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Review article

Co-occurrence of cognitive impairment and physical frailty, and incidence of dementia: Systematic review and meta-analysis

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ABSTRACT

Introduction: Cognitive impairment and frailty are important health determinants, independently associated with increased dementia risk. In this meta-analysis we aimed to quantify the association of the co-occurrence of cognitive impairment no dementia (CIND) and physical frailty with incident dementia.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used when reporting this review. We performed a systematic search on PubMed, Web of Science, and Embase databases for relevant articles. Longitudinal studies enrolling individuals with both CIND and physical frailty and reporting dementia incidence were eligible. Pooled estimates were obtained through random effect models and Mantel-Haenszel weighting.

Results: Out of 3684 articles, five (14302 participants) were included in the meta-analysis. In comparison to participants free from frailty and CIND, the pooled hazard ratio for dementia was 3.83 (95% confidence interval [CI]: 2.64–5.56) for isolated CIND, 1.47 (95%CI: 0.89–2.40) for isolated physical frailty, and 5.36 (95%CI: 3.26–8.81) for their co-occurrence.

Discussion: The co-occurrence of cognitive impairment and physical frailty is a clinical marker of incident dementia.

1. Introduction

The integrity of mental and physical functioning is crucial to maintain a good health status (World Report on Ageing and Health WHO, 2015; Grande et al., 2019a). A number of biological changes that affect the organism homeostasis accumulate during the aging process, resulting in cognitive and physical decline. This process contributes to the more rapid accrual of morbidities, higher incidence of disability, and shorter survival experienced in older age (Santoni et al., 2015). Socioeconomic factors, as well as psychological and environmental issues further contribute to the development of frailty, and modulate the association between frailty and several negative outcomes (Gobbens et al., 2012; De Witte et al., 2013). Later in life, physical and cognitive problems often co-occur and interact, mutually boosting their negative effects on a person's health, generating complex health profiles (Bullain

et al., 2016; Vetranò et al., 2018b). Recently, in aging research, an increasing amount of attention has been given to such body-mind interactions (Qiu and Fratiglioni, 2015; Vetranò et al., 2018b).

Cognitive impairment no dementia (CIND) has been consistently shown to be a robust predictor of further cognitive decline and incident dementia (Caracciolo et al., 2008). The definition of CIND requires the presence of an objective impairment in cognition, without meeting the diagnostic criteria of dementia. At the same time, a number of longitudinal studies have reported that a decreased physical function increases the risk of cognitive decline and dementia (Boyle et al., 2009; Buracchio et al., 2010; Kueper et al., 2017; Calderon-Larranaga et al., 2018). Physical frailty is a construct that captures well such physical decline, and has attracted a great deal of scientific and clinical interest during the last years (Fried et al., 2001; Clegg et al., 2013). Physical frailty, as operationalized by Fried et al, is defined as the presence of at

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least three of the following conditions: unintentional weight loss, exhaustion, muscle weakness, slowness while walking, and low levels of activity (Fried et al., 2001). Frailty may be thought as an indicator of biological age, a transversal measure of reduced resilience to negative events, which underlies multiple impairments across different organs and systems (Clegg et al., 2013). The concept of frailty has been embedded in several medical areas beyond geriatrics, being currently implemented also in neurological settings, and, in particular, in the field of cognitive disorders (Canevelli et al., 2017). Frailty has been shown to be a reliable predictor of several negative health-related outcomes, such as falls, institutionalization, hospitalization, and shorter survival (Zucchelli et al., 2018). Moreover, a meta-analysis reported a greater risk of all-cause dementia in older people presenting with physical frailty (Kojima et al., 2016).

The concept of frailty may have important implications in the clinical approach to people with cognitive problems. Additionally, different research groups have recently investigated the co-occurrence of physical frailty and cognitive impairment, and their impact on several clinical and functional outcomes, including dementia (Avila-Funes et al., 2009; Montero-Odasso et al., 2016). However, those studies have not always led to significant results. We hypothesize that including a measure of physical frailty in the assessment of people with initial cognitive impairment, may help to detect a special group of individuals at even higher risk of dementia. Hence, the aim of the present study is to systematically review the literature and to provide pooled estimations regarding the combined effect of cognitive impairment and physical frailty on dementia incidence.

