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Cognitive frailty: a conceptual systematic review and an operational proposal for future research

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Abstract

Objective

To analyze the definition of "cognitive frailty" and to study the conceptual and operational definitions used and their implications for empirical research. The relationships between this concept and cognitive reserve, the role of neuropathology and brain reserve, motor signs of aging and the reversibility of cognitive frailty are also discussed.

Study design

Systematic review of empirical studies identified from Medline Advanced 1966, CINAHL, Web of Science, PsycINFO, and Scopus until August 2017.

Main – outcome measures

Effect sizes. The quality of the articles was assessed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement. Three independent reviewers participated in the study selection and data extraction.

Results

Nineteen studies involving 31,707 participants met the inclusion criteria. Significant associations were reported between cognitive frailty and physical frailty or gait speed. Screening instruments were usually used to determine objective cognitive decline rather than extensive neuropsychological assessments. Educational level was the only indicator of cognitive reserve that was systematically included in the evaluation of cognitive frailty. Motor decline and gait variables were not systematically included in protocols for the assessment of cognitive frailty.

Conclusions

A strong operational definition would benefit both the development of treatments to counter cognitive frailty and the assessment of treatment effectiveness. Nevertheless, since there is clear agreement regarding the importance of interventions for and the prevention of cognitive frailty, randomized controlled trials investigating the efficacy of preventive interventions are necessary.

Keywords

Cognitive frailty; Cognitive aging; Cognitive impairment; Physical frailty; Cognitive reserve

1. Introduction

Consensus about the importance of early recognition of cognitive impairment and the increasing evidence that cognitive impairment and physical frailty often coexist in older adults has raised attention about the concept of cognitive frailty [1]. Beyond the original concept of frailty, which is defined by physical status, more recent definitions have considered at least three domains of frailty including physical, cognitive and psychosocial aspects, maintaining the complex relationships between them [2]. Kelaiditi et al. [3] provided the first consensus definition of cognitive frailty in older adults, considering the simultaneous presence of physical frailty and mild cognitive impairment (MCI) (Clinical Dementia Rating, CDR = 0.5) in the absence of dementia or pre-existing brain disorders. According to this working definition developed by the International Academy on Nutrition and Aging (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G) international consensus group, cognitive frailty is conceptually described as a state of reduced cognitive reserve that is different from physiological brain aging and is characterized by potential reversibility. Regarding reversibility, Ruan et al. [4] further differentiated between reversible and potentially reversible cognitive frailty. The former is indicated by subjective cognitive decline (SCD) and positive biomarkers of neurodegeneration, and the latter by MCI.

The I.A.N.A /I.A.G.G. definition has been useful for raising awareness of the relationship between poor cognitive functioning in old age and systemic physical diseases [2,5]. Nevertheless, other questions, such as the exclusion of brain disturbances that may exacerbate the symptoms of cognitive impairment, the poor differentiation between cognitive and brain reserve, and the diagnostic challenges related to individuals without cognitive impairment but with a CDR = 0.5 in certain vulnerable situations (i.e., during hospitalization, in response to stress or during changes in their physical environment), remain controversial [5]. The consensus definition developed by Kelaiditi et al. [3] also fails to specify changes in the motor system beyond the common motor manifestations included in the assessment of physical frailty, and does not highlight the roles of these changes in cognitive function. Buchman & Bennet [6] have stressed the relationship between the motoric aspects of physical frailty that are dependent on the central nervous system and cognitive aspects of daily living. Both physical and cognitive performance are measured by markers directly related to the motor function of older individuals. Finally, according to Morley et al. [1], the concept of cognitive frailty has been viewed as important because of the potential to implement preventive interventions for this condition; however, this potential needs to be empirically validated.

The aim of this systematic review is to analyze the definition of the term “cognitive frailty” implemented in the empirical literature and to study the conceptual and operational definitions used and their implications for empirical research. Complementarily, advances in the study of the relationship between cognitive frailty and cognitive reserve, the role of neuropathology and brain reserve, and the relationship between motor signs of aging and the reversibility of cognitive frailty, are discussed.

2. Materials and methods

2.1. Data source and search strategy

A systematic review was conducted in August 2017 by searching for the term “cognitive frailty” in Medline Advanced 1966, CINAHL, Web of Science, PsycINFO, and Scopus without temporal limits. All possible articles were merged into a single file, and duplicate records were removed after they were checked manually. Three independent authors reviewed the title, abstract and keywords of each article and evaluated the appropriateness for inclusion, and any conflicts were discussed until a consensus was reached.

