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A systematic review and meta-analysis on cognitive frailty in community-dwelling older adults: risk and associated factors

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ABSTRACT

Objectives: To identify which factors are associated with cognitive frailty (CF), as well as the impact of CF on the incidence of dementia and mortality.

Methods: A systematic review with meta-analysis was carried out using papers that enrolled a total of 75,379 participants and were published up to January 2020.

Results: Of the 558 identified records, 28 studies met the inclusion criteria and were included in the review. The meta-analysis of cross-sectional studies showed that CF has a significant association of having an older age and a history of falls. In longitudinal studies, the analysis showed a significant increase in risk of mortality and dementia for those with CF.

Discussion: This is the first systematic review and meta-analysis on CF, which addressed a wide variety of factors associated with the theme and which pointed out some as a potential target for prevention or management with different interventions or treatments, showing the clinical importance of its identification in the most vulnerable and susceptible groups.

Abbreviations: PF: Physical Frailty; IANA: International Academy on Nutrition and Aging; IAGG: International Association of Gerontology and Geriatrics; CF: cognitive frailty; CDR: Clinical Dementia Rating; MCI: mild cognitive impairment; OR: odds ratio; RR: risk ratio; HR: hazard ratio; CI: 95% confidence interval; CFAI: Comprehensive Frailty Assessment Instrument; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; NCGG-FAT: National Center for Geriatrics and Gerontology-Functional Assessment Tool; RCS: Rapid Cognitive Screen; SDST: Digit Symbol Substitution Test; TMT: Trail Making Test; ADL: activities of daily living; IADL: instrumental activities of daily living.Fundação de Amparo à Pesquisa do Estado de São Paulo.

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Highlights

- This review aimed to identify factors associated with cognitive frailty (CF);
- The impact of CF on the incidence of dementia and mortality was also evaluated;
- CF has a significant association of having an older age and a history of falls;
- Older adults with CF have a significant increase in the risk of mortality and dementia;
- Some of the CF-associated factors can be managed with different treatments.

Introduction

Aging represents a global, dynamic and progressive process, characterized by psychological, social, morphological, functional, and biochemical changes that can result in deficits, such as physical frailty (PF) and cognitive impairment (Proietti & Cesari, 2020). PF is described as a multifactor geriatric syndrome, characterized by both reduced energy reserve and resistance to stressors, as a result of the cumulative decline of physiological systems over time (Fried et al., 2001; Morley et al., 2013; Buchman, Schneider, Leurgans, & Bennett, 2008). This concept was further operationalized using an instrument known as "Frailty Phenotype", characterized by the presence of three or more of the following criteria: involuntary weight loss (5 kg in the last year); self-report exhaustion; weakness; low physical activity and slow gait (Fried et al., 2001). However, although PF has been previously described as a one-dimensional process, recently some authors have considered it as a multidimensional phenomenon (Hoogendijk et al., 2019; Lozupone & Panza, 2020) that includes physical, sensorial, social, cognitive, psychological and nutritional domains (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013; Gobbens & Andreasen, 2020). Therefore, PF caused by accumulated deficits is not only a multidimensional, but also a dynamic process (Rockwood et al., 2017; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008).

Recent epidemiological studies have pointed out that PF can also increase the risk of cognitive decline and vice-versa, suggesting that both conditions may interact along the aging process (Malmstrom & Morley, 2013). As a result of this new evidence, the International Academy on Nutrition and Aging (IANA) and the International Association of

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Gerontology and Geriatrics (IAGG) met on April 16, 2013, in Toulouse, France, and provided the first definition of a condition called "cognitive frailty" (CF) in older adults (Kelaiditi et al., 2013; Ruan et al., 2015). This is a heterogeneous clinical syndrome defined as the coexistence of PF and cognitive impairment, characterized by the Clinical Dementia Rating (CDR) score of 0.5 (Morris, 1993), and in the absence of a clinical diagnosis of Alzheimer's disease or other types of dementia. CF prevalence ranges from 1.0% to 12% in community-dwelling older adults (Sugimoto et al., 2018) and is a potentially reversible condition, therefore being classified in two categories, namely the potentially reversible (mild cognitive impairment – MCI and PF) and reversible (pre-MCI and PF) subtypes (Ruan et al., 2015).

The concept of CF has been widely studied but still needs to be deeply investigated (Cesari, Sloane, & Zimmerman, 2020). Although recent systematic reviews and meta-analyses have focused on the risks of all-cause mortality (Bu et al., 2020) and dementia prediction (Bu et al., 2020; Zheng et al., 2020) in this review we aimed to expand the understanding of this topic by meta-analyzing prior studies in order to identify potential CF-associated (cause and effect) factors. The identification of these CF-associated elements can contribute not only to a better understanding of this condition but can also direct future interventions in order to reduce the occurrence of adverse outcomes and to guide new studies.

Methods

Protocol and registration

This systematic review was conducted following the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement) (Moher, Liberati, Tetzlaff, Altman, & Group, 2009) and the meta-analysis followed the Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) guidelines (Stroup et al., 2000). The selected search strategy and methods of analysis were registered in the PROSPERO database (CRD42018108758).

Search strategy

Two investigators using the electronic biomedical and education databases Scopus, PubMed and Web of Science, performed a systematic search in the literature of articles published up to January 2020. As the CF topic is very recent in the scientific literature, no time limit and combination of keywords by Boolean operators were used. All the retrieved scientific literature using the unique keyword *"cognitive frailty"* was collected and analyzed.

Eligibility criteria

Articles were included according to the following criteria: (1) full-text articles published in a peer-reviewed journal; (2) participants were community-dwelling older adults with CF; (3) CF can only be identified by the simultaneous presence of cognitive impairment and physical frailty; (4) study design must be cross-sectional or population-based longitudinal studies that investigated factors associated with CF. There were no further restrictions concerning paper publication dates and languages. Systematic reviews, meta-analysis, case reports or abstracts were excluded.

Screening and selection

Two investigators examined the titles and abstracts identified during the searches. If the information provided by the title and abstract suggested that the study met the selection criteria, the full text was analyzed. Discrepancies were resolved through open discussion and certified by a third author. Reference lists of relevant studies were reviewed according to the inclusion criteria. Duplicated studies were excluded.

Data collection process

One investigator screened the results of the systematic search. Data were extracted using a structured form containing information on the authors, study design (cross-sectional and cohort/population-based longitudinal studies), sample, average age, educational level, the percentage of female gender, frailty and cognitive criteria, factor(s) measured and its measurement instruments, results, response rate (odds ratio - OR, risk ratio - RR, hazard ratio (HZ) and 95% confidence interval – CI), reported strengths and limitations, key conclusions by the authors.

Quality appraisal

One author evaluated the methodological quality of the selected studies. In case of doubt,advice was required from another author. The cross-sectional and cohort studies were evaluated using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NIH, 2014), which is recommended by Cochrane Review Groups. This tool addresses 13 elements of quality assessment: the clarity of the research objective; the definition, selection and composition of the study population; the definition and assessment of exposure and outcome variables; the measurement of exposures before outcome assessment; the study timeframe and follow-ups; study analysis and power; and other factors. Each question can be answered as "yes," "no," "cannot determine," "not applicable" or "not reported" (Supplementary material Table 1). All responses other than "yes" indicate a risk of bias. Inherent to the design, cross-sectional studies automatically score "not applicable" on criteria 6, 7, 10 and 13. The quality of each study was classified as poor, fair, or good (NIH, 2014).

Meta-analysis

We extracted the effect measures (OR in cross-sectional studies; HR in longitudinal studies) with 95% CI from the studies that examined factors associated with CF. The meta-analysis was conducted when at least three studies investigating the same variable associated with CF and compared with non-CF group presented the same experimental design and used the same effect measures.