2. Materials and methods

We reviewed studies assessing the combined effect of CIND and physical frailty on dementia incidence in adult persons (*i.e.* 18 years old or older). The protocol of the present study was *a priori* registered in the international prospective register of systematic reviews PROSPERO (registration number CRD42018093794). This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. For the present study, no ethics committee approval was necessary.

2.1. Data sources and searching

We searched the PubMed electronic database of the National Library of Medicine, the Web of Science database, and Embase for relevant articles published up to the 15th of August 2019. MeSH terms and free words referring to frailty, CIND (including the concept of mild cognitive impairment, MCI) and dementia were used as keywords. The detailed search queries are reported as supplementary material. References from selected papers and from other relevant articles were screened for potential additional studies in accordance with the snowball principle.

2.2. Study selection and data extraction

Two assessors (GG and MLH) independently screened the titles and abstracts of the retrieved studies. Original contributions with longitudinal design, reporting information on physical frailty and CIND, and their impact on dementia were included. CIND, as compared with mild cognitive impairment (MCI), is a broader definition of cognitive impairment, which includes the concept of MCI and does not require the presence of cognitive complaints, and allows the presence of functional disability. Studies on both CIND and MCI have been included in the present review. Articles were excluded if they a) investigated topics outside the aims of the review; b) had a cross-sectional or intervention design (*e.g.* randomized controlled trials); c) did not present original data (*i.e.* reviews, guidelines/recommendations, letters to editor, commentaries, editorials, case reports); d) did not provide an explicit definition, and an objective evaluation of physical frailty (Fried's criteria

and CIND; e) evaluated frailty through a single measure (*e.g.* only walking speed, muscle weakness, weight loss); f) were conducted *in vitro* or in animals; g) were written in languages other than English; and h) included people affected by dementia at baseline. The full text of the articles selected at least by one of the assessors was further evaluated. The same assessors extracted independently the information from the selected studies. Any disagreement was solved through consensus. When more than one measure of association was provided, the most adjusted estimate was used for the purposes of the present study.

2.3. Assessment of risk of bias

Study quality was evaluated independently by the two assessors through the tool for the qualitative evaluation of observational studies, the Newcastle Ottawa Scale (NOS) (Lo et al., 2014). Any disagreement in quality assessment was solved through consensus. Studies scoring > 7 were considered to pose a low risk of bias, scores of 5–7 indicated moderate risk of bias, while scores of < 5 indicated high risk of bias. Likelihood of publication bias was also assessed (see statistical analysis).

2.4. Data analysis

Considering the observational design of the retrieved studies, and the methodological differences potentially responsible for a significant share of the variance among the measures of interest, pooled estimates were obtained through random effect models and Mantel-Haenszel weighting. Lack of homogeneity among the pooled studies was assessed through the I^2 statistics (significant if $\geq 50\%$). I^2 represents the percentage of variability in the risk estimate owed to methodological heterogeneity rather than chance. Pooled hazard ratio estimations (HR) and 95% Confidence Intervals (95% CI) were examined in relation to the presence of isolated physical frailty, isolated CIND, and their co-occurrence. Publication bias was assessed by mean of the Egger's and the Begg's tests.

All statistical analyses were performed with Stata version 15.0 (StataCorp, TX, USA). A *p* value < 0.05 was considered statistically significant.

3. Results

We retrieved a total of 3684 articles (Fig. 1), of which 3671 (99%) were excluded after title and abstract screening, and eight articles after full-text reading (reasons for exclusions are reported in Fig. 1). Five articles were part of the final qualitative assessment and were analyzed in the meta-analysis.

3.1. Study description

Table 1 summarizes the main characteristics and findings of the selected studies. The overall number of participants was 14302, with the mean age ranging between 66–76 years, and the proportion of females from 44% to 65%. The mean follow-up time of the studies was between three to five years. Four studies included community-dwelling people (Avila-Funes et al., 2009; Feng et al., 2017; Solfrizzi et al., 2017; Shimada et al., 2018), and one study included geriatric outpatients (Montero-Odasso et al., 2016). Two studies were carried out in Europe (Avila-Funes et al., 2009; Solfrizzi et al., 2017), one in Canada (Montero-Odasso et al., 2016), and two in Asia (Feng et al., 2017; Shimada et al., 2018). One study reported results stratified by inflammatory (fibrinogen values) status (Solfrizzi et al., 2017). The results from the two strata have been included separately in the meta-analysis.

