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Physical Frailty and cognitive performance in older populations, part I: systematic review with meta-analysis

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Abstract *The purpose of present study was to analyze the magnitude of the effect-size in the assessment of the cognitive status of populations over 60 years of age. The search strategy included PubMed, B-on, Ebsco, Ebsco Health, Scielo, Eric, Lilacs and Sportdiscus data bases. Only observational, cohort and cross-sectional studies were included in the meta-analysis. The central descriptors were elderly-frail, older adults, cognition and geriatric assessment and other additional terms. After applying the additional search criteria, 12 manuscripts were selected from an initial universe of 1,078 identified. When comparing the mean cognitive profile scores of the participants of the pre-frail (n =11,265) and frail (n = 2,460) groups, significant statistical differences were found (p<0,001), with lower mean scores emerging in frail-group. The results showed that cognitive decline is strongly associated with frailty, being a probable main clinical outcome. In this sense, any strategy aimed at mitigating or reversing the incidence of frailty with ageing should take into account that physical and cognitive frailty seem to have similar temporal trajectories.*

Key words *Frail-older adults, Mild cognitive impairment, Geriatric assessment, Cognition*

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Introduction

The frailty syndrome (FS) is a complex condition characterized by the decline of multiple physiological systems, leading to progressive loss of the energy reserves, compromising the ability to resist the adverse effects of chronic stress[1]. There are several approaches related to FS, but recently the study developed by Fried et al.[2], is one of the most important. From this construct, emerged the main pillars considered as the pathological core of FS, such as negative energy balance, sarcopenia and low levels of physical activity.

From a frailty state, the individual tends to go through institutionalization and/or hospitalization often followed by precociously death[3,4]. The vulnerability acquired by these losses can lead to a frail state, due to exposure to aggression in multiple physiological systems[3,5]. For this reason, much of the money spent on health care for the population is concentrated on the frail individuals who progress to developing more severe clinical conditions[6]. This represents an average of 20-35% of the elderly population in contemporary societies, according to recent research[1,2,7].

The FS is aging-related, although it does not exclusively result from the aging process[8]. The gender differences indicated that frail men are more susceptible to early which was proven in studies linking the FS and the incidence of morbidity[9], however, the incidence in women has exponentially increased. In general, older frail individuals are those at increased risk for adverse clinical outcomes[10-12]. The consistent relationship between FS and the physical-functional decline does not invalidate the importance of other dimensions associated with a frailty condition[13-15]. Recent research has tried to identify other clinical conditions associated with the FS[3,5,16,17], such as the 'frailty' of neurocognitive functions[18,19].

An imminent consequence is the clinical outcomes related to mental health[20], which can also be characterized by traumas caused by falls or a high fear (risk) of falling[21], acute neurological outcomes triggered suddenly (dementia caused by a stroke)[22], Alzheimer and/or Parkinson[19]. However, recent studies try to make it increasingly clear that there is an association between the FS and low cognitive profile or so-called mild cognitive impairment (MCI)[18,22]. This condition is characterized by the transient state between normal cognitive aging and mild dementia[23]. This condition results in progressive memory loss greater than expected for its age and educational level[24], although other cognitive functions are generally preserved and do not interfere with the daily living tasks. Several studies have shown statistically significant differences in cognitive status when analyzed according to subgroups of Frailty, that is those who are pre-frail or frail tend to be more affected by MCI when compared with non-frail groups[25-27].

Currently, there is a large number of studies carried out in large population databases aimed at screening and detecting the FS[6,19,34]: Their results confirm the hypothetical premise of the existence of a 'new frailty subgroup' as a more recurring pattern, that results from a physical-functional decline and an associated neurocognitive decline[19,30]. Unlike some systematic reviews on the topic[31], the objective of this study was to investigate, through a systematic review followed by meta-analysis (SRM), the magnitude of the effects of different frailty levels (pre-frail vs. frail) in evaluating cognitive status of people over 60 years of age.

Methods

Search strategies

Scientific research studies were conducted in the following databases: PubMed, 'B-on, Scielo, Sportdiscus and PsycINFO, with access made between the months of July 2015 and January 2016, using the advanced meta-search option, in which original articles of epidemiological studies of cross-sectional, observational, cohort and population-based published between 2000-2016 were selected. To refine the search, the combination of the indexed descriptors in *Medical Subjects Headings*[32], was used: (((“frail elderly”[MeSH Terms] OR “frail” [MeSH Terms]) AND “cognition”[MeSH Terms]) OR ([mild cognitive impariment]] AND “frail older adults”[MeSH Terms]) OR “frail older adults”[MeSH Terms] AND”[mini-mental State exam]”AND”Fried criteria”AND”Frailty Phenotype AND”Phenotype of Fried.”