Heterogeneity across the studies was examined using the chi-square test, and its degree was quantified using I^2 statistic. I^2 values of 25%, 50% and 75% were considered as low, moderate and high heterogeneity, respectively

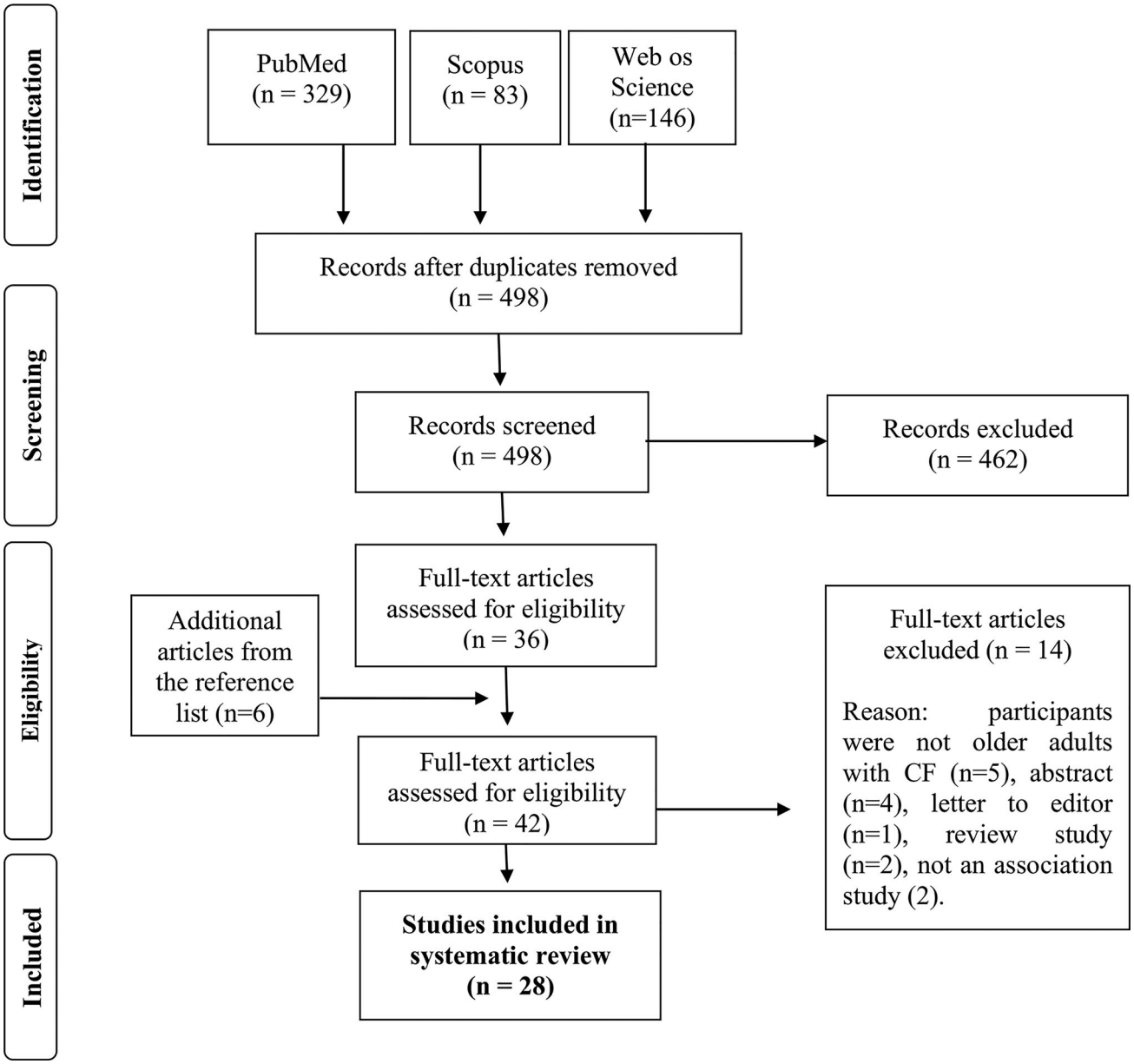

Figure 1. Flow chart of the systematic review according to the PRISMA Statement.

(Higgins, Thompson, Deeks, & Altman, 2003). When significant heterogeneity was detected, a random effects meta-analysis was performed. When unadjusted and adjusted effect measures were presented, the most adjusted ones were chosen, since they have the potential to reduce or eliminate biases in the parameter that is being estimated. Forest plots were used to show the characteristics of the studies. All meta-analyses were conducted using Review Manager 5 (version 5.3, The Cochrane Collaboration), and $p < 0.05$ was considered as statistically significant.

Results

Study selection

The initial bibliographic search identified 558 studies, of which 60 were removed due to duplicity. After the screening of the remaining 498 studies, 462 were excluded according to the pre-established inclusion criteria. Finally, 28 articles, dated between 2009 and 2020 met the selection criteria and had accessible information for research to discuss factors associated with CF (Figure 1). Although some studies have used the term *cognitive fragility* before, those references differ in their definition of the condition from the actual one, as it appeared only in 2013. Therefore, this review included only one study published before 2013 (Avila-Funes et al., 2009) as it used the CF concept according to the common validated and recognized criteria that associate PF and cognitive impairment.

Study characteristics

The characteristics of all included studies are shown in Table 1. Of the 28 studies included, 15 were population-based longitudinal studies studies (Avila-Funes et al., 2009; Esteban-Cornejo et al., 2019; Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Feng, Nyunt, Gao, Feng, Lee, et al., 2017; Hao, Dong, Yang, Dong, & Wei, 2018; Lee, Peng, Liang, Loh, & Chen, 2018; Liu, Chen, et al., 2018; Liu, Han, Gahbauer, Allore, & Gill, 2018; Montero-Odasso et al., 2016; Shimada, Makizako, et al., 2018; Shimada, Doi, et al., 2018; Solfrizzi, Scafato, Lozupone, et al., 2017; Solfrizzi, Scafato, Seripa, et al., 2017; St John, Tyas, Griffith, & Menec, 2017; Yu et al., 2018), and 13 studies were cross-sectional (Chye et al.,

Table 1. The characteristics, factors associated and results of the enrolled studies in the systematic review.

