk of developing Alzheimer's Disease. The level and the rate of this happening influences the rate of cognitive decline[81-83]. In frail older Mexican Americans, a score of at least 21 on MMSE (mini mental test examination) at baseline was an independent predictor of a deteriorating cognitive function over a 10-year period[84]. Also, frail people who at baseline were normal, except in the domain of perceptual speed, in annual follow ups during a 12 year period, were found to be at high risk of developing MCI, showing a more rapid decline in episodic/ semantic memory, working memory and visuospatial ability, in addition to the perceptual speed, and sooner than non frail people[8]. Correspondingly, a four-year prospective study demonstrated frail older adults without cognitive impairment at baseline, nevertheless developing cognitive decline over a four year period[85-87]. In 2012, community dwelling participants in Japan aged 70+ with Subjective cognitive changes at baseline, were significantly associated with development of frailty at follow up. In the same year, the results of a three-City Study identified cognitive impairment as a major factor contributing in future disability, whereas frailty showed inconsiderable association with non AD dementia, non association with incident Alzheimer's disease, yet being frail independently collaborated with incident VaD , in contrast with Boyle et al findings[88]. Similarly, in Seattle, in a population based sample of people over 65 years old, frailty was associated with 16 year incidence of non-AD dementia[42]. These results are in accord with another study, that demonstrated a higher rate of overall and particularly VaD dementia in frail individuals[89,90]. Mapt trial examined cognitive capacity in association with frailty syndrome, showing a lower level of cognitive functioning in frailty status than pre frailty. Frail older subjects scored worse at executive and attention tests, contrary to cognitively impaired subjects without frailty, plus presented a different subcortico-frontal cognitive model than those with Alzheimer Disease[91]. In recent years, a model of reversible cognitive frailty has been proposed represented by physical frailty and self-reported cognitive decline to predict overall dementia, particularly VaD[92,93]. In conclusion, cognitive deterioration seems to be strongly related to Frailty Syndrome, but whether it precedes or results from the latter is not certain. Some studies present cognitive decline as an outcome of physical frailty, an opinion which coincides with a meta-analysis that examined the mean cognitive profile of frail and pre frail participants, assessed in observational, cohort and cross-sectional studies. This study indicated the decreasing cognition to be a probable outcome of frailty[94], while other suggest that cognitive failure may be an early sign of frailty[95].

Pathophysiology of cognitive frailty

Although cognitive frailty is considered a multi-factorial and hence complex phenomenon, several mechanisms are known to participate in its pathophysiology.

Neuropathological factors: S*ubstantia nigra* neurofibrillary tangle were linked to gait speed[96], and frailty was associated by AD pathology, in people with or without dementia[97], but these findings conflict with other studies, that link frailty to non AD dementia and non amnestic cognitive impairment[98,99].

Vascular factors: vascular damage can reduce blood flow to the cerebrum, skeletal muscles, and heart and may have an effect in the pathophysiology of geriatric syndromes like frailty and cognitive impairment[100-103], perhaps through arterial blood pressure (BP), which coordinates tissue perfusion[104]. Cardiovascular deficits predict frailty, as well as cardiovascular disease and cognitive decline[100-103]. Cognitive vascular disorder represents a part of a group with different cerebrovascular lesions that cause cognitive impairment, and ultimately lead to dementia[105,106]. Several factors that increase the risk of vascular disease can affect cognitive capacity[98], such as those which promote atherosclerosis and inflammation inside the vessels, and result in the reduction of blood flow[107,108].

Inflammation: an immune response motivated by many inflammatory mediators is associated to various

conditions, such as cardiovascular disorders, infections, rheumatological, and neuroinflammatory conditions[109]. Chronic inflammation is a possible contributor to the development of frailty syndrome[110] as IL-6, TNF-a and other inflammatory proteins were found to increase the risk of morbidity and mortality with TNF-α and IL-6 levels identified as markers of frailty[111-113]. These findings concede to a systematic review and meta-analysis, which linked frailty and pre-frailty with higher levels of inflammatory factors, particularly CRP and IL-6[114]. In addition to frailty, inflammation appears to play a role in cognitive decline[115]. Higher levels of IL-8 were associated with poor memory performance, processing speed and motor function (Baune et al., 2008). Inflammatory markers have also been found in the cerebrospinal fluid of patients with dementia(AD and non AD)[109]. This inflammatory response is possibly managed by the microglia, resulting in neuronal damage and dysfunction[116]. Contrary to the previous studies, Liu et al. (2018) suggested, that perhaps inflammation does not have a significant pathophysiological role in cognitive frailty[117].

