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SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS Non-pharmacological interventions aimed at reducing the frailty in older adults

Abstract: Frailty is a well-known and accepted term by professionals working with older people in recent years for its associations with multiple adverse outcomes. The purpose of this systematic review of randomized controlled trials was to examine non-pharmacological interventions that allows reversing or reducing frailty, and its adverse outcomes, such as disability in *activities of daily living* and *instrumental activities of daily living*, lower quality of life and falls in older adults.

Systematic review of literature was performed in *PubMed*, *Scopus*, *ISI Web of Knowledge* and *Cochrane Central Register of Controlled Trials*.

This systematic review concluded that, apart from the lack of consensus on how to evaluate the frailty, there is also a lack of evidence regarding the effect of non-pharmacological interventions on frailty. The heterogeneity of interventions proposed in the literature highlights that future research should focus on determining the best way to prevent and reduce frailty.

Keywords: Frailty, older adult, non-pharmacological intervention, randomized controlled trial, systematic review.

REVISÃO SISTEMÁTICA DE ENSAIOS CLÍNICOS RANDOMIZADOS Intervenções não-farmacológicas com objetivo de reduzir a fragilidade em idosos

Resumo: A fragilidade é um termo bem conhecido e aceite pelos profissionais que trabalham com idosos, com destaque nos últimos anos pelas suas associações a vários resultados adversos. O objetivo desta revisão sistemática de ensaios clínicos randomizados é examinar as intervenções não-farmacológicas que permitem a redução da fragilidade e os seus resultados adversos, tais como incapacidade em *atividades da vida diária* e *atividades da vida diária instrumentais*, pobre qualidade de vida e quedas em idosos frágeis.

A pesquisa bibliográfica foi realizada através das bases de dados da *PubMed*, *Scopus*, *ISI Web of Knowledge* e *Cochrane Central Register of Controlled Trials*.

Esta revisão sistemática conclui que, para além da falta de consenso sobre a avaliação da fragilidade, existe também pouca evidência no efeito das diferentes intervenções não-farmacológicas. A heterogeneidade de intervenções propostas na literatura revela, que no futuro a investigação deve focar-se na determinação da melhor forma de prevenir/reduzir a fragilidade.

Palavras-chave: Fragilidade, idosos, intervenções não-farmacológicas, revisão sistemática, estudo clínico randomizado controlado.

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Introduction

Improving the health of older adults is one of the greatest challenges of ageing societies (Bergman, Béland, & Perrault, 2002). According to the World Health Organization (2002), the proportion of people older than 60 is growing more rapidly than any other age group. Such demographical changes require immediate actions to render the healthcare systems capable of sustaining the growing number of individuals with multiple age-related conditions (Groessl *et al.*, 2007).

Age-related changes often lead to frailty, which can result in serious functional limitations and susceptibility to adverse outcomes. As Clegg *et al.* (2013) suggested, frailty refers to a state of increased vulnerability to minor stressor events associated with numerous factors, particularly to physical activity levels and nutritional factors, that lead to decline in homeostatic reserve and resiliency. The brain, endocrine system, immune system and skeletal muscle are intrinsically interrelated and are currently the organ systems best studied in the development of frailty. However, loss of physiological reserve in other systems including the cardiovascular, respiratory and renal systems may also contribute to increased vulnerability. This provides evidence to suggest that when physiological decline reaches an aggregate critical mass at the multisystemic level and with accumulating disease, frailty becomes evident.

In the past few years, several operational definitions have been proposed for frailty. Two approaches of frailty operationalization have been widely applied, resulting from the biological model and from the cumulative deficit model (Clegg *et al.*, 2013; Fried *et al.*, 2001; Rockwood & Mitnitski, 2007). The most well-known of these is the biological model, described by Fried *et al.* (2001), which identifies someone as frail when 3 or more of the following criteria are present: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. On the other hand, the cumulative deficit model, developed by Rockwood *et al.* (2007) expresses the theory of the gradation of frailty with progressive accumulation of deficits, each of which has an equal weight in mathematical modeling of the frailty index (Clegg *et al.*, 2013).