Reference; Country	Participants (n; age; % female)	Cognitive Frailty Assessment		Factors associated investigated by studies	Results and rate response
		Frailty	Cognitive impairment		
Cross-sectional Studies					
De Roeck et al., 2020; Belgium	**Community** (353; 77.7 ± 8.3; 55%) **Frail** (95; 78.2 ± 8.3; 57%) **Clinical** (47; 75.3 ± 6.8; 53%)	CFAI-Plus	MoCA; CDR	Age, psychological components (CFAI-Plus), potential support network (D-SCOPE)	Factors associated with CF in community group: age (β = 0.31), mood disorder symptoms (β = 0.14), emotional loneliness (β = 0.18), potential support network (β= −0.12).
Ruan et al., 2020; China	**Prefrail** (1859; 60-69 = 31%, 70-79 = 43%, >80 = 25%; 44%) **Frailty** (228; 60-69 = 16%, 70-79 = 22%, >80 = 60%; 56%) **Reversible CF** (108; 60-69 = 36%, 70-79 = 38%, >80 = 25%; 58%) **Potentially reversible CF** (320; 60-69 = 14%, 70-79 = 30%, >80 = 55%; 50%)	FRAIL scale	RCS	Age; gender; schooling; marital status	Ages 70-79 and > 80 years are associated with resversible CF (*OR* = 1.38; *OR* = 4.45) and pottentially reversible CF (*OR* = 2.92; *OR* = 19.70). Males had low prevalence of resversible CF (*OR* = 0.74) and pottentially reversible CF (*OR* = 0.97). High education level had high rate of resversible CF (*OR* = 1.47). Married and widowed had low rate of resversible CF (*OR* = 0.47; *OR* = 0.45).
Kim et al., 2019; Japan	**Normal** (822; 76.6 ± 4.5; 61%) **PF** (30; 80.9 ± 5.3; 46%) **MCI** (314; 77.8 ± 4.7; 56%) **CF** (25; 82.3 ± 6.6; 64%)	FRAIL scale	MMSE	Age; gender; calf circumference; low back pain; falls; comorbidity (number); walking speed (TUG); nutrition (CNAQ)	Factors associated with CF-related falls: older age (*OR* = 1.15), smaller calf circumference (*OR* = 0.74), falls (*OR* = 3.57), comorbidity (*OR* = 7.41), walking speed (*OR* = 1.23) and CNAQ (*OR* = 0.73). No association with gender and low back pain.
Kwan et al., 2019; China	**Robust** (24; 87.5 ± 3.2; 54%) **PF** (81; 86.6 ± 3.1; 74%) **MCI** (14; 84.6 ± 5.1; 71%) **CF** (66; 85.6 ± 6.0; 74%)	FRAIL scale	MMSE; CDR	Nutrition (MNA-SF); Depression (GDS)	Factors associated with CF: MNA-SF (*OR* = 0.66) and depression (*OR* = 1.52).
Moon et al., 2019; Korea	**Robust** (906; 74.9 ± 3.5; 44%) **Robust + MCI** (173; 75.8 ± 3.8; 34%) **Prefrail** (829; 76.0 ± 3.8; 61%) **Prefrail + MCI** (214; 76.4 ± 3.7; 48%) **Frailty** (193; 77.9 ± 3.9; 76%) **CF** (77; 77.8 ± 3.5; 62%)	FRAIL scale	TMT; FAB; Digit Span; Word List Recall	Polypharmacy (Prescribed medications)	Factors associated with CF: polypharmacy (*OR* = 2.70). Factors associated with Prefrail + MCI: polypharmacy (*OR* = 1.57).
Rietman et al., 2019; European countries	**Nonfrail** (1628; 53.4 ± 11.0; 51%) **PF** (64; 62.8 ± 10.6; 50%) **CF** (199; 64.3 ± 8.5; 37%) **Psychological frail** (134; 57.8 ± 10.5; 70%)	Freid et al., 2001	15-Word test; Stroop; DSST	Diverse biomarkers (biological material analysis)	Factors associated with CF: lower levels of antioxidants β-cryptoxanthin (log *OR* = 0.74) and zeaxanthin (log *OR* = 0.75).
Rivan et al., 2019; Malaysia	**Robust** (490; 67.6 ± 5.5; 63%) **CF** (325; 69.4 ± 6.2; 57%)	Freid et al., 2001	MMSE; GDS, Digit Span; RAVLT	Age; depression (GDS); ADL disability (Katz); dietary intake/nutrition (DHQ); social support (MOS-SS)	Factors associated with CF: age (*OR* = 1.04), depression (*OR* = 1.49), disability (*OR* = 0.98), social support (*OR* = 0.98) and low niacin intake (*OR* = 0.94).
Sugimoto et al., 2019; Japan	**Robust** (136; 73.6 ± 5.2; 63%) **CF** (197; 75.5 ± 5.6; 60%)	Fried et al., 2001	MMSE	White matter (imaging data)	Factors associated with CF: higher WMH/PAR volumes (white matter hyperintensities / brain parenchyma) (coefficient = 0.57).
Chye et al. 2018; Singapore	**All participants** (5414; 66.4 ± 7.8; 63%), divided by frailty levels	Fried et al., 2001	MMSE	Nutrition (MNA-SF and Nutrition Screening Initiative)	Factors associated with CF: MNA-SF (*OR* = 8.16).
Tsutsumimoto et al., 2018; Japan	**Robust** (5350; 72.2 ± 4.8; 49%) **MCI** (1363; 72.4 ± 4.8; 47%) **PF** (2266; 76.2 ± 5.8; 56%) **CF** (1223; 76.9 ± 5.8; 55%)	WS and grip strength	NCGG-FAT, TMT, DSST	Falling and fall-related fractures	Factors associated with CF: falls (*OR* = 1.46), fall-related fractures (*OR* = 1.92).
Yoon et al., 2018; Korea	**Robust + MCI** (21; 74.6 ± 5.6; 67%) **CF** (27; 75.5 ± 7.2; 78%)	Fried et al., 2001	MMSE; CDR; CERAD-K	Brain amyloid-β accumulation (PET)	No association between amyloid-β and CF.
Ma et al., 2017; China	**Normal** (5521; NR) **CF** (187; NR)	CGA-FI	MMSE	Age; rural residence; comorbidity (number);	Factors associated with CF: age (>75 years) (*OR* = 4.23), rural residence (*OR* = 5.67), comorbidity (*OR* = 11.76),

(*continued*)

Table 1. Continued.

Reference; Country	Participants (n; age; % female)	Cognitive Frailty Assessment: Frailty	Cognitive Frailty Assessment: Cognitive impairment	Factors associated investigated by studies	Results and rate response
				depression (GDS); walking speed (20 min walking); hearing impairment (self-reported history); disability (ADL-IALF Scale); falls (self-reported history)	depression ($OR = 11.371$), low walking speed ($OR = 3.21$) hearing impairment ($OR = 3.51$), disability ($OR = 13.41$) and falls ($OR = 6.65$).
Shimada et al., 2016; Japan	**Robust** (7661; 72.9 ± 5.2; 51%) **PF** (634; 78.2 ± 5.8; 57%) **MCI** (460; 73.9 ± 5.1; 50%) **CF** (109; 77.6 ± 6.1; 59%)	Fried et al., 2001	NCGG-FAT	IADL disability (Lawton)	Factors associated with CF: IADL limitations (OR 2.63), and IALD items as using a bus ($OR = 2.91$), grocery shopping ($OR = 4.67$), finances ($OR = 3.01$), and house keeping ($OR = 2.35$).
Population-based longitudinal					
Esteban-Cornejo et al., 2019; Spain	**Robust** (1370; 68.8 ± 6.2; 45%) **Physical prefrail** (897;71.4 ± 7.7; 57%) **Cognitive prefrail** (578;72.1 ± 7.4;55%) **CF** (599; 75.6 ± 8.5; 72%)	FRAIL scale	MMSE	Mortality (National Death Index); physical activity level (Spanish National Health Survey)	Factors associated with CF: all-cause mortality in 14 years among CF, compared with robust ($HR = 1.69$). CF inactive physically had the highest mortality risk ($HR = 2.13$).
Lee et al., 2018; Japão	**Robust** (527; 61.1 ± 7.5; 38%) **Dynapenia** (408; 68.5 ± 9.5; 51%) **MCI** (28; 65.0 ± 8.1; 57%) **CF** (95; 74.7 ± 8.1; 67%)	Dynapenia	SPMSQ	Multimorbidity/Mortality (CCI)	Factors associated with CF: all-cause mortality in 4 years among CF, compared with robust ($HR = 3.10$).
Liu, Han, et al., 2018; USA	**Elderly** (690; >85years = 12%; 65%)	Fried et al. 2001	MMSE	Hospitalization; nursing home admission; ADL (questions)	Factors associated with CF: highest hospitalization ($RR = 1.9$); nursing home admission ($RR = 50.7$), ADL disability ($RR = 20.6$), IADL disability ($RR = 2.3$), and mobility disability ($RR = 3.1$) in 9 years.
Shimada, Doi, et al., 2018; Japan	**Robust** (2561; 70.6 ± 4.5; 49.4%) **PF** (752; 74.4 ± 6.3; 59.7%) **MCI** (676; 71.0 ± 4.6; 45.3%) **CF** (412; 75.7 ± 6.5; 59.7%)	WS and grip strength	NCGG-FAT	Incidence of dementia	Factors associated with CF: higher incidence of dementia (HR:3.43) in 3 years.
Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Singapore	**Robust** (1552; 64.2 ± 6.2; 65%) **Prefrail** (792; 68.0 ± 8.3; 63%) **Frailty** (61; 75.3 ± 8.6; 61%)	Fried et al. 2001	MMSE	IADL (Lawton; Barthel); QL (SF-12); mortality	Factors associated with CF: disability ($OR = 12.2$), poor QL ($OR = 26.9$) and fivefold increased mortality risk ($OR = 5.12$), in 3 years. Factors associated with prefrail with MCI: disability ($OR = 2.04$), and 1.8 increased mortality ($HR = 1.83$), in 3 years.
Feng, Nyunt, Gao, Feng, Lee, et al., 2017; Singapore	**Robust** (1044; 64.6 ± 6.1; 67%) **Prefrail** (502; 67.9 ± 8.1; 63%) **Frail** (29; 75.9 ± 8.0; 59%)	Fried et al. 2001	MMSE; CDR	Incidence of dementia	Factors associated with CF: increased incidence of dementia ($OR = 6.37$) at baseline.
Hao et al. (2018); China	**Nonfrail** (86; 92.52.6; 33%) **MCI** (170; 93.3 ± 3.1; 77%) **PF** (96; 93.1 ± 3.4; 51%) **CF** (353; 94.2 ± 3.5; 75%)	Frailty Index	MMSE	Mortality	Factors associated with CF: increased risk of mortality ($HR = 2.13$), in 4 years.
Liu, Chen, et al., 2018; Taiwan	**Robust** (588; 73.0 ± 5.1; 44%) **CF** (90; 75.5 ± 5.9; 60%)	Dynapenia	MMSE; CVVLT; BNT; VFT; CFT; CDT	Age; gender; schooling; nutrition (MNA-SF); depression (CES-D); ADL disability (SMAF); multimorbidity (CCI); blood A1c and eGFR levels; mortality	Factors associated with CF: age ($OR = 1.09$), gender-male ($OR = 0.52$), schooling ($OR = 0.89$), MNA-SF ($OR = 0.75$), depression ($OR = 1.12$), disability ($OR = 0.78$), multimorbidity ($OR = 1.20$), A1c ($OR = 1.29$), eGFR ($OR = 0.98$) and all-cause mortality in 25 months among CF, compared with robust ($HR = 6.68$).
Shimada, Makizako, et al., 2018; Japan	**Robust** (3601; 71.1 ± 4.9; 49%) **PF** (206; 76.9 ± 6.5; 43%)	FRAIL scale	NCGG-FAT	Incidence of dementia	Factors associated with CF: higher incidence of dementia (HR: 6.19), in 2 years.