Metabolic factors: the relationship between frailty and metabolic parameters has been explored by several researchers. In a study of older people without frailty at baseline, insulin resistance was associated with incident frailty[118], whereas four vascular risk factors (type 2 diabetes, hypertension, obesity and dyslipidemia) were related to cognitive decline, particularly type 2 diabetes and hypertension[119]. In *Diabetes Mellitus*, hyperglycemia due to insulin resistance leads to inappropriate secretion of insulin and hyperinsulinemia. Consequently, the cells are exposed to high levels of insulin for an extended period of time, with adverse outcomes especially for neurons[120] resulting in cognitive impairment[121]. Some authors have expanded this concept of cognitive decline to the point of referring to Alzheimer's disease as a type 3 diabetes mellitus (T3DM), involving specific domains of the brain, and overlapping with both type 1 and type 2 DM[122]. Type 2 diabetes is also associated with reduced volumes in the brain, and progressive atrophy, independent of cerebrovascular disease[123], contributing perhaps to neurodegeneration and tau pathology[124]. Metabolic syndrome (MetS) was found to be associated with amnestic MCI, especially in individuals with APOE-ε4 at younger age[125], frailty and cognition[126]. Similarly, midlife total cholesterol, low-density serum lipids, lipoprotein cholesterol, and triglycerides correlate with later impaired cognition, with low HDL-C being an independent risk marker for later cognitive decline.

Hormones: age related hormonal changes may have some effect in the health status decline and play a significant role in the development of frailty, by leading to sarcopenia caused by the reduction of muscle strength and mass[127-131]. Dehydroepiandrosterone (DHEA), a neurosteroid of the HPA axis ,is the predecessor of androgens and estrogens, and mostly exists in circulation as DHEA-S[132]. Lower DHEA-S levels has been found in frail people, while higher serum DHEAS levels were associated with better working memory, with a trend toward better executive function in men. Decreased sex steroids may also be a factor in the development of frailty in men. As testosterone promotes synaptic plasticity in the hippocampus, and regulates the accumulation of amyloid beta protein , low androgen hormone levels may also have a role in cognitive dysfunction. Growth hormone (GH) level decreases with age, and is considered to be related both to frailty and cognitive impairment[133]. Disruption in regulation of the hypothalamic-pituitary adrenal axis could have an adverse outcome in the cognitive function of the elderly, with respect to the relationship of hypercortisolemia with lower cognitive performance in specific domains of cognition. Ghrelin, the "hunger hormone" may contribute significantly to both frailty and cognitive impairment[134]. A study suggested that frail women had a higher possibility of lower levels of fasting ghrelin and 120 min ghrelin[135,136], while in men with AD, metabolic alterations may be the result of reduced secretion of this hormone[137]. There is a relationship between low levels of vitamin D and poor muscle performance, through molecular mechanisms of Vitamin D3 activity in muscle tissue[138], that might explain the significant role of Vit D in the development of sarcopenia, a major component of frailty[139]. Hypovitaminosis D was associated with prevalent and incident frailty in older men[140,141], and with sarcopenic status in elderly women[142]. Low vitamin D levels were independently associated with frailty[143]. A cross-sectional study also linked 25(OH)D with performance in specific domains of cognition, in particular executive functioning and possibly information-processing speed[144-146].