For the search in Lilacs and Scielo database, we selected Health Sciences Descriptors (DeCS), available at the online Health Library portal [http://decs.bvs.br], with the following combination: elderly-frail [Subject descriptor] and cognition [subject descriptor] and elderly [Subject descriptor] OR (weakened elderly) AND (slight state of mind) OR mild cognitive impairment AND (tw: (Fried criteria)) OR (tw: of Fragility)) OR (tw: (Fried Phenotype)). The terms 'Fried

criteria', 'Fried fragility phenotype' and 'Fried phenotype' in English and Portuguese were used as additional search terms, following a strategy used in a previous study[9].

Central criterion studies selection

The main criterion for the selection of articles in the SRM, is reflected in the inclusion of articles that used the evaluation criteria of the FS, according to the Phenotype of Frailty (PF) Theory[2], as well as the use of the test Mini-Mental State Examination (MMSE)[33] in the assessment of cognitive status in the populations.

The criterion of 'weight loss' is checked by self-report, which questions the individual on the loss of ' four or more kilograms of weight' in the last year or, when there is a loss of 5% of total body weight in the three months prior to the evaluation date. The dimension "exhaustion" is verified through the negative concordance between two questions (number seven and twenty) of the assessment questionnaire called the CES-D[34]. For measurement of the 'physical activity levels' through weekly energy expenditure in the elderly, we used the short version of the Minnesota Questionnaire[35]. 'Walking speed' is measured through a walking test of 4.6 meters, measuring the time taken by the elderly to go this distance at a comfortable speed, and whose values are adjusted for age and gender[36]. 'Strength' is assessed using the handgrip test for grip strength, adjusting the values according to age and body mass index[37]. The evaluation of these criteria allows to classify the individual in frail (three or more obvious criteria), pre-frail (two of the obvious conditions) and non-frail or 'robust' (with nullity in five criteria)[2,15].

The Mini-Mental State Examination (MMSE)[33] is an instrument composed of 30 questions, which is able to assess the five dimensions of cognitive profile[38]. Its score can range from zero to 30 points, and according to the criteria established in several studies, cut-off values that classify individuals on the following cognitive profiles are accepted: a) Severe Cognitive Disorder (from 1 to 9 points), b) Moderate Cognitive Disorder (10 to 18 points) c) Mild Cognitive Impairment (19 to 24 points), d) Normal Cognitive Profile (equal to or over 25 points)[39]. The MMSE is the most used assessment tool of cognitive status in studies of frailty since it is able to assess what it is intended to evaluate[40].

The exclusion criteria of this study presented the elimination of all the manuscripts that did not meet the initial selection criteria, as well as all those that presented as opinion articles, letters to editor, systematic reviews and protocol format studies.

Data extraction

The initial search for the present SRM study was carried out by two researchers independently, following the ultimate criterion for selection of the articles. For the final selection we included all manuscripts that evaluated older populations by FS subgroups of 'pre-frail' and 'frail', as well as comparing the mean scores (as a continuous variable) of the results of the MMSE according to the aforementioned subgroups, regardless of the gender of the participants in study samples included in the review[39].

Methodological design of the research

This study followed the PRISMA Positioning guidelines to aid in the methodological design of this study[41]. These guidelines describe the four stages (identification, screening, eligibility, final selection) needed to perform the search and selection of manuscripts under an RS, and feature the graphics option to draw a flowchart[42]. At the same time, the SRM presents the PICOS acronym ('patient, problem or population', 'intervention', 'comparison, control or comparison', 'outcomes'), which directs the refinement of the systematic search, making the process more effective (Table 1)[41].

Quality of information assessment

In addition to this method, we chose to use the *Strobe* Positioning[43]. This method consists of a checklist comprising 22 items, which characterizes a manuscript based on the Quality Assessment (QA) that it presents. In this study, we used a combined model of study designs, specific to assess observational, epidemiological, population-based, cross-sectional or cohort studies[44]. After applying all the above criteria, to the total score of the 22 items has a value equal to 100%. However, the percentage was used to identify studies in which low QA could have interfered with the results of the SRM.

Statistical analysis

The results are expressed by calculating the values of the differences of mean MMSE values

Table 1. Descriptive characteristics of all studies included in quantitative analysis following PRISMA guidelines.