However, multidimensional standardized measures, such as the Edmonton Frail Scale (Rolfson, Majumdar, Tsuyuki, Tahir & Rockwood, 2006), the Groningen Frailty Indicator (Steverink, Slaets, Schuurmans & Van Lis, 2001) and the Tilburg Frailty Indicator (Gobbens, Van Assen, Luijckx, Wijnen-Sponselee & Schols, 2010), have been developed as alternatives to the traditional approaches of frailty assessment. From these measures, the Tilburg Frailty Indicator is highlighted due to the well supported conceptual model from which it results: the integral model of frailty (Gobbens, Krans & Van Assen, 2015). According to this perspective, frailty is manifested in the physical, psychological and social domains of human functioning, resulting from the interplay between diseases, life-course determinants and the decline of the physiological reserves (Sternberg, Wershof Schwartz, Karunanathan, Bergman & Mark Clarfield, 2011).

Regardless of the conceptual model, it seems consensual that frailty can be reduced or prevented, as well as its adverse outcomes (Clegg *et al.*, 2013). Thus, the interventions can be focused both on cure and on primary, secondary and tertiary prevention. The overall objectives of the secondary and tertiary preventive interventions are the improvement of physical, social and psychological functions, reduction of hospitalization and iatrogenic adverse events, develop adaptive strategies addressing disability and dependence, improvement of quality of life, and decrease of early mortality in older adults (Bouillon *et al.*, 2013; Chen, Mao & Leng, 2014; Clegg *et al.*, 2013; Fairhall *et al.*, 2011). Currently, the evidence is limited due to few studies testing the efficacy of non-pharmacological interventions for this purpose.

Consequently, the aim of this systematic review of randomized controlled trials (RCTs) is to investigate the effects of non-pharmacological interventions in reversing or reducing frailty, and its adverse outcomes, such as disability in Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs), quality of life and falls in older adults.

Methods

Search strategy

The main method to search for the eligible papers was a broad literature search using PubMed with the following keywords and MeSH terms: ("Aged"[MeSH Terms] OR "Aged, 80 and over"[MeSH Terms] OR "Older People"[All fields] OR "Older adults"[All fields] OR "elderly"[All fields] OR "seniors"[All fields] OR "aging"[All fields] OR "ageing"[All fields]) AND ("Frail Elderly"[MeSH Terms] OR "Frailty"[All fields] OR "Frail"[All fields]) AND ("Inter-

vention Programs"[All fields] OR "Intervention"[All fields] OR "Nonpharmacological treatment"[All fields] OR "Group Programs"[All fields] OR "Programs"[All fields] OR "Therapeutic interventions"[All fields] OR "Rehabilitation interventions"[All fields]). Literature searches were also undertaken in Scopus database, ISI Web of Knowledge and Cochrane Central Register of Controlled Trials (CENTRAL) using the same search keywords: (Aged OR Older People OR Older adults OR elderly OR seniors OR aging OR ageing) AND (Frail Elderly OR Frailty OR Frail) AND (Intervention Programs OR Intervention OR Group Programs OR Programs OR Therapeutic interventions OR Rehabilitation interventions). The search was restricted to the last 16 years (January 2001–November 2017), because the first model that standardized and operationalized the definition of frailty was created in 2001.

Selection process

The studies were screened and selected by two reviewers independently. First, all titles and abstracts were read and the inclusion and exclusion criteria were applied. After that, both reviewers read the full text of the papers that were included after abstract selection, and analyzed if the data that can be drawn to respond to aim of the study. Remaining disagreements were resolved by discussion or by a third investigator.