Nutrition: sarcopenia includes reduced muscle mass/strength[147] and associates with pre-frailty and frailty[71]. Frailty and malnutrition are distinctly related[148,149], but the lower muscle mass , a component of Frailty Phenotype, may be irrelevant to weight status[150], and more related to specific or a combination of nutrients intake[151]. An inadequate diet is a major cause of frailty[152]. Insufficient protein consumption is one of the main nutritional deficits among frail persons[153], while a systematic review recognized the impact of energy intake and nutrient quality upon the development of the syndrome[154]. Regarding the construct of cognitive frailty, sarcopenia[71] and its component reduced muscle strength and/or physical performance related to non-muscle etiology, were associated with cognitive impairment[155]. Lower energy and protein nutrition were found to have a negative impact on cognitive performance. Anorexia of aging, a contributor to weight loss, and cognitive decline have some peripheral and central peptides involved in their pathophysiology[156]. Fatigue, linked perhaps to anemia, vitamin B12 and/or vitamin D deficiency, also associated with cognitive decline[157]. Nutritional factors may affect brain health and this influence pertains to several mechanisms like oxidative stress, inflammation, and neuroinflammation[158,159]. The brain vulnerability to oxidative damage[160], the influence

of neuroinflammation, the suggested altered immune responses in the brain caused by the linked systemic chronic low-grade inflammation with obesity, aging and chronic diseases[161], plus the link between autophagy deterioration and deregulated mTOR signaling (a key regulator of autophagy) with glucose metabolism and neurodegenerative diseases, are proposed to affect the progression of cognitive decline[158,159].

Reversible and potentially reversible cognitive frailty

Frailty affects quality of life and reduces the lifespan. Frailty status when complicated with cognitive degeneration further jeopardizes health status. It is of the utmost importance to address frailty in a manifold manner, identifying factors that lead to successful and cost effective social care interventions[162]. Approximating cognitive frailty and impairment in cognition together as a unique complex phenotype may be critical to forestall all cause dementia[163]. Cognitive frailty is caused by physical or pre-physical frailty and encompasses two subtypes: the reversible cognitive frailty, indicated by subjective cognitive decline (SCD) and/or biomarkers of amyloid-β accumulation and neurodegeneration and the potentially reversible is MCI[164]. A model of reversible cognitive frailty was identified as predictor of all-cause mortality and dementia, especially VaD[93]. In non demented elders with advanced inflammation, a potentially reversible cognitive frailty model could also predict the additional risk of disability better than frailty or MCI alone[92]. SCD may be a determinant of frailty in elders without apparent cognitive impairment thus being included in the assessment/detection of frailty will help the implementation of suitable planning for the maintenance of healthy aging[80].

Prevention and management of cognitive frailty: conclusions

Any policy including multi-domain interventions intended to alleviate or converse cognitive frailty should consider the complicated concept of this condition[17]. Multi-domain interventions may be capable of preventing cognitive frailty[165]. Interventions focused on physical, nutritional, and cognitive domain were effectual in reversing frailty among community-dwelling older people. A home-based conducted intervention of physical training, nutritional, and social support helped to address malnutrition and frailty[166]. A systematic review on the influences of multi-domain (physical exercise, nutritional, pharmacological, psychological, social) versus a single domain interventions on functional and cognitive status in frailty recognized limited but increasing evidence of the multi-domain approach e.g. exercise with nutritional support[167]. Combined exercise training, intake of hyper-protein nutritional shakes, memory training and medication review reversed frailty measures among frail elders168. lindicatively, a moderate exercise program was effective in the improvement of cognitive frailty[19,117]. Resistance exercise training combined with additional protein intake had a positive effect on information processing speed whereas exercise training alone benefited attention and working memory in frail and pre frail individuals[169]. In addition, high-speed resistance exercise training improved cognitive and physical function in cognitively frail older adults[170]. A combination of Mediterranean diet with standard physical and mental exercise was hypothesized to be the best prevention against future cognitive decline[158,159]. The management of under nutrition could be improved by higher energy/protein intake, physical activity and by having a less unsafe approach to glycemic targets in frail diabetic older people with respect to hypoglycemic risk[171]. Evidence doesn't yet support hormone supplementation[172] but anti-cholinergic drugs may have a role in the prevention of both physical and cognitive declines[173] and new treatments which affect the gut microbiota-muscle-brain axis could be useful[174]. In conclusion interventions conducted in carefully chosen evidence-based circumstances advocate clinical investment in the management of frailty and its outcomes such as cognitive decline[172].

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