2.2. Inclusion and exclusion criteria

We included original empirical studies that explicitly used the term "cognitive frailty". We excluded reviews, editorials, notes, conference papers, letters, books, book chapters, book series and study protocols. Only full-text articles published in either English or Spanish were considered. Finally, only articles that explicitly measured frailty and cognitive performance were included after full-text review.

2.3. Data extraction

Three independent authors reviewed the full-texts, and the studies were organized according to the following characteristics: authors and year, country, study design, sample size and sample characteristics (age, sex and diagnostic group), setting, operational definition of cognitive frailty, cognitive frailty and physical frailty measurement tools, prevalence of frailty and main findings. Complementarily, explicit mentions of cognitive reserve, the role of neuropathology, the relationship of cognitive frailty to motor capabilities or the reversibility of cognitive frailty were recorded.

Three measures of effect size (ES) were computed according to the outcomes to be compared. Cohen's *d* values were included as indicators of effect size for comparing the mean values and defined as "small ES" ($d = 0.2$), "medium ES" ($d = 0.5$) and "large ES" ($d = 0.8$) as proposed by Cohen [7]. The ES of the difference between two proportions was estimated according to the arcsine transformation by Cohen [7], and Cohen's *h* values were obtained and defined as "small ES" ($h = 0.2$), "medium ES" ($h = 0.5$) and "large ES" ($h = 0.8$). Finally, odds ratios were converted into Cohen's *d* ES using a method proposed by Hasselblad & Hedges [8].

3. Results

The review procedure is described in Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was followed [9] to assess the quality of the included articles (see Appendix 1). As shown in the figure, a total of 191 studies were identified. After removing duplicates, 80 were considered potentially relevant and were screened. Of these studies, 60 were excluded after review of the title and abstract (see Appendix 2 for details). Accordingly, 20 studies were retrieved for full-text assessment. Ultimately, 19 studies met the criteria and were included in this review.

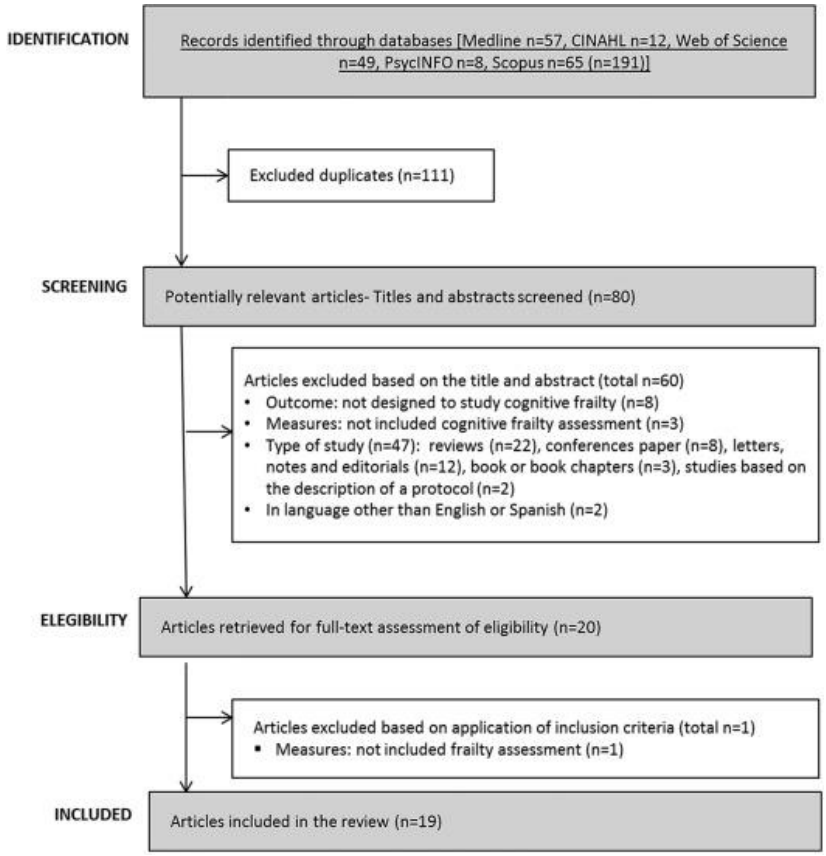

Fig. 1. Flow diagram of study selection.