3.2. CIND and frailty assessment

All the studies included in the meta-analysis assessed cognition via objective tests. Two studies defined CIND using the Mini-Mental State Examination (MMSE), either with a cutoff of 24 out of 30 (Feng et al.,

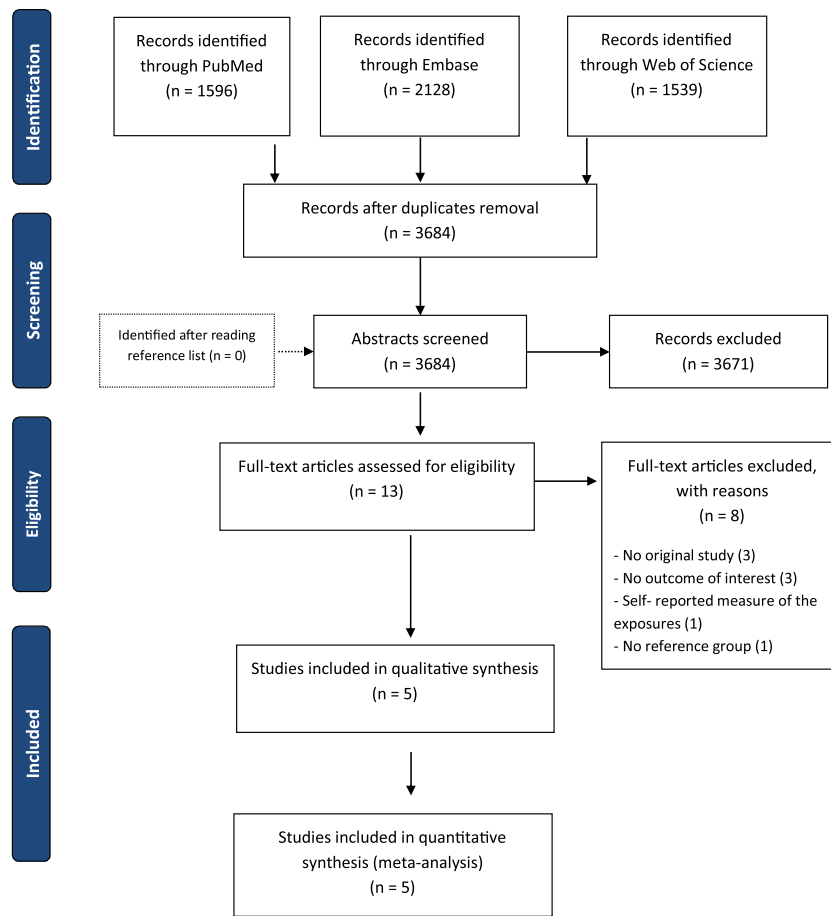


Fig. 1. Systematic review and meta-analysis flow-chart.

2017) or by using the lowest quartile of the MMSE score (Avila-Funes et al., 2009). One study (Montero-Odasso et al., 2016) used the Montreal Cognitive Assessment (MoCA), and two (Solfrizzi et al., 2017; Shimada et al., 2018) based the cognitive assessment on an extensive neuropsychological battery. To note, in contrast to the other studies, Solfrizzi et al. operationalized cognitive impairment according to the diagnostic criteria of MCI, therefore including the presence of subjective cognitive complaints and the evaluation of daily functioning (Winblad et al., 2004). When only community-based studies ($n = 4$) were considered, the presence of CIND ranged from 3.5% to 11.8% in the study populations. On the other hand, in a clinical based setting the presence of CIND reached 55%. In line with previous findings (Di Carlo et al., 2007), the lowest proportion of cognitive impairment was detected when the diagnostic criteria for MCI were adopted.

All the studies defined physical frailty in accordance with the Cardiovascular Health Study (CHS) criteria, proposed by Fried et al., which defined frailty as the presence of at least three of the following conditions: weight loss, low handgrip strength, slow walking speed, exhaustion, and reduced physical activity (Fried et al., 2001). When only community-based studies were considered, physical frailty prevalence spanned from 2.0% to 8.0%. In the study by Montero-Odasso, the only one carried out in a clinical setting, the proportion of people with physical frailty was 13%.

3.3. Risk of bias

Overall, the studies presented a low-moderate risk of bias. In most cases, the absence of information regarding the loss at follow-up was responsible for a lower score. In general, many studies applied a modified version of the frailty phenotype, in order to adapt the

assessment to the available data. Finally, according to the Egger's and the Begg's tests, no strong evidence of publication bias was detected in our meta-analyses ($P > 0.05$ for all).