Studies	Population Total study sample	Age (M±SD)	Study type	Frailty subgroups Total (100 %)		Sex	Controlled outcomes	Statistical treatment	Main goal of study
				Pre-frail (%)	Frail (%)				
1. Abizanda et al. (2013)	Albacete, Spain (n = 993)	79,4±6,4	Cohort	n = 650		M/F	Physical Frailty, morality, disability and activities of daily living	Descriptive statistics and frequency, logistic regression, comparative analysis and relative risk.	To analyse whether frailty implies increased risk of death and incident disability.
				n = 482 (74)	n= 168 (26)				
2. Alencar et al. (2013)	Belo Horizonte, Brazil (n = 207)	78,37±7,2	observational	n = 160		M	Physical Frailty, cognitive status, hospitalization and death	Descriptive statistics and frequency; comparative analysis and relative risk.	Evaluate associations between frailty status and cognitive decline as well as the incidence of cognitive impairment over 12-month period.
				n = 112 (70)	n = 48 (30)				
3. Ávila-Funes et al. (2009)	3 cities, France (n = 6030)	74,1±5,2	longitudinal	n = 3292		M/F	Physical Frailty, mortality incidence, disability and cognitive profile	Descriptive statistics and frequency; logistic regression; relative risk; analysis of variance.	To determine whether adding cognitive impairment to frailty improves its predictive validity for adverse health outcomes.
				n = 2871 (87)	n = 421 (13)				
4. Gonzalez-Vaca et al. (2014)	Albacete, Spain (n = 331)	84,2±6,8	cross-sectional	n = 324		M/F	Physical Frailty, falls risk and incidence, disability and cognitive profile	Descriptive statistics and frequency; logistic regression; relative risk; analysis of variance	To determine the prevalence of FS in institutionalized elderly as well as the incidence of hospitalization, falls and disabilities
					n = 223 (68)				
5. Han et al. (2014)	25 cities, South Korea (n = 4294)	68,1±5,4	cross-sectional	n = 1554		M	Physical Frailty and cognitive abilities	Descriptive statistics and frequency; logistic and linear regression, relative risk; analysis of variance	To analyse Association between frailty and cognitive disorder in community people.
					n = 375 (25)				

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Table 1. Descriptive characteristics of all studies included in quantitative analysis following PRISMA guidelines.

Studies	Population Total study sample	Age (M±SD)	Study type	Frailty subgroups Total (100 %)		Sex	Controlled outcomes	Statistical treatment	Main goal of study
				Pre-frail (%)	Frail (%)				
5. Han et al. (2014)	25 cities, South Korea (n = 4294)	64,8±3,72	cross-sectional	n = 3501		F	Physical Frailty and cognitive abilities.	Descriptive statistics and frequency; logistic and linear regression, relative risk; analysis of variance	To analyse association between frailty and cognitive disorder
				n = 2894 (83)	n = 607 (17)				
6. Jacobs et al. (2011)	Jerusalem – Israel (n = 840)	87,5±5,4	Longitudinal	n = 634		M	Physical Frailty and cognitive status.	Descriptive statistics and frequency; relative risk; comparison, adjustment measures, linear and logistic regression.	To examine the association between frailty and cognitive impairment and the impact on 5-years survival
				(n = 840)	n = 164 (26)				
7. Kiely et al. (2008)	Boston – United Estates (n = 765)	78,1±5,4	Observacional	n = 331		M/F	Physical Frailty, falls, disability and hospitalization.	Descriptive statistics and frequency; relative risk; analysis of variance, and linear regression	To validate two established frailty indexes and compare their ability to predict adverse outcomes.
				(n = 765)	n = 76 (11)				
8. Robertson et al. (2014)	Ireland (n = 4651)	61,8±1,4	Longitudinal	n = 1534		F	Physical Frailty and cognitive abilities	Descriptive statistics and frequency; relative risk; analysis of variance, adjustment measures, linear regression and relative risk	To explore the relationship between cognitive function and physical frailty syndrome.
				Ireland	n = 90 (6)				
9. Samper-Tenent et al. (2008)	Hispano-descents residents United States (n = 1370)	75,2±5,8	Observacional	n = 686		M/F	Physical Frailty and cognitive profile	Descriptive statistics and frequency; relative risk; analysis of variance, adjustment measures, linear regression	Examine the association between frailty status and change in cognitive function over time
				(n = 1370)	n = 60 (9)				

it continues

Table 1. Descriptive characteristics of all studies included in quantitative analysis following PRISMA guidelines.