3.1. Participants and study characteristics

The included articles encompassed a sample of 31,707 middle-aged and older adults. A total of 27,779 adults participated in population studies, and 3928 were assessed in clinical settings. Nine studies were conducted in Europe [[10], [11], [12], [13], [14], [15], [16], [17], [18]], 5 in Asia [[19], [20], [21], [22], [23]], 3 in North America [[24], [25], [26]] and one each in South America [27] and Australia [28] (a more detailed description of the samples is included in Appendix 3).

The identification of cognitive frailty was based on the I.A.N.A /I.A.G.G. consensus definition in 10 studies [11,13,[16], [17], [18],[21], [22], [23],25,26]. Of those, only 4 used the CDR = 0.5 score criteria [11,13,21,25], 3 used Mini-Mental State Examination (MMSE) scores [16,22,26], 2 used MCI clinical criteria [17,18], and one used the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT) scores for diagnosis [23]. Globally, 12 studies used the MMSE [[10], [11], [12], [13],[16], [17], [18], [19], [20], [21], [22],26], and 3 studies used the Montreal Cognitive Assessment (MoCA) [24,25,28]. In terms of more specific cognitive assessments, 6 studies analyzed data from complete neuropsychological assessments (in addition to the cognitive tests used for MCI diagnosis) [[10], [11], [12],14,15,23], and one study used dual tasks [12]. In terms of physical frailty, 5 studies [10,11,13,23,25] used the frailty phenotype as described by Fried et al. [29], and 9 used modifications of this frailty phenotype [[15], [16], [17], [18], [19],21,22,24,28] including 2 modifications for specific clinical populations [24,28]. Three studies used other physical frailty tools (Gobbens' frailty criteria as a complement to the Fried Frailty Index [15], Frailty Index [26] and Edmonton Frail Scale [27]), and 3 used gait measures as a unique frailty proxy [12,14,20]. The specific measurement tools employed in each paper are described in Table 1. The effect sizes are included in the "Main outcomes" column for studies in which results were available for these analyses.

Table 1. Empirical studies using the concept of "cognitive frailty".

Authors (year)	Study design (sample size)	Setting (community / clinical settings)	Definition of cognitive frailty	Cognitive frailty assessment	Physical frailty assessment	Prevalence	Main outcomes
Arts et al. [10]	Cross-sectional data of a cohort of patients with depression/prospective study (n = 378)	Outpatient and inpatient clinics for mental health care	The lack of a definition of cognitive impairment in the current models of cognitive frailty is criticized. The paper emphasizes the complex association between physical frailty and depression	MMSE, short version of the Stroop test, Digit Span Forward and Backward, a modified version of the Auditory Verbal Learning Test	Fried Frailty Index (FFI)	56.6% prefrail, 27.2% physical frail	The sum of FFI and gait speed scores were significantly associated with verbal memory (β -0.13), processing speed (β -0.38), and working memory (β -0.18), but not with interference control
Delrieu et al. [11]	Cross-sectional data from a 4-arm randomized controlled trial (n = 1617)	Memory clinics	I.A.N.A./I.A.G.G. consensus definition	Free Cued Selective Reminding Test (FCSRT), COWAT, CNT, WAIS-R coding, TMT-A & TMT-B, MMSE, CDR-SB, memory visual scales, GDS	FFI, ADCS-ADL, SPPB	24% frail, 20% MCI without frailty, 22% cognitive frailty (at least 1 Fried criterion and CDR = 0.5)	Individuals with cognitive frailty showed worse performance than frail and robust older adults for all cognitive tests, visual analogue scales, handgrip strength and gait speed and had worse performance than those with cognitive impairment without physical frailty in terms of visual analogue scale 1, CDR-SB, TMT-A, and WAIS-R coding. In subjects with CDR = 0.5, those with only 1 Fried criterion performed better than subjects with 3 criteria and more for WAIS-R coding and CDR-SB
Gillain et al. [12]	Cross-sectional study (n = 24)	Community	Presence of cognitive impairment as a risk factor for falling	MMSE, Mattis scale, Grober, and Buschke recall test, counting backward, Rey's complex figure test, alertness and divided attention subtests from the TAP battery	Single-leg balance test, pull test, get-up-and-go test, 30-meter stable gait test	n.a.	Significant differences in gait performance tests between controls and AD, and between controls and MCI in dual-task conditions of the tests; significant correlations between neuropsychological and gait variables