3.4. Overlap between CIND and physical frailty

Fig. 2 shows the proportions of people with CIND and physical frailty, reported by the retrieved studies. In population-based studies (four out of five, including a total of 11254 persons), 173 (1.5%) persons presented with both CIND and physical frailty, 742 (6.6%) with only physical frailty, and 990 (8.8%) with only CIND. According to pooled estimations, among participants with physical frailty, 20% (95% CI: 11–28%) had also CIND. Conversely, 15% (95% CI: 9–21%) of people with CIND presented also with physical frailty.

3.5. Combined effect of CIND and physical frailty on dementia incidence

Fig. 3 depicts the association between isolated physical frailty, isolated CIND, and the combination of CIND and physical frailty with the incidence of dementia. In comparison to participants free from frailty and CIND, the HR for dementia was 3.83 (95% CI: 2.64–5.56; $I^2 = 0\%$) for isolated CIND, 1.47 (95% CI: 0.89–2.40; $I^2 = 0\%$) for isolated physical frailty, and 5.36 (95% CI: 3.26–8.81; $I^2 = 0\%$) for the co-occurrence of CIND and physical frailty. The results remained consistent in terms of direction and magnitude after excluding the study by Montero-Odasso et al., which was the only one including a clinical population (HR for isolated CIND: 3.90, 95% CI: 2.68–5.69; HR for isolated physical frailty: 1.47, 95% CI: 0.89–2.40; HR for CIND and physical frailty: 5.32, 95% CI: 3.21–8.84).

Table 1
Five studies on cognitive impairment and physical frailty: study methods and main results.

Country, Study name, Population type	N	Mean age ± SD	Women (%)	Mean follow-up time	Cognitive impairment diagnosis/definition and overall prevalence (%)	Frailty criteria and overall prevalence (%)	Prevalence (%) of cognitive and frailty profiles	Main results	NOS
Avila-Funes et al. (2009)	6030 (N = 4827 included in the statistical analyses)	74.1 ± 5.2	61.2	4 years	Lowest quartile in the MMSE and IST 11.8%	Modified Fried criteria. Overall frail = 7.0%, prefrail = 47.6%	Isolated cognitive impairment: 10.3% Isolated physical frailty: 5.5% Cognitive impairment and physical frailty: 4.98 (2.17–11.41) Multi-adj model (age, sex, education, income, smoking, alcohol consumption, number of chronic diseases, self-reported health, depression, mobility, disability, and ApoE4 genotype).	HR (95% CI) of dementia: Only cognitive impairment: 4.66 (2.36–9.22) Only physical frailty: 0.74 (0.27–2.02) Cognitive impairment and physical frailty: 4.98 (2.17–11.41) Multi-adj model (age, sex, education, income, smoking, alcohol consumption, number of chronic diseases, self-reported health, depression, mobility, disability, and ApoE4 genotype).	8
Feng et al. (2017)	1575 (N = 1491 included in the statistical analyses)	66.0 ± 7.6	64.8	3 years	MMSE < 23.9%	Modified Fried criteria. Overall frail = 1.8%, prefrail = 31.9%	Isolated cognitive impairment: 6.0% Isolated physical frailty: 1.0% Cognitive impairment and physical frailty: 0.7%	HR (95% CI) of dementia: Only cognitive impairment: 4.04 (1.91–8.55) Only physical frailty: 1.09 (0.21–5.51) Cognitive impairment and physical frailty: 6.37 (1.74–23.28) Multi-adj model (age, sex, education, diabetes, heart failure, atrial fibrillation, current smoking, alcohol consumption, APOE genotype, and depressive symptoms.)	8
Montero-Odasso et al. (2016)	252	76.7 ± 8.6	62.7	5 years	MoCA < 26 and CDR = 0.5 55.6%	Modified Fried criteria. Overall frail = 13.9%, prefrail = 52.0%	Isolated cognitive impairment: 44.8% Isolated physical frailty: 3.2% Cognitive impairment and physical frailty: 10.7%	HR (95% CI) of dementia: Only cognitive impairment: 2.0 (0.2–18.4) Only physical frailty: n.a. Cognitive impairment and physical frailty: 6.3 (0.5–75.8) Multi-adj model (age, sex, education, and number of chronic diseases)	7
Shimada et al. (2018)	4072	71.6 ± 5.2	51.3	2 years	Neuropsychological test battery, 1.5 SD below age and education specific means 6.6%	Modified Fried criteria. Overall frail = 6.2%, prefrail = n.r.	Isolated cognitive impairment: 5.1% Isolated physical frailty: 5.5% Cognitive impairment and physical frailty: 1.1%	HR (95% CI) of dementia: Only cognitive impairment: 3.85 (2.09–7.10) Only physical frailty: 1.95 (0.97–3.91) Cognitive impairment and physical frailty: HR: 6.19 (2.7–13.99). Multi-adj model (age, sex, education, and number of chronic diseases)	7