Selection criteria

The inclusion criteria were: papers referring to randomized controlled trials; papers with subjects aged 65 or more; papers with older adults classified as frail; papers describing non-pharmacological interventions to reduce the frailty and/or frailty's adverse outcomes (disability in ADLs and IADLs, quality of life and falls); and papers written in English or Portuguese. Papers with unclear operational definition/measurement of frailty, and papers without clear information about the intervention were excluded.

Data extraction and methodological quality of included studies

Papers were synthesized according to the following characteristics: authors and year; sample; identification of frailty; type of intervention; intervention and control groups; duration and frequency of intervention; assessments and follow-up; outcomes measures; and effects of intervention. Data were extracted by one researcher and checked by a second reviewer. The same reviewers independently assessed the quality of the included papers through the Physiotherapy Evidence Database (PEDro) scale (Moseley, Maher, Herbert, & Sherrington, 1999), and disagreements were resolved by consensus or by a third investigator. The items on the PEDro scale were derived from a Delphi consensus procedure (Verhagen *et al.*, 1998), and there are 11 items. Each satisfied item (except for item 1, which, unlike other scale items, pertains to external validity) contributes one point to the total PEDro's score, with a higher score indicating better methodological quality (9-10 = excellent; 6-8 = good; 4-5 = fair; <4 = poor). In randomized trials, reliability of this total PEDro's score is fair to good. The reliability of this scale was evaluated with acceptable good results in intraclass correlation coefficients 0.56–0.91 (Foley, Bhogal, Teasell, Bureau & Speechley, 2006; Maher, Sherrington, Herbert, Moseley & Elkins, 2003).

Results

Search and study selection

2484 papers were identified in total, thirteen of which were included for review considering inclusion and exclusion criteria. The flow chart for inclusion of papers is presented in figure 1.

Participants and intervention characteristics

The following details of each paper are included in Table 1: sample; identification of frailty; type of intervention; intervention and control groups; duration and frequency of intervention; assessments and follow-up.

The mean ages of the participants in the included studies were 78.2 ± 5.2 years (ranging from 70 ± 4.7 to 91.9 ± 4.1 years). The included papers encompassed a sample of 4944 older individuals, of which 64.18 % were female. Ng *et al.* (2015) Cadore *et al.* (2014), Cesari *et al.* (2015), Tarazona-Santabalbina *et al.* (2016), Cameron *et al.* (2013), Fairhall *et al.* (2012), Chan *et al.* (2012), Serra-Prat *et al.* (2017), Chan *et al.* (2017), Neumann *et al.* (2017), identified the frailty in older people based on Fried's criteria, Clegg *et al.* (2014) and Tarazona-Santabalbina *et al.* (2016) used the Edmonton Frail Scale, Groningen Frailty Indicator was applied by Metzelthin *et al.* (2013) and Haider *et al.* (2017) used the Survey of Health, Ageing and Retirement in Europe - Frailty Instrument (SHARE-FI).

The types of intervention were divided as follows:

- 4 RCTs (Cameron *et al.*, 2013; Metzelthin *et al.*, 2013; Neumann *et al.*, 2017; Fairhall *et al.* (2012) described an Interdisciplinary Intervention, which included case management, exercise, nutritional and psychological management by an interdisciplinary team (e.g. dietician, geriatrician, rehabilitation physician, practice nurse, psychologist, pharmacist, physiotherapist and occupational therapist). The programs of these interventions were tailored to the individual's needs, and reviewed and modified regularly.
- 5 RCTs used Multidomain Interventions included physical and nutritional interventions (Chan *et al.*, 2017; Chan *et al.*, 2012; Haider *et al.*, 2017; Ng *et al.*, 2015; Seino *et al.*, 2017; Serra-Prat *et al.*, 2017). In the trial of Ng *et al.* (2015) and Haider *et al.* (2017) cognitive training was also included and the others trials from Chan *et al.* (2012) and Chan *et al.* (2017) included a problem solving therapy and training education booklet. Six papers present an intervention which combined these different approaches, however one of the papers evaluated each type of intervention separately and together (Ng *et al.*, 2015), and the others remaining papers evaluated exercise and nutrition combined and problem solving therapy alone (Chan *et al.*, 2017; Chan *et al.*, 2012).
- 4 RCTs reported Exercise Intervention that involved: - papers with multicomponent exercise (progressive resistance exercise training): Tarazona-Santabalbina *et al.* (2016) used endurance, strength, coordination, balance and flexibility exercises that have the potential to impact a variety of functional performance measures; and Cadore *et al.* (2014) applied muscle power training combined with balance and gait retraining; - other two papers (Clegg *et al.*, 2014; Cesari *et al.* (2015) tested the effects of home-based physical activity with exercise sessions of strength, flexibility, mobility, balance, aerobic capacity and functionality, and also sessions with phone contacts.