Studies	Population Total study sample	Age (M±SD)	Study type	Frailty subgroups Total (100 %)		Sex	Controlled outcomes	Statistical treatment	Main goal of study
				Pre-frail (%)	Frail (%)				
10. Woo et al. (2015)	West Region communities, China (n =816)	74,4±1,4	Longitudinal	n = 549		M/F	Physical Frailty, sarcopenic and cognitive profile.	Descriptive statistics and frequency; relative risk; analysis of variance, adjustment measures, regression linear	To test several established frailty indexes and compare their ability to predict adverse outcomes (cognition and sarcopenic).
				n = 427 (78)	n = 122 (22)				
11. Al-Kuwaiti et al. (2015)	United Arab Emirates (n = 160)	65,6± 6,2	cross-sectional	n = 128		M/F	Descriptive statistics and frequency; relative risk; analysis of variance and logistic regression.	Estatística descritiva e frequência; risco relativo; análise da variância e regressão logística	Determinar a prevalência de SIF em uma amostra de idosos da comunidade
				n = 53 (41)	n = 75 (59)				
12. Macuco et al. (2012)	Brazil, Sao Paulo (n = 384)	72,3±5,8	cross-sectional	n = 342		M/F	Physical Frailty and cognitive profile	Descriptive statistics and frequency; relative risk; analysis of variance, adjustment measures, logistic regression	To examine the association between frailty and cognitive functioning
				n = 311 (91)	n = 31 (9)				

Notes: M = mean; SD = standard deviation; SF = frail syndrome; % = percentage; M = male; F = female

when comparing the groups of pre-frail and frail groups, as well as their respective standard deviation, variance, confidence intervals (95%), the magnitude of the effects and levels of statistical significance (p £ 0.05)[45]. The global average of the studies included in the SRM was calculated based on the random effects model in relation to the methodological heterogeneity of the studies and their participants. The risk of publication bias was assessed by the method of the visual inspection method of scatter plot generated by the Egger's intercept test[46]. The statistical heterogeneity of the studies included in the review was checked with the calculation of the Cochran Q test and the Higgin I^2, which represent the percentage of the variance attributed to the heterogeneity of the study, ranging from low (25% <I^2 <50%) to high (I^2> 75%)[46]. The statistical treatment was performed using the statistical program Comprehensive Meta-Analysis - Version 3.0[47].

Results

Study manuscripts sample

Figure 1 depicts in detail the steps undertaken in conducting the SRM. After completion of the initial search, a total of 1078 manuscripts were initially identified. After applying the first study selection criteria, 954 were excluded and 124 studies passed the screening stage. At this stage, in which the selection criterion was to read the abstracts, 79 studies were excluded. From the 45 studies that passed the eligibility stage, 28 were excluded after a full reading of the manuscripts and 17 studies remained.

From the 17 manuscripts eligible for evaluation of the QA according to the criteria established by the Strobbe positioning[44], two were excluded as they presented the values of the MMSE categorically. Three other studies were excluded at the end of the eligibility stage as they used different definitions of the FS or submitted incomplete or agglutinated subgroups of the FS. A total of 12 manuscripts were selected to be integrated into the quantitative analysis (Table 1).

Study sample

The 12 selected manuscripts defined the FS according to the operational criteria proposed by Fried et al.[2]. The use of this protocol for the evaluation of the participants requires a multidimen-