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Fougere et al. [13]	Cross-sectional prospective study (n = 1620)	Frailty day hospital	I.A.N.A./I.A.G.G. consensus definition; cognitive frailty as a fundamental determinant of an individual's vulnerability or resilience to stressors	MMSE and CDR	FFI	44,7% frail, 45.2% prefrail, 26.7% cognitively frail, 28.1% motoric cognitive risk	Increased odds of association with frailty for patients with cognitive impairment (small Hasselblad & Hedges' *d* ES, 0.12). Using each frailty criterion separately, the association was observed only with gait speed (small Hasselblad & Hedges' *d* ES, 0.15)
Kubicki et al. [14]	Cross-sectional study (n = 42)	Community	Cognitive frailty as the link between MCI and motor efficiency; early motor impairments	TMT-A & TMT-B, Digit Span forward and backward, FCSRT and Delayed Matching to Sample	Gait speed test, arm raising task	n.a.	Earlier recruitment of trunk muscles in MCI. Multiple regression models applied to the absolute difference score in activation timings between older adults with and without MCI showed a large ES, with TMT-A as a significant predictor
Rietman et al. [15]	Prospective cohort study (n = 3999)	Community	Cognitive frailty defined as the $<10^{th}$ percentile in global cognitive functioning	15 Words Verbal Learning Test; Stroop Color–Word Test; Word Fluency Test; Letter Digit Substitution Test	Physical frailty was defined as having ≥ 2 of 4 frailty criteria from a modified FFI, and ≥ 4 of 8 from the Gobbens' frailty criteria. BMI was divided into four classes	3.8% physical frailty, 9.2% cognitive frailty, 6.2% psychological frailty (depression, mental health), 4.1% social frailty (loneliness, social support, social participation)	U-shaped association observed between BMI and physical frailty. The small linear association observed for BMI and cognitive frailty. Limited overlap between the different frailty domains
Roppolo et al. [16]	Cross-sectional study (n = 594)	Community	I.A.N.A./I.A.G.G. consensus definition	MMSE. A disability scale, the Groningen Activity Restriction Scale	FFI (CHS criteria)	59% prefrail, 14% frail, 4.4% cognitively frail	A significant interaction of physical frailty and cognitive functioning on disability. Frail individuals with low cognitive functioning showed more disability than frail individuals with higher cognition (Cohen's *d* ES for mean scores was 0.77)
Solfrizzi et al. [17]	Longitudinal cohort study (n = 2150)	Community or institutionalized	I.A.N.A./I.A.G.G. consensus definition. Differentiates between potentially reversible and reversible cognitive frailty	MMSE. SCD assessed with the item 14 of the GDS-30: "Do you feel you have more problems with memory than most?"	FFI (CHS-modified criteria)	2.5% reversible cognitive frailty	Participants with reversible cognitive frailty showed an increased risk of overall dementia (HR: 2.30, 2.12), vascular dementia (HR: 6.67, 4.76) and mortality (HR: 1.74, 1.39) over 3.5- and 7-year follow-up periods

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Authors (year)	Study design (sample size)	Setting (community / clinical settings)	Definition of cognitive frailty	Cognitive frailty assessment	Physical frailty assessment	Prevalence	Main outcomes
Solfrizzi et al. [18]	Longitudinal cohort study (n = 2373)	Community or institutionalized	I.A.N.A./I.A.G.G. consensus definition. Differentiates between potentially reversible and reversible cognitive frailty	MMSE	FFI (CHS-modified criteria). Inflammatory states	2.8% MCI, 7.2% physical frailty, 0.7% potentially reversible cognitive frailty	A significant difference (contrasts of adjusted predictions: 0.461) in the rates of disability was found between MCI and non-MCI groups in frail individuals with high inflammatory states
Chong et al. [19]	Prospective cohort study (n = 122)	Memory clinic	Simultaneous occurrence of physical frailty and cognitive impairment in the absence of dementia (without explicit mention to Kelaiditi et al., 2015; both papers were submitted in June 2015)	Chinese MMSE and Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores	Modified FFI, including gait speed, hand grip strength, exhaustion and weight loss. Vascular risk profile. Muscle mass measurements. Lipid status	Frailty in MCI: 36% at baseline, 29% at 6 months, 21% at 12 months	Random effects modeling with longitudinal frailty score as the dependent variable showed significant effects of age and cognition (CDR-SB). In the MCI group, only female gender was significant
Doi et al. [20]	Prospective study with follow-up (n = 3482)	Community	Cognitive function is thought to have a linkage with mobility. MCI causes deterioration in mobility, such as slow gait (SG); slower gait predicts future cognitive decline	MCI diagnosis based on subjective memory complaints, intact global function (MMSE), and cognitive domains (National Center for Geriatrics and Gerontology Functional Assessment Tool)	Gait time measured over 2.4 m of the walkway with 2 m of acceleration and deceleration zones	67.2% without MCI and SG, 8.2% with SG, 19.7% with MCI, and 4.9% with SG and MCI	SG and MCI participants had significant risks for disability compared with the control group, especially those with multidomain MCI and those with both MCI and SG (medium Cohen's *h* ES, 0.539)
Feng et al. [21]	Prospective study with follow-up (n = 1575)	Community	I.A.N.A./I.A.G.G. consensus definition. State of reduced brain neurophysiological reserve	MMSE, CDR	Modified FFI (Cardiovascular Health Study –CHS- criteria)	32% prefrail, 2% frail, 1% cognitively frail	Frailty and prefrailty were significantly associated with cognitive impairment. Cohen's *d* ES for mean scores was 1.73 and 0.37 for frailty and prefrailty, respectively. Participants with cognitive frailty had the highest risk (OR, 6.37; with small Hasselblad & Hedges' *d* ES, 0.44) of conversion to cognitive impairment compared to robust participants