Methodological quality

PEDro scores ranged from 5 to 10 points, with a mean score of 7.1. All of the selected papers scored 5 or more, indicating the fair quality of the selected trials. According to the PEDro scale, methodological quality of 3 papers were rated as "excellent" (Fairhall *et al.*, 2012; Ng *et al.*, 2015; Seino *et al.*, 2017), 8 papers were rated as "good" (Cadore *et al.*, 2014; Cameron *et al.*, 2013; Chan *et al.*, 2017; Chan *et al.*, 2012; Clegg *et al.*, 2014; Metzelthin *et al.*, 2013; Serra-Prat *et al.*, 2017; Tarazona-Santabalbina *et al.*, 2016) and 2 paper had a score equivalent to "fair" (Cesari *et al.*, 2015; Neumann *et al.*, 2017). No papers were excluded on the basis of their methodological quality (Table 2).

Table 2 - PEDro scale rating

Reference	Eligibility criteria	Random allocation	Concealed allocation	Group similar at base-line	Blinded subjects	Blinded therapist	Blinded assessors	Less than 15% dropouts	Intention-to-treat analysis	Between-group comparisons	Point measure and variability	PEDro score
Ng <i>et al.</i> (2015)	1	1	1	1	0	1	1	1	1	1	1	9
Cadore <i>et al.</i> (2014)	1	1	1	0	0	0	1	1	1	1	1	7
Clegg <i>et al.</i> (2014)	1	1	1	0	1	0	0	1	1	1	1	7
Tarazona-Santabalbina <i>et al.</i> (2016)	1	1	0	1	0	0	1	1	1	1	1	7
Cesari <i>et al.</i> (2015)	1	1	0	0	0	0	1	0	1	1	1	5
Cameron <i>et al.</i> (2013)	1	1	0	1	0	0	1	1	1	1	1	7
Metzelthin <i>et al.</i> (2013)	1	1	1	1	0	0	1	0	1	1	1	7
Fairhall <i>et al.</i> (2012)	1	1	1	1	1	1	1	1	1	1	1	10
Chan <i>et al.</i> (2012)	1	1	1	1	0	0	1	1	1	1	1	8
Serra-Prat <i>et al.</i> (2017)	1	1	1	1	0	0	0	0	1	1	1	6
Haider <i>et al.</i> (2017)	1	1	0	1	0	0	0	0	1	1	1	5
Chan <i>et al.</i> (2017)	1	1	1	1	0	0	1	1	1	1	1	8
Neumann <i>et al.</i> (2016)	1	1	1	1	0	0	0	0	1	1	1	6

Outcome measurements

This review found seven papers that examined the effects on frailty, Ng *et al.* (2015), Cesari *et al.* (2015), Tarazona-Santabalbina *et al.* (2016), Cameron *et al.* (2013), (Haider *et al.*, 2017), (Serra-Prat *et al.*, 2017) and Chan *et al.*(2012), whereas regarding frailty's adverse outcomes: eight measured the ADL/IADL disability; five measured quality of life and four used falls as an outcome.