(*continued*)

Table 1. Continued.

Reference; Country	Participants (n; age; % female)	Cognitive Frailty Assessment		Factors associated investigated by studies	Results and rate response
		Frailty	Cognitive impairment		
	MCI (222; 72.9 ± 5.2; 48%) **CF** (43; 77.2 ± 6.0; 30%)				
Yu et al. (2018); China	**All participants** (3491; 72.0 ± 4.9; 49%)	Fried et al. 2001	MMSE	QL (SF-12), incident physical limitation, hospitalization, mortality	Factors associated with CF: poor QL ($OR = 1.53$), increased physical limitation ($OR = 1.78$), hospitalization ($OR = 1.48$), and mortality over an average of 12 years ($OR = 1.46$), at baseline.
Solfrizzi, Scafato, Seripa, et al., 2017; Italy	**Without reversible CF** (2096; 73.1 ± 5.6; 42%) **With reversible CF** (54; 76.7 ± 4.5; 53%)	Fried et al. 2001	MMSE	Incidence of dementia; VaD; mortality	Factors associated with reversible CF: increased incidence of dementia ($HR = 2.30$), VaD ($HR = 6.63$) and mortality ($HR = 1.74$), in 3.5-years. And increased incidence of dementia ($HR = 2.12$), VaD ($HR = 4.76$) and mortality ($HR = 1.39$) over 7-year follow-up.
Solfrizzi, Scafato, Lozupone, et al., 2017; Italy	**Nonfrail** (2117; 72.4 ± 5.3; 41%) **MCI** (67; 80.5 ± 3.1; 41%) **PF** (172; 75.9 ± 4.9; 59%) **CF** (17; 78.0 ± 4.1; 88%)	Fried et al. 2001	MMSE; CDR	Mortality incidence of dementia; ADL disability (Katz); inflammatory state (blood test)	Factors associated with CF: higher incidence of all-cause mortality ($RR = 3.0$), dementia ($RR = 7.2$) and disability ($RR = 3.1$). In the presence of a high inflammatory state, the risk of disability increased 0.46, in 3.5 years.
St John et al., 2017; Canada	**Nonfrail** (953; 75.3 ± 6.2; 58%) **MCI** (326; 80.0 ± 7.4; 45%) **PF** (261; 79.0 ± 6.4; 77%) **CF** (211; 82.0 ± 7.5; 59%)	Frailty Index	MMSE	Mortality	Factors associated with CF: increased risk of mortality ($HR = 2.28$), in 2 years.
Montero-Odasso; et al., 2016; Canada	**Nonfrail** (252; 76.7 ± 8.6; 62%) **Prefrail** (86; 75.1 ± 7.0; 51%) **Frail** (131; 76.7 ± 7.8; 66%)	FRAIL scale	MMSE; CDR; MoCA	Incidence of dementia	Factors associated with CF: increased incidence of dementia ($HR = 35.9$), in 5 years.
Ávila-Funes et al. 2009; French	**Nonfrail** (2738; 73.5 ± 5.1; NR) **Prefrail** (2871; 74.4 ± 5.2; NR) **Frail** (421; 76.6 ± 5.5; NR)	Fried et al. 2001	MMSE	Disability (Katz, Lawton, Rosow–Breslau scale); mortality; hospitalization; incidence of dementia	Factors associated with CF: mobility disability ($OR = 3.88$), IADL disability ($OR = 3.17$), ADL disability ($OR = 5.60$). And increased risk of hospitalization ($HR = 1.90$), mortality ($HR = 1.91$) and incidence of dementia ($HR = 4.98$) in four years among CF, compared with robust.

Note: ADL (Activities of Daily Living); A1c (whole blood glycated hemoglobin A1c); BNT (Boston Naming Test); CCI (Charlson Comorbidity Index); CDR (Clinical Dementia Rating); CDT (Clock Drawing Test); CFT (Taylor Complex Figure Test); CGA-FI (Comprehensive Geriatric Assessment-Frailty); CERAD-K (Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet); CES-D (Center for Epidemiologic Studies Depression Scale); CF (cognitive frailty); CFAI-Plus (Comprehensive Frailty Assessment Instrument); CNAQ (Council on Nutrition Appetite Questionnaire); CVVLT (Chinese Version Verbal Learning Test); DHQ (Dietary History Questionnaire); DSST (Digit Symbol Substitution Test); D-SCOPE (Detection, Support and Care for older people: Prevention and Empowerment); eGFR (estimated glomerular filtration rate); FAB (Frontal Assessment Battery); GDS (Geriatric Depression Scale); IADL (Instrumental Activities of Daily Living); Katz Index (Katz Index of Independence in Activities of Daily Living); Lawton Index (Lawton Instrumental Activities of Daily Living Scale); MCI (mild cognitive impairment); MMSE (Mini-Mental State Examination); MNA-SF (Mini-Nutrition Assessment-Short Form); MoCA (Montreal Cognitive Assessment); MOS-SS (Medical Outcomes Study Social Support Survey); NCGG-FAT (National Center for Geriatrics and Gerontology Functional Assessment Tool); NR (Not related); PASE (Physical Activity Scale for the Elderly); PET (Positron Emission Tomography); PF (physical frailty); RAVLT (Rey Auditory Verbal Learning Test); RCS (Rapid Cognitive Screen); SMAF (Functional Autonomy Measurement System; SNHS (Spanish National Health Survey); SF-12 (Medical Outcomes Study SF-12 PCS of QOL); SPMSQ (Short Portable Mental Status Questionnaire); TMT (Trail Making Test); TUG (Timed Up and Go); VFT (Verbal Fluency Test); USA (United States of America); VaD (Vascular Dementia); WS (Walking Speed); 15-Word Test (15-Picture Word Learning Test).