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Authors (year)	Study design (sample size)	Setting (community / clinical settings)	Definition of cognitive frailty	Cognitive frailty assessment	Physical frailty assessment	Prevalence	Main outcomes
Feng et al. [22]	Prospective study with follow-up (n = 2375)	Community	I.A.N.A./I.A.G.G. consensus definition	MMSE	Modified FFI (CHS criteria).	33.4% prefrail, 2.6% frail, 8.9% physical prefrail with cognitive impairment, 1.8% physical frail with cognitive impairment	Physical prefrailty with cognitive impairment was associated with two-fold increased prevalence and incidence of functional disability, a two-fold increased incidence of poor quality of life, and a 1.8-fold increased mortality risk. For all variables, small Hasselblad & Hedges' *d* ES was observed with values between 0.14 and 0.21. Physical frailty with cognitive impairment was associated with a 12- to 13-fold increased prevalence and incidence of functional disability, a 5-fold and 27-fold increased prevalence and incidence, respectively, of low QOL, and a 5-fold increased mortality risk. For functional disability and the incidence of low QOL, the ES was medium, with values ranging from 0.60 to 0.79. A small ES of 0.40 and 0.39 was obtained for the prevalence of low QOL and mortality, respectively
Shimada et al. [23]	Cross-sectional data of a prospective cohort study (n = 8864)	Community	I.A.N.A./I.A.G.G. consensus definition, with cognitive impairment characterized by two or more tests in the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT)	NCGG-FAT includes tests of word list memory, the tablet version of the TMT-A & TMT-B, the tablet version of the Digit Symbol Substitution Test	FFI	7.2% physical frailty, 5.2% cognitive impairment, 1.2% cognitive frailty	Cognitive frailty included proportionally more participants who had IADL limitations. Older adults with cognitive frailty had an increased risk of IADL limitations compared with robust older adults (OR, 2.63; with small Hasselblad & Hedges' *d* ES, 0.23), and this risk was higher than the risk presented by either frailty or cognitive impairment
Kistler et al. [24]	Prospective cohort study (n = 35)	Hospitalized older patients with hip fracture	Cognitive impairment as an indicator of 'cognitive frailty, less well known in a population with hip fracture	MoCA. Participants with "high MoCA'' (>19) versus "low MoCA'' (<19) scores	Modified FFI for a population with hip fracture, excluding weakness (94% weak) and activity criteria	51% frail, 40% frail and a low MoCA	Frail participants with low MoCA had a higher prevalence of complications during hospitalization than participants with a high MoCA (large Cohen's *h* ES, 1.15)
Montero-Odasso et al. [25]	Prospective cohort study (n = 252)	Community (with recruitment based on geriatric clinics)	I.A.N.A./I.A.G.G. consensus definition	MoCA, CDR	FFI; Gait velocity (cm s^{-1}) during normal pace (evaluated using an electronic walkway with embedded pressure sensors)	15.9% nonfrail/cognitively (c.) normal, 18.3% nonfrail/c. impaired, 25.4% prefrail/c. normal, 26.6% prefrail/c. impaired, 3,2% frail/c. normal, 10.7% frail/c. impaired	Stratification by physical frailty and cognitive frailty status did not show a significant risk for cognitive decline or progression to dementia. Of all five criteria of the frailty phenotype, only slow gait was associated with cognitive impairment (HR, 14.8)