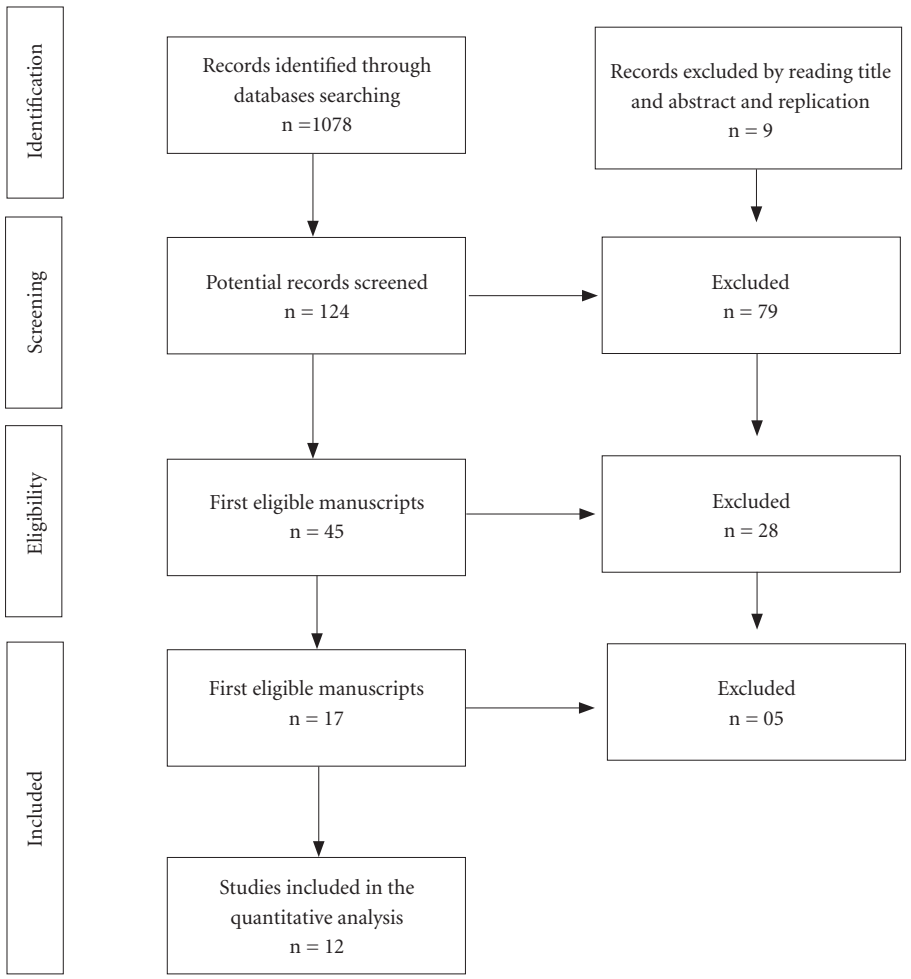

Figure 1. Flowchart of studies included following PRISMA guidelines.

sional, categorical approach, based on the evaluation of the five dimensions described above[48]. In the assessment of the cognitive status, all selected studies used the MMSE[49] in the form of a continuous variable, describing the mean values and standard deviation, and comparing these values to the subgroup of the FS.

Only one study has clearly presented the data in relation to gender[38], being introduced and subsequently analyzed in the meta-analysis as two independent studies, thus justifying a total of 13 entries in the statistical meta-analysis. A total of eight studies analyzed the data without separation by gender, presenting values only for the total sample[19,25,26,49-53], which determines the shape of the meta-analysis to be carried out. A total of two studies were developed only with samples of elderly men[38,54], and three were prepared with samples of elderly female participants only[18,55]. Regarding the QA of the studies, an average value of 94% was recorded.

Characteristics of participants

Regard to the total number of participants analyzed in the selected studies under this SRM, we identified a total of n = 26,935 elderly participants. From these, a total of 13,725 participants (51.0%) represent the sum of the pre-frail and frail individuals in the total of people evaluated, being 11,265 considered pre-frail and 2,460 frail. Considering the absolute and relative values of the sample (n = 13725), the pre-frail presented percentage values ranging from 32 to 94%, being

75% the mean value of the individuals in this category. In the subgroup of the frail, the amplitude values range from 6 to 68% of the sample, being 25% the mean value of individuals in this category. The studies carried out in South Korea[38], Spain[19] and Ireland[55] are the ones with broader samples (Table 2).

From the 12 studies included (13 entries) in this meta-analysis, they all started from the same research assumption, in which the elderly with classifications according to the FS (pre-frail versus frail) differ in the assessment of their cognitive performance, having frail individuals' lower cognitive performance in comparison to the pre-frail. The effect size is represented here by the difference in means (Table 3).

Effect Size of the differences between groups

Regarding the central hypothesis of the present study, it was verified that the difference of averages found between the two subgroups of the FS for the evaluation of the DC was equal to 2,676, which means that the pre-frail had higher mean values (2.7 points) compared to frail subgroups. The confidence interval for the mean difference is 1.794 to 3.558, which means that the gross difference of means is within this range. On the other hand, this range does not include the difference of zero, which means that the true difference of averages is probably non-zero. The Z values obtained to test the null hypothesis, according to which the means difference is zero, showed a Z = 5.948, with the corresponding value of p <0.001. In this way, we can reject the null hypothesis and affirm that the sample presented different DC levels in by FS subgroups, these differences being statistically significant.