(continued on next page)

Table 1 (continued)

Country, Study name, Population type	N	Mean age ± SD	Women (%)	Mean follow-up time	Cognitive impairment diagnosis/definition and overall prevalence (%)	Frailty criteria and overall prevalence (%)	Prevalence (%) of cognitive and frailty profiles	Main results	NOS
Solfrizzi et al. (2017) Italy, Italian Longitudinal Study of Aging (ILSA), Community	2373	72.8 ± 5.5	44.5	3.5 years	Neuropsychological test battery and MMSE score, MCI diagnostic criteria (Winblad et al., 2004) 3.5%	Modified Fried criteria. Overall frail = 8.0% prefrail = n.r.	Isolated cognitive impairment: 2.8% Isolated physical frailty: 7.2% Cognitive impairment and physical frailty: 0.7%	Subsample with low fibrinogen: IRR (95% CI) of dementia: Only cognitive impairment: 0.76 (0.09-6.79) Only physical frailty: 1.08 (0.17-6.75) Cognitive impairment and physical frailty: 0.93 (0.07-11.94) Subsample with high fibrinogen: IRR (95% CI) of dementia: Only cognitive impairment: 2.4 (0.23-24.84) Only physical frailty: 3.07 (0.62-15.21) Cognitive impairment and physical frailty: 6.15 (0.71-53.41) Multi-adj model (age, sex, education, smoking, Charlson comorbidity index, and APOE genotype)	8

Abbreviations: SD: standard deviation; NOS: Newcastle Ottawa Scale; MMSE: Mini-Mental State Examination; IST: Isaac Set Test; MoCA: Montreal Cognitive Assessment; HR: hazard ratio; CI: confidence interval; CDR: Clinical dementia rating scale; n.r.: not reported; IRR: incidence rate ratio.

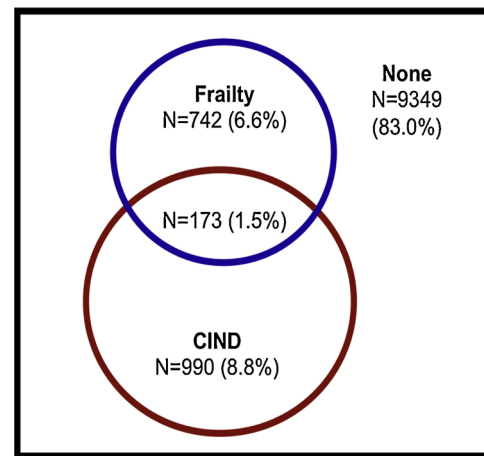


Fig. 2. Cognitive impairment no dementia (CIND) and physical frailty overlap (pooled data from four retrieved population based studies; n = 11254).

4. Discussion

According to this systematic review and meta-analysis, including more than fourteen thousand participants, people presenting simultaneously with cognitive impairment and physical frailty had more than a five-fold higher risk of developing dementia, than people free from both conditions. The combined effect described here, supports the existence of an interplay between physical and cognitive dimensions in the development of dementia. This systematic review and meta-analysis provides for the first time a pooled estimation of such a relationship, which has been otherwise vitiated by contrasting findings derived from single studies.