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Authors (year)	Study design (sample size)	Setting (community / clinical settings)	Definition of cognitive frailty	Cognitive frailty assessment	Physical frailty assessment	Prevalence	Main outcomes
St. John et al. [26]	Longitudinal cohort study (n = 1751)	Community	I.A.N.A. /I.A.G.G. consensus definition leading to consider cognitive frailty as a complement of physical frailty	Modified MMSE (3MS)	The Frailty Index (FI), based on the accumulation of deficits model	27.0% physical frailty, 12.1% cognitive frailty	There is a cumulative effect of low cognition and frailty on mortality: those who were both frail and cognitively impaired were most likely to die (OR, 2.28; small Hasselblad & Hedges' *d* ES, 0.20)
Del Brutto et al. [27]	Cross-sectional cohort study (n = 298)	Community	The current definition implies normal or only age-related changes in neuroimaging studies, with unclear pathogenic mechanisms of cognitive frailty	Clock-drawing test, included in the Edmonton Frail Scale (EFS). Brain magnetic resonance imaging	EFS includes items about cognition, general health status, medication use, nutrition, incontinence, and mobility (Get Up & Go)	22% prefrail, 31% frail	A significant relationship between frailty and the presence of moderate-to-severe global cortical atrophy was identified, but there was no relationship between frailty and moderate-to-severe white matter hyperintensities
Jha et al. [28]	Prospective cohort study (n = 156)	Patients with advanced heart failure referred to a Transplant Unit	MoCA was used, given its sensitivity for the detection of MCI, to study cognitive frailty by creating a modified, complementary frailty index	MoCA test: MoCA <26 was used as a complementary criterion. Patients were determined to be cognitively frail if > 3 domains were present from a 6-criteria frailty scale	Modified FFI for heart failure population	33% physical frailty, 40% cognitive frailty (physical frailty + MoCA criteria), 40% depressive frailty, 42% cognitive + depressive frailty	Frailty was associated with significantly lower survival, with patients with physical frailty + MoCA showing the higher rates of early mortality than those without these criteria.

AD = Alzheimer's Disease; ADCS-ADL = Alzheimer Disease Cooperative Study-Activities of Daily Living Prevention Instrument; BMI = Body Mass Index; CDR = Clinical Dementia Rating; CDR-SB = Clinical Dementia Rating Score-Sum of Boxes; CHS = Cardiovascular Health Study; CNT = Category Naming Test; COWAT = Controlled Oral Word Association Test; EFS = Edmonton Frail Scale; ES = Effect Size; FCSRT = Free Cued Selective Reminding Test; FFI = Fried Frailty Index; GDS = Geriatric Depression Scale; HR= Hazard Ratio; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NCGG-FAT = National Center for Geriatrics and Gerontology-Functional Assessment Tool; n.a.= Not Available; QOL = Quality of Life; SG = Slow Gait; SPPB = Short Physical Performance Battery; TAP = Test for Attentional Performance; TMT = Trail Making Test.

3.2. Relationship between cognitive frailty and cognitive reserve

Current definitions indicate that cognitive frailty is characterized by reduced cognitive reserve, although the role of reduced cognitive reserve in cognitive frailty is dependent on the existence of physical frailty [3,5]. In line with the concept of cognitive reserve, one paper in our review conceptualized cognitive frailty as "a state of reduced brain neurophysiological reserves (brain frailty) that is related to both the appearance of neurodegenerative and vascular diseases and also to the appearance of physical frailty" (pp. 373–374) [21]. Except for those studies with a more clinical profile [14,24,28], all the papers analyzed recorded the education status of participants, and most of them included this variable in the adjusted predictive models developed to study negative outcomes linked to cognitive frailty. Two other cognitive reserve proxies were controlled as potential confounding factors in one study each: sociocultural level [11] and hobbies [23].