2018; De Roeck et al., 2020; Kim et al., 2019; Kwan et al., 2019; Ma et al., 2017; Rivan et al., 2019; Moon, Huh, Won, & Kim, 2019; Rietman et al., 2019; Ruan et al., 2020; Shimada et al., 2016; Sugimoto et al., 2019; Tsutsumimoto et al., 2018; Yoon, Lee, Shin, Kim, & Song, 2018).

Studies were conducted in Asia ($n = 19$ studies) (Chye et al., 2018; Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Feng, Nyunt, Gao, Feng, Lee, et al., 2017; Hao et al., 2018; Kim et al., 2019; Kwan et al., 2019; Lee et al., 2018; Liu, Chen, et al., 2018; Ma et al., 2017; Rivan et al., 2019; Moon et al., 2019; Ruan et al., 2020; Shimada, Doi, et al., 2018; Shimada et al., 2016; Shimada, Makizako, et al., 2018; Sugimoto et al., 2019; Tsutsumimoto et al., 2018; Yoon, Lee, Shin, et al., 2018; Yu et al., 2018), Europe ($n = 6$ studies) (Esteban-Cornejo et al., 2019; Rietman et al., 2019; Solfrizzi et al., 2017; Solfrizzi, Scafato, Lozupone, et al., 2017; St John et al., 2017; De Roeck et al., 2020), and in North America ($n = 3$ studies) (Avila-Funes et al., 2009; Liu, Han, et al., 2018; Montero-Odasso et al., 2016).

Concerning the sample characteristics, studies included information from a total of 75,379 participants, of these 35,292 participated in population-based longitudinal studies. Mean age ranged from 53.4 years (Rietman et al., 2019) to 94.2 years old (Hao et al., 2018). Follow-up period of the population-based longitudinal studies ranged from three years (Shimada, Doi, et al., 2018) to 12 years (Esteban-Cornejo et al., 2019).

From the 28 selected studies, ten included the terms "non-frail/robust", "MCI", "cognitive impairment", "PF" and "CF" (Hao et al., 2018; Kim et al., 2019; Kwan et al., 2019; Lee et al., 2018; Shimada, Makizako, et al., 2018; Shimada et al., 2016; Shimada, Doi, et al., 2018; Solfrizzi, Scafato, Seripa, et al., 2017; St John et al., 2017; Tsutsumimoto et al., 2018); eight divided the sample by frailty levels as "pre-frail" and "frail" (Avila-Funes et al., 2009; Chye et al., 2018; Esteban-Cornejo et al., 2019; Feng, Nyunt, Gao, Feng, Lee, et al., 2017; Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Montero-Odasso et al., 2016; Moon et al., 2019; Ruan et al., 2020); five stratified the subjects into groups of "non-frail/robust" and "CF" (Liu, Chen, et al., 2018; Ma et al., 2017; Rivan et al., 2019; Sugimoto et al., 2019; Yoon, Lee, Shin, et al., 2018); two included a single group of older adults (Liu, Han, et al., 2018; Yu et al., 2018); one included a group with "psychological frailty" (Rietman et al., 2019); one compared three different groups referred as the "community," "potentially frail," and "clinical" samples (De Roeck et al., 2020); and lastly, one investigated the construct "without reversible CF" and "with reversible CF" (Solfrizzi, Scafato, Seripa, et al., 2017).

To determine PF, 13 studies (Avila-Funes et al., 2009; Chye et al., 2018; Feng, Nyunt, Gao, Feng, Lee, et al., 2017; Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Liu, Han, et al., 2018; Rivan et al., 2019; Rietman et al., 2019; Shimada et al., 2016; Solfrizzi, Scafato, Lozupone, et al., 2017; Solfrizzi, Scafato, Seripa, et al., 2017; Sugimoto et al., 2019; Yoon, Lee, Shin, et al., 2018; Yu et al., 2018) used the Fried's phenotype criteria; seven studies (Esteban-Cornejo et al., 2019; Kim et al., 2019; Kwan et al., 2019; Montero-Odasso et al., 2016; Moon et al., 2019; Ruan et al., 2020; Shimada, Makizako, et al., 2018) used the FRAIL scale; two used the Frailty Index (Hao et al., 2018; St John et al., 2017); two used the "dynapenia" (Lee et al., 2018; Liu, Chen, et al., 2018); two used the "walking speed and grip strength" (Shimada, Doi, et al., 2018; Tsutsumimoto et al., 2018); one study (De Roeck et al., 2018) used the modified Comprehensive Frailty Assessment Instrument (CFAI); and another one used the Comprehensive Geriatric Assessment-Frailty (Ma et al., 2017).

In order to evaluate cognition, most papers used the Mini Mental State Examination (MMSE, $n = 19$ studies) (Avila-Funes et al., 2009; Chye et al., 2018; Esteban-Cornejo et al., 2019; Feng, Nyunt, Gao, Feng, Lee, et al., 2017; Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Hao et al., 2018; Kim et al., 2019; Kwan et al., 2019; Liu, Chen, et al., 2018; Liu, Han, et al., 2018; Ma et al., 2017; Rivan et al., 2019; Montero-Odasso et al., 2016; Solfrizzi, Scafato, Lozupone, et al., 2017; Solfrizzi, Scafato, Seripa, et al., 2017; St John et al., 2017; Sugimoto et al., 2019; Yoon, Lee, Shin, et al., 2018; Yu et al., 2018). Other instruments used to evaluate cognition were the Montreal Cognitive Assessment (MoCA, $n = 2$ studies) (De Roeck et al., 2020; Montero-Odasso et al., 2016), the Clinical Dementia Rating (CDR, $n = 6$ studies) (De Roeck et al., 2020; Feng, Nyunt, Gao, Feng, Lee, et al., 2017; Kwan et al., 2019; Montero-Odasso et al., 2016; Solfrizzi et al., 2017; Yoon, Lee, Shin, et al., 2018), and the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT, $n = 4$) (Shimada, Doi, et al., 2018; Shimada et al., 2016; Shimada, Makizako, et al., 2018; Tsutsumimoto et al., 2018). Other cognitive tests included the Rapid Cognitive Screen (RCS, $n = 1$) (Ruan et al., 2020), the Short Portable Mental Status Questionnaire (SPMSQ, $n = 1$) (Lee et al., 2018), the Digit Symbol Substitution Test (DSST, $n = 2$) (Rietman et al., 2019; Tsutsumimoto et al., 2018), and the Trail Making Test (TMT, $n = 2$) (Moon et al., 2019; Tsutsumimoto et al., 2018). Some studies applied a cognitive battery with specific tools for each cognition component, as executive functions, attention, memory, and others (Liu, Chen, et al., 2018; Rivan et al., 2019; Moon et al., 2019; Rietman et al., 2019; Tsutsumimoto et al., 2018). All these data are summarized in Table 1.

Methodological quality

Supplementary Table 2 and Supplementary Figure 1 present the methodological quality evaluation of all 28 studies included in this review. Among cross-sectional studies, seven studies were considered "good" and six were considered "fair" quality. Most of the longitudinal studies presented "good quality" (12 studies), two were considered "fair", and one was classified as "poor". It is important to emphasize that the main questions that presented negative answers, "not applied" or "not reported", were related to questions 6, 10, 12 and 13 of the Quality Assessment Tool, which refer to the subject's pre-evaluations, reassessments over time, blinding of the evaluators and loss of adherence.