Increasing efforts have been made to detect modifiable risk and protective factors for dementia, and to find early predictors of its development (Fratiglioni et al., 1993; Winblad et al., 2016). The results of the present study suggest that impairments in cognitive and physical domains are relevant predictors of future dementia, and call for the need of a multidimensional approach in the assessment of older adults' health who present an initial cognitive impairment. Notably, impairments in physical domains may strengthen the association between CIND and dementia. In fact, mental and somatic conditions frequently coexist, interact, and affect each other (Calderon-Larranaga et al., 2018; Vetrano et al., 2018b). Slow walking speed, one of the criteria that define frailty, has been associated with an increased risk of incident dementia (Grande et al., 2019b). In general, motor changes (Dodge et al., 2012; Verghese et al., 2014), including the temporal variability in walking speed and in the pattern of gait, are early markers of future cognitive decline. Similarly, weight loss and reduced muscle strength – both reflecting a poor nutritional status and an impaired multi-organ homeostasis – have been described as risk factors for future cognitive impairment and dementia (Boyle et al., 2009; Bell et al., 2017). Interestingly, the presence of cognitive impairment seems to increase the risk of falling in people with slow walking speed, impaired balance, and muscle weakness, highlighting the existence of an interplay between physical and cognitive domains (Welmer et al., 2017). In clinical settings, the evaluation of such parameters of physical performance and status is possible, even in the case of limited resources and time (Studenski et al., 2011). Integration of such parameters with a neuropsychological assessment might help to detect older adults at risk of cognitive decline and dementia (Grande et al., 2019b).

Executive cognitive and motor functions rely on common brain regions and networks. Smaller prefrontal regions have been described in people exhibiting a slower gait speed, and smaller basal ganglia, superior posterior parietal cortex, and cerebellum have been associated with balance difficulty (Rosano et al., 2012). A possible explanation for these associations is the fact that the same areas are also involved in