Homogeneity of the effects

It is known that the magnitude of the observed effects may vary between studies, due to sample error[56]. Thus, it was necessary to determine if the observed variation was located within the range attributed to the sampling error, which translates into an absence of evidence as to the variation of the true effects. To this, we determined the value expected from the Q Cochran statistics, normally used as a significance test and we also tested the null hypothesis according to which all the studies involved in this meta-analysis share a magnitude of common effects, being that any variation would result from the sampling error within the studies. If all studies share the same magnitude of effects, the expected value of Q will be equal to the degrees of freedom, i.e., the number of studies minus 1[56]. The value obtained from Q is 361.762 with 12 degrees of freedom and with a value of $p < 0.001$. Thus, we can accept the alternative hypothesis, according to which the true magnitude of the effect varies from study to study.

The statistics of I^2 corresponds to the ratio of the real heterogeneity of the total variation of the observed effects, that is, it tells us what proportion (percentage) of the observed variance reflects the differences in the true magnitude of the effect rather than in the error of the sample[57]. In the current meta-analysis, the obtained value of I^2 is 96,683, which means that about 96.7% of the variance on the observed effects reflects the variance of the true effects. T^2 corresponds to the variance of the true effect sizes among studies which, in the current study, depicts a value of 2.358. On the other hand, the value of T^2, refers to the standard deviation of the true magnitude of the effects, being in this meta-analysis equal to 1.536. Regarding the publication bias of integrated studies in this SRM, we used the visual inspection of the funnel plot, which is the effect size of each study in relation to its standard error.

For the visual analysis of the graph, it is assumed that when there is no publication bias, the distribution of the studies should be symmetric around the magnitude of the effect of the true population and the graph becomes narrower as the size of the sample increases[58]. Additionally, the Egger intercept test was performed which is intended to test the null hypothesis according to which the intercept is equal to zero, in the population. In Figure 2, the intercept is 1.34143. 95% of the confidence interval (-3.18799, 5.87086), with t = 0,65184, gl = 11. The recommended value of p (2-tailed) is 0.52789. Thus, there is no statistical evidence of the existence of publication bias.

Discussion

A great number of studies use the FS construct designed by Fried et al.[2] to evaluate the FS[59-61]. Nevertheless, the literature contains over twenty different methods of assessing FS. However, there is some evidence that the multidimensional assessment provided by this construct seems to be more sensitive to detect the FS in the populations aged 60 years and over, as well as to establish associations with mortality, morbidity and other adverse clinical outcomes[59], and its replication in

Table 2. Quality assessment of manuscript information by STROBE guidelines (n=12 studies and 13 inputs in the metanalysis).

Author (year of publication)	Title and abstract	Introduction (background rationale)	Introduction (objectives)	Methods (study design)	Methods (setting)	Methods (participants)	Methods (variables)	Methods (risk of bias)	Methods (study sample size)	Methods (variables)	Methods (quantitative variables)	Methods (statistical methods)	Results (participants)
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
1. Abizanda et al. (2013)	1	1	1	1	1	1	1	0	1	1	1	1	1
2. Alencar et al. (2013)	0	1	1	1	0	1	1	0	1	1	1	1	1
3. Ávila- Funes et al. (2009)	1	1	1	1	1	1	1	1	1	1	1	1	1
4. Gonzalez Vaca et al. (2014)	1	1	1	1	1	1	1	1	1	1	1	1	1
5. Han et al. (2014)	1	1	1	1	1	1	1	1	1	1	1	1	1
5. Han et al. (2014)	1	1	1	1	1	1	1	1	1	1	1	1	1
6. Jacobs et al. (2011)	0	1	1	1	1	1	0	1	1	1	1	1	1
7. Kiely et al. (2011)	1	1	1	1	1	1	1	0	1	1	1	1	1
8. Robertson et al. (2014)	0	1	1	1	1	1	1	0	1	1	0	1	1
9. Samper-Tenent et al. (2008)	1	1	1	1	1	1	1	1	1	1	1	1	1
10. Woo et al. (2015)	1	1	1	1	1	1	1	0	1	1	1	1	1
11. Al-Kuwaiti et al. (2015)	0	1	1	1	1	1	1	0	1	1	1	1	1
12. Macuco et al. (2012	0	1	1	1	1	1	1	0	0	1	1	1	1

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large[38] or small samples[62]. In the final selection stage of the study, studies were removed from the systematic review in which the change of evaluation criteria for each dimension was introduced. The QA studies that integrated the SRM show the scientific rigor of the researchers in this area. However, it is important to note that in the original study[2], the QA was reported systematically and accurately, which may have influenced the replication, with high quality, of the studies in other countries[31].