Meta-analysis findings of longitudinal studies examining CF-associated factors

From the 15 population-based longitudinal studies on CF, 17 variables were extracted (Table 2). Of them, according to the criteria adopted, the perform of the meta-analysis was only possible with mortality and incidence of dementia. Seven out of ten population-based studies that

Table 2. Factors associated with cognitive frailty investigated by the studies used in the review.

Associated Factors	Cross-sectional studies	Longitudinal studies
Sociodemographic factors		
Older age	De Roeck et al. (2020); Ruan et al. (2020); Kim et al. (2019); Rivan et al. (2019); Ma et al. (2017)	Liu, Chen, et al. (2018)
Gender - male	Ruan et al. (2020) #; Kim et al. (2019)	Liu, Chen, et al. (2018)
Low schooling	Ruan et al. (2020)	Liu, Chen, et al. (2018)
Marital status: single	Ruan et al. (2020)	————
Rural residence	Ma et al. (2017)	————
Health-related factors		
Low social support	De Roeck et al. (2020); Rivan et al. (2019)	————
Low physical activity / walking speed / grip strength	Kim et al. (2019); Ma et al. (2017)	Esteban-Cornejo et al. (2019)
Smaller calf circumference	Kim et al. (2019)	————
Hearing impairment	Ma et al. (2017)	————
ADL disability	Rivan et al. (2019). Ma et al. (2017)	Liu, Chen, et al. (2018); Liu, Han, et al. (2018); Solfrizzi, Scafato, Lozupone, et al. (2017); Ávila-Funes et al. (2009)
IALD disability	Shimada et al. (2016)	Liu, Han, et al. (2018); Feng, Nyunt, Gao, Feng, Yap, et al. (2017); Ávila-Funes et al. (2009)
Poor quality of life	————	Feng, Nyunt, Gao, Feng, Yap, et al. (2017); Yu et al. (2018)
Falls / fractures-related	Kim et al. (2019); Ma et al. (2017)	Tsutsumimoto et al. (2018)
Incident physical limitation	————	Yu et al. (2018)
Nutrition	Kim et al. (2019) Chye et al. (2018) Kwan et al. (2019); Rivan et al. (2019)	Liu, Chen, et al. (2018)
Depression	Kwan et al. (2019); Rivan et al. (2019); Ma et al. (2017)	Liu, Chen, et al. (2018)
Psychological disorder	De Roeck et al. (2020)	————
Chronic disease	Kim et al. (2019); Ma et al. (2017)	Liu, Chen, et al. (2018)
Mortality	————	Esteban-Cornejo et al. (2019); Hao et al. (2018); Lee et al. (2018); Liu, Chen, et al. (2018); Yu et al. (2018); Feng, Nyunt, Gao, Feng, Lee, et al. (2017); St John et al. (2017); Solfrizzi, Scafato, Lozupone, et al. (2017); Solfrizzi, Scafato, Seripa, et al. (2017); Ávila-Funes et al. (2009)
Incidence of dementia	————	Shimada, Doi, et al. (2018); Shimada, Makizako, et al. (2018); Feng, Nyunt, Gao, Feng, Yap, et al. (2017); Solfrizzi, Scafato, Lozupone, et al. (2017); Solfrizzi, Scafato, Seripa, et al. (2017); Montero-Odasso; et al. (2016), Ávila-Funes et al. (2009)
Hospitalization / Nursing Home Admission	————	Liu, Han, et al. (2018); Ávila-Funes et al. (2009); Yu et al. (2018)
Polypharmacy	Moon et al. (2019)	————
Blood and brain alterations factors		
Low levels of cryptoxanthin and zeaxanthin	Rietman et al. (2019)	————
High levels of A1c and low levels of eGFR	————	Liu, Chen, et al. (2018)
High inflammation	————	Solfrizzi, Scafato, Lozupone, et al. (2017)
White matter	Sugimoto et al. (2019)	————

Note: ADL (Activities of Daily Living); IADL (Instrumental Activities of Daily Living); A1c (whole blood glycated hemoglobin A1c); eGFR (estimated glomerular filtration rate); #not significant statically. #Not statistically significant.

investigated the impact of CF on mortality provided HR and CI values and were included in the meta-analysis (Figure 2). The summary statistics of the meta-analysis indicated a significant association between CF and an increased risk of mortality (HR = 2.18; 95% CI 1.65–2.87; I^2=72%). Yu et al. (2018), Solfrizzi, Scafato, Lozupone, et al. (2017) and Liu, Chen, et al. (2018) were excluded of the meta-analysis since they presented OR values, incidence rate ratios values, and "poor" methodological quality respectively.

Four out of seven population-based studies that investigated the impact of CF on the incidence of dementia provided HR and CI values and were included in the meta-analysis (Figure 2). Our findings indicated that older adults with CF had an increased risk of developing dementia as compared with those without CF (HR = 4.01; 95% CI 2.96–5.43; I^2=0%). The study of Solfrizzi, Scafato, Seripa, et al. (2017) was excluded of the meta-analysis due to the use of a different model named reversible cognitive frailty to evaluate the variable of interest. Solfrizzi, Scafato, Lozupone, et al. (2017) and Feng, Nyunt, Gao, Feng, Yap, et al. (2017) were excluded because they used different effect measures.

Meta-analysis findings of cross-sectional studies examining CF-associated factors

From the 13 cross-sectional studies on CF, 19 factors were extracted, which included sociodemographic and health conditions, as well as blood and brain alterations (Table 2). Of these factors, according to the adopted criteria, meta-analysis could be applied only to two factors: older age and falls.

Figure 3 shows the forest plots of the factors associated with CF using random-effects meta-analysis. Four out of five cross-sectional studies that investigated the association between having an older age and CF provided sufficient data and were included in the meta-analysis. The summary statistics of the cross-sectional studies indicated a significant association between having an older age and CF (OR = 1.99; 95% CI 1.24–3.18; I^2=99%). De Roeck et al. (2020) could not be included in the meta-analysis due to the lack of information on OR. Three cross-sectional studies that investigated the association of falls and CF were included in the meta-analysis and found a significant association between them (OR = 3.02; 95% CI 1.10–8.30; I^2=85%).