• Frailty

Seven intervention papers, showed favorable effects on reducing frailty outcomes (Table 3) (Cameron *et al.*, 2013; Cesari *et al.*, 2015; Chan *et al.*, 2012; Haider *et al.*, 2017; Ng *et al.*, 2015; Serra-Prat *et al.*, 2017; Tarazona-Santabalbina *et al.*, 2016). The reduction of frailty was significant compared to the control group ($p < .05$) in the multi-domain interventions in all papers, except in the Chan *et al.* (2017) paper. In the exercise intervention, the results were also significant in the reduction of frailty, where the prevalence of frailty was reduced by 31.4% ($p < 0.001$)(Tarazona-Santabalbina *et al.*, 2016) and OR 2.12 (95%CI) ($p < 0.05$) (Cesari *et al.*, 2015). On the other hand, only one paper obtained significant results relative to interdisciplinary intervention (Cameron *et al.*, 2013).

Table 3- Results of the included papers interventions on the frailty status

Reference	Interventions groups	Reduction of frailty compared to the control group		p value
Ng et al. (2015)	Nutritional	OR(95%CI)	2.98 (1.10-8.07)	<0.01
	Cognitive		2.89 (1.07-7.82)	
	Physical		4.05(1.50-10.8)	
	Multi-domain		5.00 (1.88-13.3)	
Chan et al. (2012)	Multi-domain	Rate of Frailty Reduction (%)	EN vs control 45% vs 27%	<0.01
			PST vs control 44% vs 28%	>0.05
Serra-Prat et al. (2017)	Multi-domain	OR(95%CI)	0.23 (0.06-0.91)	<0.05
Haider et al. (2017)	Multi-domain	OR(95%CI)	2.70 (1.01-7.22)	<0.05
Chan et al. (2017)	Multi-domain	Rate of Frailty Reduction (%)	Intervention vs control 42% vs 39%	>0.05
Cesari et al. (2015)	Exercise intervention (home-based)	OR(95%CI)	2.12 (1.17-3.84)	<0.05
Tarazona-Santabalbina et al. (2016)	Exercise intervention	Prevalence of frailty reduction (%(95%CI))	31.4%(20.3-45.0)	<0.001
Cameron et al. (2013)	Interdisciplinary intervention	Prevalence of Frailty (%(95%CI))	14.7% (2.4%-27%)	<0.05
Neumann et al. (2016)	Interdisciplinary intervention	OR(95%CI)	0.77 (0.57-1.03)	>0.05

CI, Confidence Interval; EN, Exercise and nutritional; PST, Problem solving therapy

• Adverse outcomes

Disability in ADL was measured in 8 papers (Table 4), using the Barthel Index (Cameron *et al.*, 2013; Chan *et al.*, 2012; Clegg *et al.*, 2014; Serra-Prat *et al.*, 2017; Tarazona-Santabalbina *et al.*, 2016), the Nottingham Extended Activities of Daily Living Index (NEADL)(Fairhall *et al.*, 2012) and the Groningen Activity Restriction Scale (GARS)(Metzelthin *et al.*, 2013). In general, it was found that non-pharmacological intervention showed non-significant differences in this outcome. In the disability of IADL only one paper reported significant improvements ($p=0.001$) (Tarazona-Santabalbina *et al.*, 2016). Quality of life was measured through the EQ- 5D questionnaire (Shah, Mulhern, Longworth, & Janssen, 2016) and showed that interventions do not cause a significant

improvement in these parameters. Regarding the falls this outcome was examined in Cadore *et al.* (2014), Ng *et al.* (2015), Serra-Prat *et al.* (2017) and Metzelthin *et al.* (2013) papers, by testing falls incident rates and fear of falling (Short Falls Efficacy Scale (Short FES-I))(Kempen *et al.*, 2008)). After intervention, the incidence of falls was significantly ($P < 0.001$) lower in the intervention group (0.0 ± 0.0) than the control group (0.8 ± 0.4 in the Cadore *et al.* (2014) paper that measured this outcome. In other trials no significant differences were observed between the control group and intervention group.