The fact that the subgroup of frail older people has lower values in cognitive status when evaluated using the MMSE test, was clearly shown in this SRM. The values found for all analyzed studies showed significant values statistically. Some of

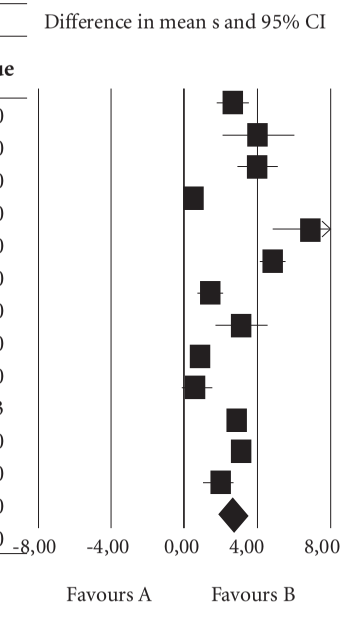
Table 2. Quality assessment of manuscript information by STROBE guidelines (n=12 studies and 13 inputs in the metanalysis).

Author (year of publication)	Results (descriptive data) XIV	Results (outcomes data) XV	Results (main results) XVI	Results (other analysis) XVII	Discussion (Key results) XVIII	Discussion (limitations) XIX	Discussion (Interpretation) XX	Discussion (Generalisability) XXI	Funding/Knowlegdments XXII	Total intens 22	Total Percentage 100%
1. Abizanda et al. (2013)	1	1	1	1	1	1	1	1	1	21	95%
2. Alencar et al. (2013)	1	1	1	1	1	1	1	1	1	19	86%
3. Ávila- Funes et al. (2009)	1	1	1	1	1	1	1	1	1	22	100%
4. Gonzalez Vaca et al. (2014)	1	1	1	1	1	1	1	1	1	22	100%
5. Han et al. (2014)	1	1	1	1	1	1	1	1	1	22	100%
5. Han et al. (2014)	1	1	1	1	1	1	1	1	1	22	100%
6. Jacobs et al. (2011)	1	1	1	1	1	1	1	1	1	20	91%
7. Kiely et al. (2011)	1	1	1	1	1	1	1	1	1	21	95%
8. Robertson et al. (2014)	1	1	1	1	1	1	1	1	1	19	86%
9. Samper-Tenent et al. (2008)	1	1	1	0	1	1	1	1	1	21	95%
10. Woo et al. (2015)	1	1	1	1	1	1	1	1	1	21	95%
11. Al-Kuwaiti et al. (2015)	1	1	1	1	1	1	1	1	1	20	91%
12. Macuco et al. (2012	1	1	1	1	1	1	1	1	1	19	86%
Mean of total percentage											**94%**

these studies explicitly related the FS to the cognitive performance[18,55]. However, this seems to be the first SRM that sought to test the magnitude of the effect of the differences between the groups of pre-frail and frail. On the other hand, a very recent SRM carried out by Chang and Lin[9], also pointed to the existence of a strong association between mortality and the FS in the population evaluated using the Fried protocol. Individuals with higher levels of FS (pre-frail and frail) also have a higher risk of mortality when compared to non-frail elderly individuals.

Table 3. Studies summary of mean differences in cognitive status on pre-frail (favour A) and frail (favour B) groups comparison.

Análise estatística para cada estudo							
Study name	**Difference in mean**	**Standard error**	**Variance**	**Lower limit**	**Upper limit**	**Z- value**	**P- value**
Abizanda et al. (2013)	2,600	0,453	0,206	1,711	3,489	5,734	0,000
Alencar et al. (2013)	4,080	1,006	1,011	2,109	6,051	4,057	0,000
Al-Kuwaiti et al. (2015)	4,000	0,602	0,363	2,819	5,181	6,640	0,000
Ávila et al. (2013)	0,500	0,100	0,010	0,304	0,696	5,008	0,000
Gonzales et al. (2008)	6,900	1,092	1,193	4,759	9,041	6,318	0,000
Jacobs et al. (2011)	4,800	0,352	0,124	4,110	5,490	13,626	0,000
Kiely et al. (2008)	1,390	0,364	0,132	0,677	2,103	3,823	0,000
Macuco et al. (2012)	3,110	0,737	0,544	1,665	4,555	4,218	0,000
Robertson et al. (2014)	0,800	0,198	0,039	0,411	1,189	4,033	0,000
Samper et al. (2008)	0,600	0,430	0,185	-0,243	1,443	1,395	0,163
Han et al. (2014)	2,900	0,221	0,049	2,466	3,334	13,100	0,000
Han et al. (2014)	3,100	0,211	0,045	2,686	3,514	14,682	0,000
Woo et al. (2015)	1,900	0,448	0,201	1,021	2,779	4,237	0,000
Resultados Globais	2,676	0,450	0,202	1,794	3,558	5,948	0,000