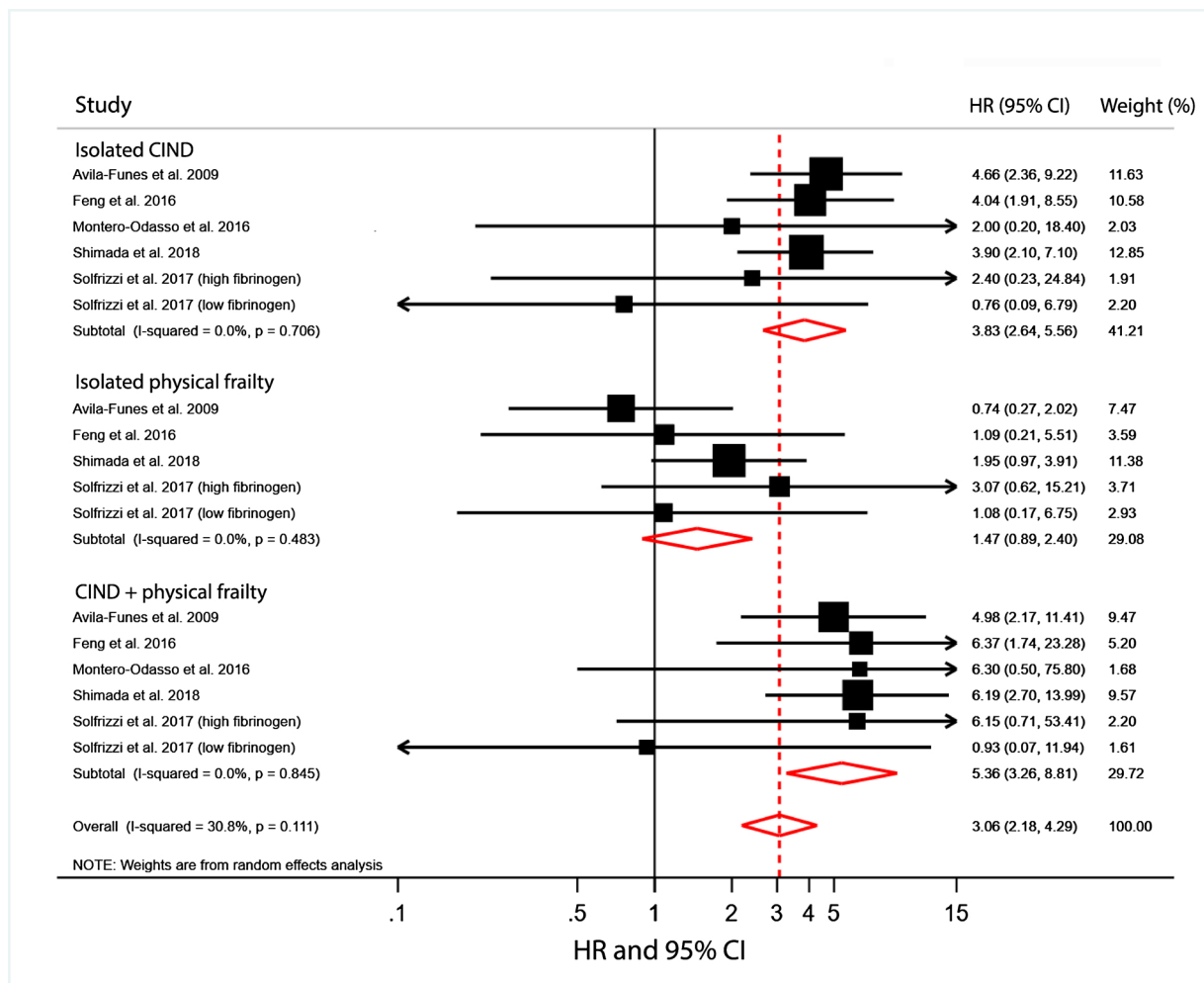


Fig. 3. Association of cognitive impairment no dementia (CIND), physical frailty, and their combination with incident dementia (reference group: participants free from both conditions).

HR: hazard ratio; CI: confidence interval.

executive functioning and processing speed (Welmer et al., 2014), which can in turn result in a slower gait speed, which is one of the main contributors to the frailty syndrome. Sharing common underlying mechanisms, both physical and cognitive decline can be simply seen as two downstream consequences of such dysfunctions (Beauchet et al., 2012; Grande et al., 2019b). The co-occurrence of cognitive and physical impairments – and consequently the higher associated risk of dementia – may be interpreted as the result of a greater brain pathology burden (Buchman et al., 2008; Yoon et al., 2018).

Frailty, which is characterized by the reduction of the individual's homeostatic reserve, leading to an increased vulnerability to external and internal minor stressors, is the cumulative consequence of declines in several physiological systems, and is considered a strong predictor of negative health-related events (Clegg et al., 2013; Vetrano et al., 2017, 2018a). Beyond this definition, several operationalizations have been proposed (Cesari et al., 2016). In this study, we chose to define frailty in accordance with the construct of the frailty phenotype, which well captures the somatic dimensions of the frailty syndrome. Previous studies from our group (Grande et al., 2019b; Vetrano et al., 2019) and others (Verghese et al., 2014; Montero-Odasso et al., 2017) have demonstrated that walking speed alone is able to trace the deterioration in health of older people that will develop dementia. However, the definition of physical frailty based on the frailty phenotype offers the possibility to capture in a more holistic way several physical aspects of the frailty syndrome, including muscle weakness, nutritional issues and

energy. The frailty index by Rockwood et al., alternatively used in a number of studies, has received much attention both in clinical and research contexts. However, such index embeds in its operationalization a number of cognitive signs and symptoms, as well as mood and affective disorders, making it less suitable to explore the somatic components of the frailty syndrome. Systemic inflammation, cell senescence, hormonal changes, and mitochondrial dysfunction have been identified as the upstream causative conditions of physical frailty (Franceschi and Campisi, 2014; Ferrucci and Fabbri, 2018). Interestingly, the same mechanisms may promote the neurodegenerative and vascular damages associated with cognitive decline and dementia (Qiu and Fratiglioni, 2015; Haaksma et al., 2017). To note, one of the studies included in our meta-analysis showed a significant association between the combination of CIND and physical frailty and dementia only in participants characterized by a pro-inflammatory status, identified by higher fibrinogen blood concentration (Solfrizzi et al., 2017). This suggests that inflammation may boost the negative prognosis of the interplay between cognitive and physical dysfunctions.

Physical frailty may identify a special group of biologically old persons, with a reduced ability to cope with the systemic consequences of cognitive decline, accelerating the progression to dementia. The frailty assessment implies carrying out a multidimensional evaluation of those somatic aspects that may accelerate, or even cause, cognitive impairment. To note, not only somatic conditions, but also psycho-social and environmental factors contribute to the development of frailty;

given the dynamic nature of frailty, all these factors need to be regularly assessed in older persons (Gobbens et al., 2012; De Witte et al., 2013; Vetrano et al., 2018a; Haaksmma et al., 2019; Melis et al., 2019). This holistic approach is strongly advocated by modern medicine, especially when dealing with the complex heterogeneity encountered in old ages. Interestingly, frailty has been shown to significantly increase the risk of the progression towards dementia in people with MCI who have been referred to a memory clinic. This suggests that models of frailty might be adopted in neurological clinical settings with the aim of improving the prediction of prognosis and the management of these patients (Trebboni et al., 2017).