3.3. Role of neuropathology and brain reserve

Although the potential mechanisms that may underlie cognitive frailty including neuropathological changes and vascular damage were mentioned in different papers and there was general agreement about the need for more data from neurobiological markers [30], only two studies in this review provided results about neuroimaging and biomarkers [18,27]. Del Brutto et al. [27] found a significant relationship between frailty and the presence of global cortical atrophy and a marginal relationship between frailty and white matter hyperintensities, both of which markedly influenced by increasing age. Solfrizzi et al. [18] performed separate analyses regarding the inflammatory state, with low inflammatory states being defined as serum fibrinogen levels < 339 mg/dl and high inflammatory states being defined as serum fibrinogen levels ≥ 339 mg/dL. A significant difference in disability rates was found between the MCI and non-MCI groups in frail individuals with high inflammation, which led the authors to conclude that in presence of inflammation, the cognitive frailty model presented an additional predictive advantage in terms of assessing the disability risk compared to evaluations of frailty or MCI alone.

3.4. Relationship between cognitive frailty and motor signs of aging

It is well established that cognitive impairment is strongly associated with functional decline and accordingly, a decline in motor performance including a slow gait and that slow gait is related to predementia and dementia syndromes [20,21,25]. Different studies included in the review placed a particular focus on gait variables [10,[12], [13], [14],20,25]. Gait was the only criterion of the frailty phenotype that was related to cognitive impairment and dementia when the frailty criteria were compared individually in two of these studies [13,25].

Two papers [13,20] also studied the prevalence of Motoric Cognitive Risk (MCR), which is a recently described syndrome defined by the presence of a slow gait and cognitive complaints in the absence of dementia and motor disability that is related to an increased risk of developing dementia and vascular dementia [31]. In summary, the incidence of MCR in a clinical population treated at a frailty day hospital was 28.1% [13], whereas the incidence of CDR = 0.5 + slow gait diagnoses in another population study was 4.9% [20]. These percentages are higher than those presented for cognitive frailty in the studies based on the I.A.N.A./I.A.G.G. consensus definition [17].

3.5. Cognitive frailty as a reversible condition

Although different papers explicitly mentioned reversibility as a characteristic of cognitive frailty [11,13,16,[19], [20], [21],25], in our review, only the papers based on the Italian Longitudinal Study on Aging [17,18] differentiated between reversible and potentially reversible subtypes according to the classification proposed by Ruan et al. [4]. An increasing presence of reversible and potentially reversible classifications are expected to be reported in more recent studies.

The reversibility of cognitive frailty is thought to be important with regard to intervening and potentially preventing or delaying dementia, functional decline and premature death [11,22]. Nevertheless, none of the papers reviewed included interventional studies. Due to the lack of randomized controlled trials investigating the efficacy of preventive interventions [30,32], there is a clear need for multidomain prevention trails including multifactorial tasks assessed over long time periods [11,26].

4. Discussion

The present review illustrates the increase in empirical research using the term "cognitive frailty" in recent years. Most of these recent studies used the I.A.N.A./I.A.G.G. consensus definition and did not include complete neuropsychological assessments or motor tasks, such as dual paradigms. Apart from the positive increase in empirical evidence, some key aspects of the research on cognitive frailty remain unresolved including the role of cognitive reserve and the common etiopathogenesis between cognitive and physical impairments.

Although physical and cognitive functioning often present certain parallelism throughout an individual's lifespan, in old age it is not uncommon to observe that this parallelism is broken. On the one hand, data from different longitudinal studies including the English Longitudinal Study of Ageing (ELSA), the Health and Retirement Study (HRS), and the Singapore Longitudinal Ageing Study (SLAS) have provided an account of this parallelism; and on the other hand, they have highlighted certain dissonances in this common evolution due to the consequences of advancing age [21,22,33,34]. The dissimilar evolution between physical and cognitive functioning leads us to assume the need for a more open view when considering the possible relationships between physical frailty and cognitive impairment than the view assumed by the I.A.N.A./I.A.G.G. definition of cognitive frailty. In our review, significant associations were shown for cognitive frailty and physical frailty or gait speed, although the effect sizes for longitudinal comparisons were small and only a minority of the effect sizes were medium-sized [16,[20], [21], [22]]. These outcomes indicated a slight association between cognitive impairment and physical frailty, which is of minor importance and unlikely to be clinically significant.

Regarding the choice of cognitive and neuropsychological assessment tools, tests developed for early stages of the cognitive impairment are preferable according to the specific nature of cognitive decline in individuals with cognitive frailty. However, although MMSE has been shown to have very limited value in confirming a diagnosis of MCI [35], a majority of the papers included in the review used it to determine objective cognitive decline. Extensive cognitive and neuropsychological assessments are preferable to screening evaluations alone to study cognitive frailty. Even when a screening instrument is chosen to establish cognitive status in potentially prefrail patients, alternative instruments, such as MoCA, should be used because of the higher validity of these instruments for MCI identification than other screening instruments [36].