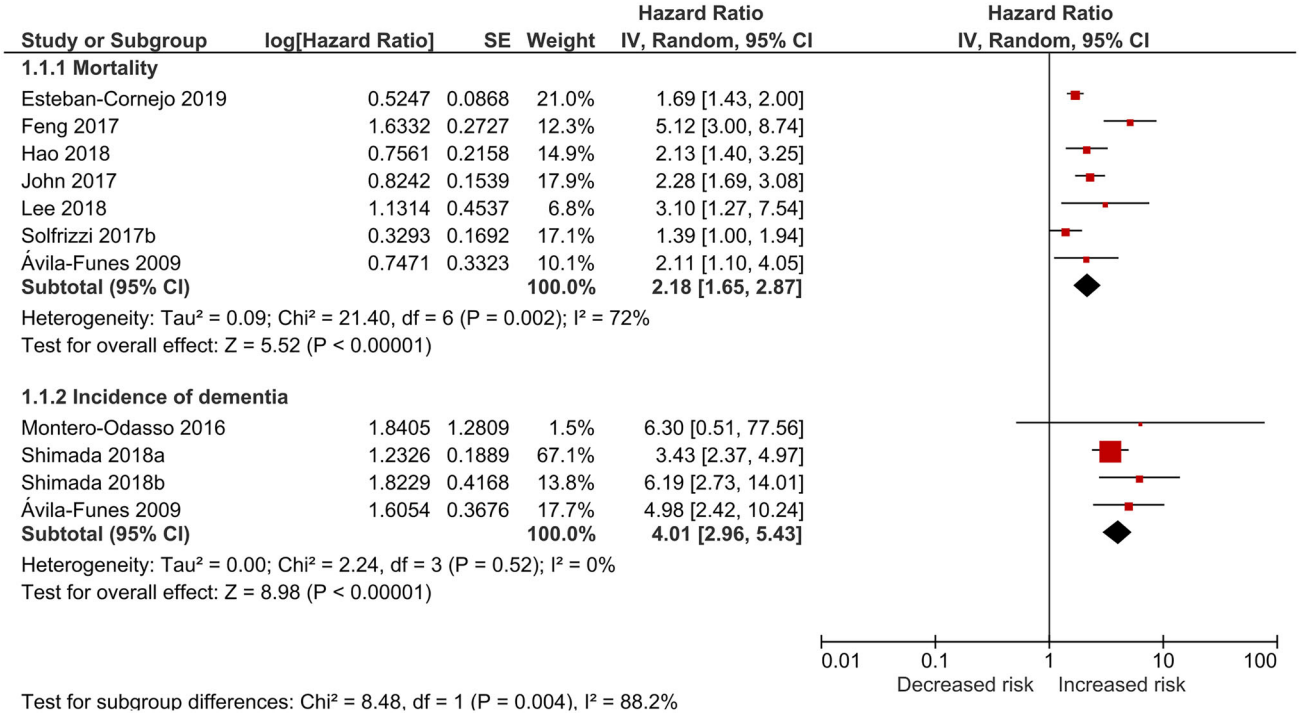

Figure 2. Forest plots of population-based longitudinal studies investigating the factors associated with cognitive frailty, using random-effects meta-analysis.

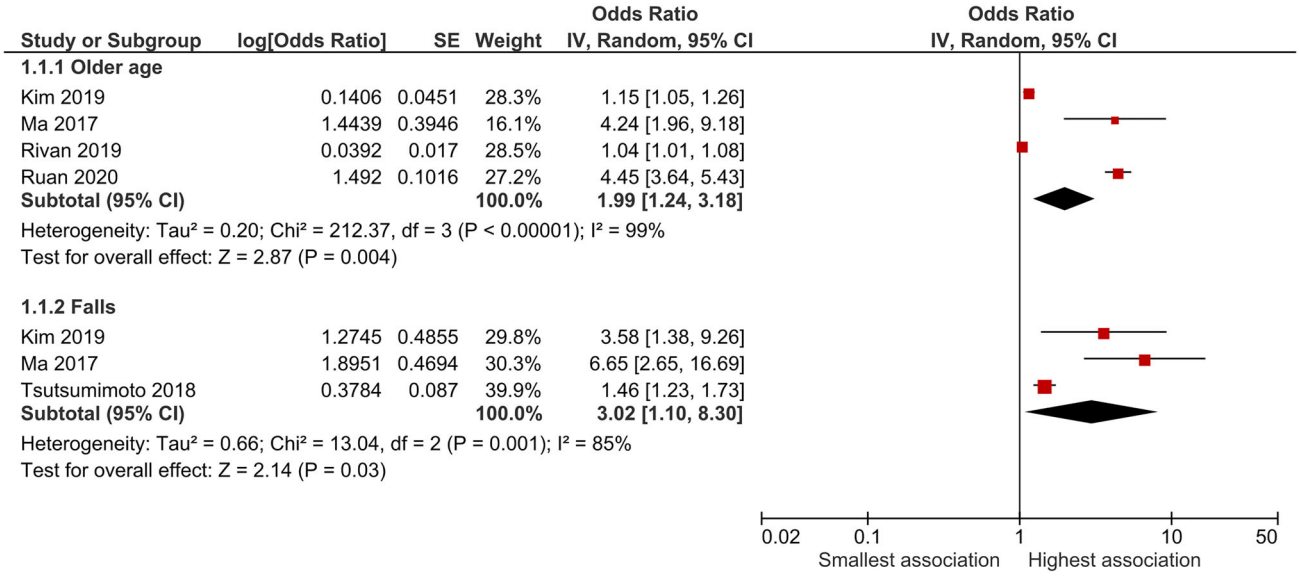

Figure 3. Forest plots of cross-sectional studies investigating the factors associated with cognitive frailty, using random-effects meta-analysis.

Heterogeneity

The heterogeneity was examined using the chi-square test and I^2 statistics. Variable "incidence of dementia" presented low heterogeneity, whereas "mortality" presented moderate heterogeneity, and "older age" and "falls" presented high heterogeneity.

Other CF-associated factors

Other 22 variables were also investigated by few cross-sectional and population-based studies but could not be included in the meta-analysis due to the adopted criteria. The reasons for these exclusions included "less than three studies published available," "different experimental design," "different effect measures" and "data not available." More information is presented in Supplementary Table 3. Despite few records, these studies suggested associations between CF and gender (Kim et al., 2019; Liu, Chen, et al., 2018; Ruan et al., 2020), low schooling (Liu, Chen, et al., 2018; Ruan et al., 2020), single marital status (Ruan et al., 2020), malnutrition (Chye et al., 2018; Kim et al., 2019; Kwan et al., 2019; Liu, Chen, et al., 2018; Rivan et al., 2019), rural residence (Ma et al., 2017), low social support (De Roeck et al., 2020; Rivan et al., 2019), low physical activity (Esteban-Cornejo et al., 2019; Kim et al., 2019; Ma et al., 2017), smaller calf circumference (Kim et al., 2019), hearing impairment (Ma et al., 2017), ADL disability (Avila-Funes et al., 2009; Liu, Chen, et al., 2018; Liu, Han, et al., 2018; Rivan et al., 2019; Solfrizzi, Scafato, Seripa, et al., 2017), IADL disability (Avila-Funes et al., 2009; Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Liu, Han, et al., 2018; Ma et al., 2017; Shimada et al., 2016), poor quality of life (Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Yu et al.,

2018), incident physical limitation (Yu et al., 2018), depression (Kwan et al., 2019; Liu, Chen, et al., 2018; Ma et al., 2017; Rivan et al., 2019), psychological disorder (De Roeck et al., 2020), chronic disease (Kim et al., 2019; Liu, Chen, et al., 2018; Ma et al., 2017), hospitalization/nursing home admission (Avila-Funes et al., 2009; Liu, Han, et al., 2018; Yu et al., 2018), polypharmacy (Moon et al., 2019), low levels of cryptoxanthin and zeaxanthin (Rietman et al., 2019), high levels of A1c and low levels of eGFR (Liu, Chen, et al., 2018), high inflammation (Solfrizzi, Scafato, Lozupone, et al., 2017), and white matter alterations (Sugimoto et al., 2019). The single variable that was not significantly associated with CF was brain amyloid-β accumulation (Yoon, Lee, Shin, et al., 2018).

Discussion

This review aimed to identify potential CF-associated factors that have cause/effect relationships with the condition, confirmed by previous studies and characterized as sociodemographic, health or biological-related elements. Findings related to longitudinal studies indicated that participants with CF present an increased risk of dementia and mortality. Although mortality was significantly associated with CF, there was a "moderate" heterogeneity across the studies used in the meta-analysis analysis (Avila-Funes et al., 2009; Esteban-Cornejo et al., 2019; Feng, Nyunt, Gao, Feng, Yap, et al., 2017; Hao et al., 2018; Lee et al., 2018; Solfrizzi, Scafato, Seripa, et al., 2017; St John et al., 2017). This heterogeneity could be related to the selection criteria for participants, diversity of instruments used and definition of CF. In relation to the participants, in all studies the exposed group was the CF group, on the other hand, unexposed groups were classified as robust, non-frail, robust/no MCI" and "non-frail/no MCI". However, although we understand that the unexposed group is the "control" group, the criteria used for the unexposed group was not well determined by the studies. The only study that provided detailed criteria for the unexposed group was from St John et al. (2017) that classified it as non-frail/no MCI. It is important to highlight that all studies included in this meta-analysis were considered as "good" quality. Liu, Chen, et al. (2018) was classified as "poor" and was excluded of the meta-analysis. Therefore, this review identified limitations in previous studies related to different conditions, particularly those involving group classifications (*e.g.* CF *vs* PF, CF *vs* MCI, CF *vs* robust). Future studies should carefully choose the comparison groups to investigate the differences and to demonstrate whether CF is a clinically important entity compared with PF and MCI.