Similarly to frailty, different operationalizations of CIND have been proposed. In the present review, we encountered assessments based on either measures of global cognition (e.g. MMSE and MoCA) or on extensive neuropsychological batteries. As discussed below, this may represent a potential limitation of our study. At the same time, the consistency – in terms of direction and strength of association – of the results of the single studies, supports the idea that all these different methods are capable to identify people with increased risk of developing dementia.

In line with previous studies supporting the existence of a body-mind connection, our meta-analysis points to a higher risk of dementia risk in cognitively impaired people; conversely, we do not observe a statistically significant higher risk of dementia in persons with isolated physical frailty. This might be due to some methodological issues of the included studies, which, for example, did not consider death as a competing risk for the onset of dementia. However, when considering these conditions together, the risk of dementia was almost six times higher than in people free from these conditions, suggesting the existence of a biological interaction between cognitive impairment and frailty.

4.1. Strengths and limitations

The major strength of the present study is its comprehensive and reproducible search strategy and the use of multiple electronic databases. The screening of the titles, abstracts, and full-texts, as well as the data extraction were conducted independently by two trained researchers. Along with the careful study selection and quality assessment, this provides a reliable overview of the evidence in the field. Second, the overall quality of the studies included in the meta-analysis was moderate to high; all studies used physical frailty to define frailty and applied standardized criteria to diagnose dementia. Moreover, a proper adjustment (see Table 1) was carried out in the retrieved studies.

However, some limitations need to be considered. First, we retrieved only five longitudinal studies assessing the association of physical frailty and CIND and the development of dementia. This small number can represent an issue in the assessment of heterogeneity, and prevented us from running subgroup analyses. For example, it would have been interesting to check to what extent regional differences and different CIND assessments might affect generalizability. Notwithstanding, the absence of evident publication bias, the non-significant heterogeneity tests, and the low-to-moderate risk of methodological bias increased the reliability of our results. Finally, the magnitude of the association between the concurrent presence of CIND and frailty and incident dementia was replicated across the five retrieved studies, further reinforces the generalizability of our findings. Second, several operationalization methods of CIND have been used, and this might have led to substantial heterogeneity in the results. The diverse operationalization of CIND reflects the absence of a shared definition of this construct both in the clinical and research fields. Finally, the mean follow-up time was relatively short, ranging from three to five years; this limited us in generating hypotheses regarding any causal link between frailty profiles and the occurrence of dementia. At the same time, the presence of CIND and the concurrent presence of physical frailty – which potentially share common pathological mechanisms with cognitive impairment – may represent the clinical marker of an ongoing neurodegenerative process that eventually will be recognized as overt dementia. In this perspective, future studies with

longer follow-ups are needed in order to better elucidate this association, and to further explore this relationship. In this perspective, future studies with longer follow-ups are needed in order to better elucidate this association, and to further explore this relationship.

4.2. Implications and future perspectives

Currently, healthcare systems are mostly focused on a single-disease approach to patients. However, older people – including those with cognitive decline – usually suffer from multi-system problems (Lakhani, 2012). In this perspective, frailty is a concept that shifts the attention from organ-specific conditions towards a more integrated approach to the patient. From a public health standpoint, the assessment of physical frailty might ease the identification of a more complex group of older people with cognitive problems, in order to provide them with person-centered interventions and preventive care paths. At the same time, such information may be used by clinicians to diagnose dementia at an early stage and with better accuracy.

In conclusion, the co-occurrence of cognitive impairment and frailty identifies a group of people with a significantly increased risk of dementia, suggesting that the implementation of investigating frailty in the assessment of people with cognitive problems may enable more reliable risk stratifications. The study of mechanisms underlying both cognitive and functional decline might open new research avenues for the prevention and treatment of dementia.

Contributorship

Conception of the work: GG, MLH, DLV. Articles evaluation: GG, MLH. Data analysis: DLV. Results interpretation: all the co-authors. Drafting the article: GG, DLV. Critical revision of the manuscript: all the co-authors. Final approval of the manuscript: all the co-authors. All the authors fulfil the ICMJE criteria for authorship.

Transparency Declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2019.09.001>.

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