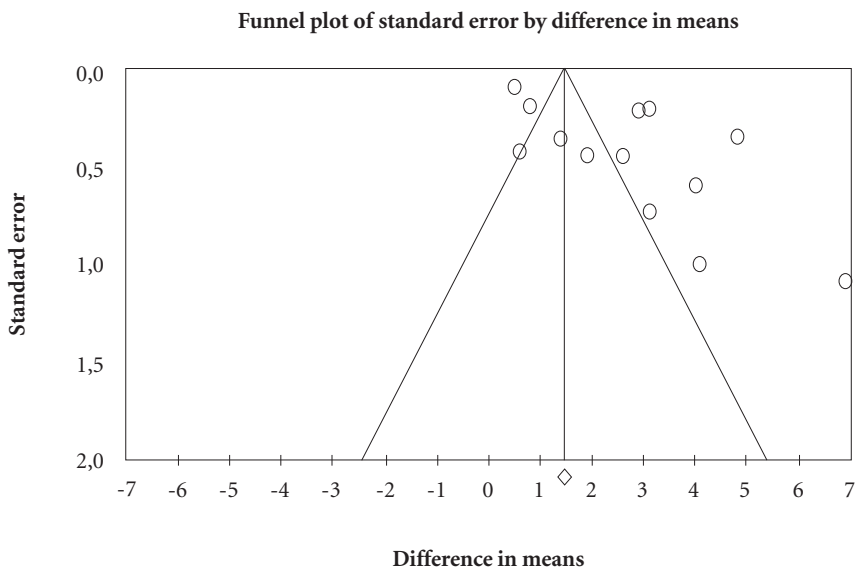


Figure 2. Funnel plot and Egger's test.

The results found in this study corroborate with the literature, it being increasingly evident that the FS is strongly related to cognitive status[22,26]. The present study makes it more evident that the pre-frail and frail groups, respectively, have a tendency to an imminent risk of suffering from more severe cognitive impairments, when the FS is detected. The geographic distribution and diversity in the countries involved in the study of this issue show that there is a global concern about the phenomenon of the FS in adverse populations[25,50,52], accompanied by an increasing interest in terms of research, as well as evidence that this pattern occurs in countries on several continents. Currently, the term 'cognitive frailty' associated with the concept of disorder or MCI appears, which shows a growing interest in the search for other explanations for this phenomenon[63].

The non-consideration of data from non-frail individuals under this SRM as the first limitation of this study. The participants from the group of non-frail showed average values below 24.0 points, i.e., a score that, according to the cut-off values of the MMSE, indicates the existence of an MCI[18,21]. In this sense, it is reinforced that overall, non-frail individuals have a 'preserved' cognitive status. Regarding gender differences, it is valid to indicate that the literature points to a trend similar to the FS for both genders[38], with earlier death for men, due to a higher incidence of metabolic diseases when compared to older women. However, in this study, it was not possible to further explore these differences, since only one of the studies presented analyses by gender and most samples investigated only females.

Thus, we can infer that cognition, as well as frailty, can appear as potential predictors of early mortality in the populations aged 60 and over, besides pointing out that the evaluation of the FS cannot be dissociated from the assessment of the cognitive function[54,64,65]. Comparing a pre-frail population pool with a frail population sample, the poor cognitive function associated with the FS is a likely clinical outcome in these populations which should be assessed[27].

Conclusion

By analyzing the magnitude of the effect in the mean difference of the studies included in this SRM, we found a low cognitive function associated with the FS, i.e., we identified this as a probable clinical outcome, with the occurrence of a decrease in cognitive performance as the elderly progress from a pre-condition of frailty to a frail condition. Therefore, any strategy or public health policy that aims to mitigate or reverse the incidence of this condition should take into ac-

count that these two outcomes seem to have similar temporal trajectories, caused in a population phenotype to be investigated with due attention.

Collaborations

GE Furtado participated in all stages of the manuscript. R Letieri assisted in the final meta-search. E Hogervorst contributed with its expertise in the topic of discussion. AB Teixeira made substantial contributions in the framework of the proposed theme. JP Ferreira assisted in methodological structure and interpretation of the results.

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