Our review has also shown that although the current definitions include reduced cognitive reserve as the main characteristic of cognitive frailty, educational level is the only cognitive frailty indicator that was systematically included in empirical studies about cognitive frailty. Apart from the well-established need to control for educative level when studying cognitive performance, the empirical presence of cognitive reserve proxies and, in general, the study of lifestyles and personal trajectories can be considered infrequent. Due to their uniqueness, lifestyles and trajectories that

occur in some specific environments and changing social environments and that constitute the cognitive reserve of an individual play key roles in the understanding of the relationship between cognitive impairment and physical frailty in the aging process and should be considered more systematically, also including psychological variables such as meaning of life. Similarly, intellectual engagement reflected in leisure activities [37] or occupation [38] has been linked to favorable late-life cognitive outcomes including better cognitive function, slower decline and lower risk of dementia; in other words, in addition to an individual's previous physical level, his or her previous level of cognition plays a significant role in cognitive frailty. Accordingly, the inclusion of other cognitive reserve proxies, such as occupational attainment, reading habits and social activities, should be included in the study of cognitive frailty.

Different studies in the review placed a particular focus on motor decline and gait variables. MCR syndrome, which is defined by the presence of cognitive complaints and slow gait [31], is linked to the definition of reversible cognitive frailty [4]. Motor tasks may not only be reliable markers of physical frailty but also useful measures of the impact of the cognitive dedifferentiation process on highly automatized motor behaviors [39]. According to the relevance of motoric aspects in the interplay between cognitive performance, cognitive impairment, and physical frailty, the inclusion of dual tasks in the assessment protocols for cognitive frailty can be used to measure sensorimotor-cognitive interdependencies in the aging process [40].

Finally, this review demonstrates the lack of empirical studies regarding interventions for the clinical concept of "cognitive frailty". The I.A.N.A./I.A.G.G. consensus definition is based on the idea that individuals with cognitive frailty could benefit from preventive interventions other than the interventions currently used to treat cognitive impairments due to neurocognitive disorders. The absence of intervention studies on the reversal of cognitive frailty may stem from the lack of clarity in the definition of the term and the absence of well-defined operational criteria to guide the choice of cognitive processes to be measured to evaluate the effectiveness of the treatments. Nevertheless, since there is clear agreement on the importance of interventions for and prevention of cognitive frailty, the development of randomized controlled trials investigating the efficacy of preventive interventions are highly necessary.

5. Conclusion

The combination of physical frailty and cognitive impairment needs to be more clearly understood, both semantically [16] and operationally. Assuming that the physical and cognitive areas of functioning are not subordinated to each other and that physical, cognitive, social and affective functioning present interrelated but differentiated developmental trajectories through adulthood and the old age, the evolution of the operational definitions of frailty and cognitive frailty should progressively incorporate cognitive, social and affective markers in a differentiated and independent manner. Beyond the valuable differentiation between reversible and potentially reversible cognitive frailty [4], operational criteria for precognitive frailty based on psychometric cut-off scores may be useful for clearly determining cognitive frailty status and hence for distinguishing between reversible low cognitive performance and cognitive decline associated with possible pathological processes.

In terms of the intervention approaches, if we understand cognitive frailty as reversible and caused by factors that can be eliminated or by those whose influence can be neutralized, preventive interventions should be centered on strengthening the protective factors of cognitive reserve. Interventions should therefore be focused on restoring cognitively healthy lifestyle habits. The significant associations between cognitive frailty and physical frailty or gait speed, possibly related to the functioning of the prefrontal executive and motor circuits [41], suggest that interventions based on relatively new and cognitively challenging motoric tasks should be developed.

Contributors

David Facal was responsible for study concept and design, acquisition, analysis and interpretation of data, and drafting of the manuscript.

Ana Maseda was responsible for study concept and design, acquisition of data, and drafting of the manuscript.

Arturo X. Pereiro was responsible for acquisition, analysis and interpretation of data, and drafting of the manuscript.

Manuel Gandoy-Crego was responsible for analysis and interpretation of data, and drafting of the manuscript.

Laura Lorenzo-López was responsible for analysis and interpretation of data, and drafting of the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Provenance and peer review

This article has undergone peer review.

AppendixA. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.maturitas.2018.12.006.

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