Table 4 - Results of papers interventions included in adverse outcomes

Reference	Interventions	Outcome	Analysis adverse outcomes by interventions groups	p value
Ng et al. (2015)	Nutritional	ADL /IADL disability, n (%); Falls, n (%)	2(4.6); 2 (4.3)	>0.05
	Cognitive		1(2.2); 1 (2.1)	
	Physical		4 (8.3); 3 (6.3)	
	Multi-domain		2 (4.3); 1 (2.1)	
	Control		2 (4.3); 5 (10.4)	
Chan et al. (2012)	Exercise and nutritional	ADL disability, M (SD)	1.09 (3.81)	>0.05
	Control		1.53 (4.11)	
	Problem solving therapy		1.05 (3.98)	
	Control		1.58 (3.96)	
	Exercise and nutritional	QL, M (SD)	0.02 (0.08)	
	Control		0.03 (0.08)	
	Problem solving therapy		0.01 (0.09)	
	Control		0.03 (0.08)	
Serra-Prat et al. (2017)	Multi-domain	ADL Disability, MD (95%CI)	-0.31(-1.01 to 0.40)	>0.05
		Falls, OR (95%CI)	0.87 (0.36 - 2.11)	
		QL, MD (95%CI)	2.31 (-2.28 to 6.91)	
Metzelthin et al. (2013)	Interdisciplinary intervention	ADL Disability, MD (95%CI)	0.77 (-0.05 to 1.59)	>0.05
		IADL Disability, MD (95%CI)	0.40 (-0.54 to 1.34)	
		Falls, MD (95%CI)	-0.04 (-1.01 to 0.93)	
Cameron et al. (2013)	Interdisciplinary intervention	ADL disability, MD (95%CI)	0.67 (-4.23 to 5.56)	>0.05
		QL, MD (95%CI)	0.30 (-4.59 to 5.18)	
Fairhall et al. (2012)	Interdisciplinary intervention	ADL disability, MD (95%CI)	0.08 (-0.96 to 1.11)	>0.05
Cadore et al. (2014)	Exercise intervention	Falls, M (SD)	0.0 (0.0)	<0.001
	Control		0.8 (0.4)	
Tarazona-Santabalbina et al. (2016)	Exercise intervention	ADL disability, M (SD)	91.6 (8.0)	<0.001
	Control		82.0 (11.0)	
	Exercise intervention	IADL Disability, M (SD)	6.9(0.9)	=0.001
	Control		5.7(2.0)	
	Exercise intervention	QL, M (SD)	8.2(1.6)	<0.05
Control	7.6(1.3)			
Clegg et al. (2014)	Exercise intervention	ADL disability, MD (95%CI)	0.6 (-0.07 to 1.8)	>0.05
		QL, MD (95%CI)	0.04 (-0.09 to 0.18)	

ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MD, Mean difference between control group and intervention group; CI, Confidence Interval; M, Mean; SD, Standard Deviation; QL, Quality of life

Discussion

This systematic review aimed to examine recent evidence about reversing or reducing frailty and its adverse outcomes in older adults using non-pharmacological interventions. To our knowledge, this is the first systematic review that specifically focuses frailty reduction through this type of intervention (Cadore *et al.*, 2014; Cameron *et al.*, 2013; Cesari *et al.*, 2015; Chan *et al.*, 2017; Chan *et al.*, 2012; Clegg *et al.*, 2014; Fairhall *et al.*, 2012; Haider *et al.*, 2017; Metzelthin *et al.*, 2013; Neumann *et al.*, 2017; Ng *et al.*, 2015; Serra-Prat *et al.*, 2017; Tarazona-Santabalbina *et al.*, 2016).