Bu et al. (2020) has already demonstrated an increased mortality risk among older adults with cognitive impairment in the presence of PF. According to the authors, this may occur because although these conditions have similar time trajectories and pathological mechanisms, they interact with each other, which can cause an increase in mortality (Bu et al., 2020).

CF was also significantly associated with an increased risk of dementia, with "low" heterogeneity and "good" methodological quality for most of the studies included in the meta-analysis (Avila-Funes et al., 2009; Montero-Odasso et al., 2016; Shimada, Doi, et al., 2018). The fact that there are studies with good methodological quality has implications for increasing the confidence in the information presented in this review and the replicability of the information for clinical practice, making it an important and reliable resource to identify the most vulnerable and susceptible groups to CF-related health problems and to direct effective interventions (Silva et al., 2019).

Our findings corroborate a previous meta-analysis conducted by Zheng et al. (2020), which found CF as a predictor of dementia. It is known that one of the pillars of the CF condition involves cognitive impairment (Proietti & Cesari, 2020), and that the probability of progression of this condition to any form of dementia has been suggested to occur at a rate of 3 to 5 times higher than those with normal cognition (Campbell, Unverzagt, LaMantia, Khan, & Boustani, 2013). In addition, Facal et al. (2019) have also shown that cognitive impairment is strongly associated with functional and motor decline, including slow walking, which is also associated with to predementia and dementia syndromes. Although all these studies have demonstrated a strong relationship between CF and dementia outcomes, further studies are needed to better understand the influence of PF on the development of dementia, since so far there are very few population-based studies regarding this issue; however, Li et al. (2020) observed that multidimensional frailty may play an inherent role in incident dementia, especially in the people older than 68 years, which can strengthen the idea of increased risk of dementia when associated with cognitive impairment, hence in CF.

Results from cross-sectional studies evaluated in this review showed that having an older age and falls were factors associated with CF. Although the association between age and CF have had already been reported, these studies presented high heterogeneity (Kim et al., 2019; Ma et al., 2017; Rivan et al., 2019; Ruan et al., 2020). One study was considered "good" (Kim et al., 2019) and three were considered "fair" (Ma et al., 2017; Rivan et al., 2019; Ruan et al., 2020). This progressive decrease in the quality of evidence was attributed to several factors such as the lack of information on the study population, low participation rate of eligible persons (at least 50%), and the absence of justification for the sample size, account of the power description, or variance and effect estimates.

The influence of aging on the frailty syndrome is already well known and is related to the gradual and cumulative decline in the physiological reserves, as well as the appearance of age-related pathological conditions (Facal et al., 2019).

The CF was highly associated with falls, despite presenting high heterogeneity among the studies (Kim et al., 2019; Ma et al., 2017; Tsutsumimoto et al., 2018). For this variable, one of the included studies (Kim et al., 2019) was considered "good", while the other two (Ma et al., 2017; Tsutsumimoto et al., 2018) were considered "fair". The "fair" methodological quality of this factor is due to the lack of information on the study population and absence of justification for the sample size, account of the power description, or variance and effect estimates in this regard.

The association of MCI and PF with falls was reported by previous studies (Tyrovolas, Koyanagi, Lara, Santini, & Haro, 2016), while the investigation of its association with CF is more recent and the complexities of this association are not fully comprehended (Kim et al., 2019). Falling, as

many geriatric syndromes, occurs not from a result of a single disease but from the accumulated effect of multiple factors, including impaired cognition, as cognitively impaired older people often engage in unsafe activities, which increases the risk of falls (Fischer et al., 2014; Delbaere et al., 2012). On the other hand, the PF-related alterations, as weakness and abnormal gait, exceedingly increases this risk (Fischer et al., 2014). As a consequence, they can acquire injuries and/or fractures, leading to restriction on their activities, dependence, social isolation and depression (Cheng & Chang, 2017; Kendhapedi & Devasenapathy, 2019).

Although other systematic reviews on CF and associated factors have been published (Zheng et al., 2020; Bu et al., 2020), the current work presented an extension of the concept comprehension since it was able to meta-analyze a larger number of studies and to identify more CF-associated factors than those already described. Zheng et al. (2020) and Bu et al. (2020) considered the variable dementia in their meta-analyses. Bu et al. (2020) also included the mortality variable in a similar analysis; however, the present review expanded the number of investigated studies and was able to identify that CF is strongly associated with an increased risk of four aggravating variables among the older adults: mortality, dementia, falls and old age. In this way, we believe this meta-analysis brings important information and contributions to the field, by pointing out novel CF-associated factors that can assist in the identification of the most vulnerable and susceptible groups that can be a target for interventions before developing the condition. Furthermore, this review can indirectly assist in the indication of accompanying and intervention measures capable of delaying the outcome and progression of the CF condition.

This review emphasizes that due to its potential reversal character, CF should be seen as an important target for non-pharmacological therapies. Kwan et al. (2020) point out that moderate-to-vigorous physical activity is protective against the progression of the condition. In addition, Yoon, Lee, and Song (2018) demonstrate that high-speed resistance exercise training approaches are effective in improving cognitive function and physical performance in older adults with CF. However, this review also indicates the need for further research, that provide evidence-based guidance, to examine whether preventive strategies against CF would effectively reduce the incidence of dementia and the mortality rate in older adults (Feng, Nyunt, Gao, Feng, Yap, et al., 2017).

The limitations of this review include a high heterogeneity that could be related to the sample, the diversity in design, recruitment methods, screening instruments, time of outcome measurements and/or analytical methods. To overcome this limitation, this meta-analysis used the random-effects model, which is widely recommended in the context of high heterogeneity, since it allows differences in the treatment effect across studies. Moreover, we considered the possibility of subgroup analyses, however in this review they were not feasible due to the reduced number of studies.

Another important remark is that some associated factors, as low physical activity, walking speed and grip strength are symptoms of physical frailty and are part of the established criteria for its diagnosis. However, the studies used in this review have investigated their association with CF and in the exclusive presence of frailty. As these factors were included by the studies as associated factors, we have considered them as variables to be analyzed. Due to this variability of associated factors, we reinforce that future studies should be performed in order to shed light on the complex interplay between cognition, PF and their related factors.

Of note, diverse models of frailty evaluation were used in the studies, such as Fried criteria, FRAIL scale, "dynapenia" and, consequently, population target was different across the studies. Besides, different measures used to operationalize the cognitive impairment were shown to be another important limitation. These differences could have an impact on the results presented here and need to be considered, but did not substantially alter the findings, despite reinforce the need for more standardized procedures to evaluate CF. Lastly, the number of studies by factor were small and did not allow us to carry out an analysis by subgroup to reduce the heterogeneity found.

Conclusion

Our study provided evidence, based on a meta-analysis of longitudinal studies, that the CF condition is strongly associated with an increased risk of dementia and mortality. In cross-sectional studies, having an older age and falls were the factors significantly associated with CF. This systematic review showed that there are other CF-associated factors, as sociodemographic and health factors, which could not be meta-analyzed in our work due to the still limited literature on the theme and may represent a future target of research on the theme. In summary, this review can contribute to identify CF-associated factors in the clinical practice, and help to apply effective early interventions, leading to the potential benefit of preventing its outcome. Examples of these interventions can be related to strength, balance and exercise programs to prevent falls, combined with cognitive stimulation to counteract cognitive impairment. Additional implications of this review include a contribution to increase the knowledge and comprehension on CF, besides directing future studies.

Disclosure statement

The authors declare no conflict of interests.

PROSPERO database

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Data availability statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

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