The present study found that different interventions have been employed for frailty reduction, even if the frailty definition is similar. These different approaches translate a lack of evidence on the topic, as there is no

consensus regarding the best type of intervention. Most of the proposed interventions were focused on physical and nutritional aspects, meeting the traditional views of frailty, more specifically the operational definition by Fried *et al.* However, a substantial number of studies proposed interventions implemented by interdisciplinary teams, which attests to the complexity of the frailty syndrome. Indeed, the multidimensional nature of frailty and of its outcomes may demand an integral view of the human being and a broader approach. Furthermore, some papers chose to analyze the effect of frailty interventions on its adverse outcomes, perhaps because there is no consensus about the measurement of frailty, or because the used frailty measures might not be considered sensitive enough. Consequently, there is an urgent need for research not only in regard frailty operational definition, but also regarding effective treatments for frailty (Fried *et al.*, 2001; Gill *et al.*, 2002; Schuurmans, Steverink, Lindenberg, Frieswijk, & Slaets, 2004).

Therefore, if a better operational definition of frailty can be successfully developed, it may be expected that a more complete and validated frailty indicator can also be developed, enabling the actual identification of frail community-dwelling older people. This may lead to the construction of more specific, coherent, organized, and consistent interventions (Gobbens, Luijckx, Wijnen-Sponselee, & Schols, 2010).

In general, it was observed that the reduction of frailty is possible. This supports the notion that frailty, unlike the ageing process, is in part reversible and amenable to interventions (Pel-Littel, Schuurmans, Emmelot-Vonk & Verhaar, 2009). Often, frailty is misconstrued to be part of the normal ageing process and older patients are treated based on their medical conditions alone, rather than accounting for their frailty *status* (Dent, Kowal & Hoogendijk, 2016).

On the other hand, the effects of the interventions on frailty's adverse outcomes, such as disability, falls and worse quality of life, were not as evident. This may be due to the fact of the used scales were less sensitive to change, as is the case of the EQ-5D and the Barthel index. Indeed, these measures that are likely to be insufficiently responsive, as mentioned in previous studies (Eurich, Johnson, Reid, & Spertus, 2006; Hocking, Williams, Broad, & Baskett, 1999). These findings may also be explained by the fact that the participants' disability, quality of life and falls may be influenced by many other factors rather than frailty. For example, one's quality of life may be influenced by social support and relationships, and falls may result mainly from environmental hazards. Therefore, reducing frailty may improve certain domains of life, while other domains depend of other determinants.

The present study only included papers with frail older adult subjects, and with a clear operational definition of frailty. Also, this review provided the best evidence about the different types of non-pharmacological interventions that reduced frailty and its adverse outcomes, because it had a restrictive inclusion of RCTs. All the randomized controlled trials were considered to have enough methodological quality to be included in this review. Nonetheless, there were several limitations in the present study. First, the descriptions of the interventions in some of the trials were incomplete, mainly regarding interdisciplinary interventions and home-based physical activity interventions. The description in the interdisciplinary interventions by the different intervening professionals is not detailed about the kind of service that they provide. Regarding the home-based physical activity, the plan of exercises is not detailed enough or not detailed at all. Second, some included trials contained very limited information about the outcome measures.

This study shows that it is feasible to identify frail older people in the community and primary care settings, and to intervene effectively to reduce their level of frailty and possibly prevent future risks of hospitalization, functional dependency, institutionalization, and deaths.

Conclusion

To summarize, the non-pharmacological interventions showed positive effects in reducing frailty, although in most papers, there were no significant differences in the adverse outcomes, such as ADLs / IADLs, quality of life and falls.

The evidence reviewed demonstrates that there is limited data from RCTs to thoroughly explain the intervention on frailty. The type of the interventions being assessed is limited and remains focused on exercise and nutrition intervention. Our study found an increasing interest in multifactorial interventions aimed at optimizing the physical, psychological and social functions of frail elder.

In the future, it would be desirable to have larger trials with more rigorous methodology conducted to provide more robust evidence on this topic. We also recommend a rigorous description of a theoretical foundation for the intervention with the complete protocols and the context in which the intervention is delivered. This will enable comparison, evaluation and a possible future replication of the intervention in question, to improve the life of frail older people.

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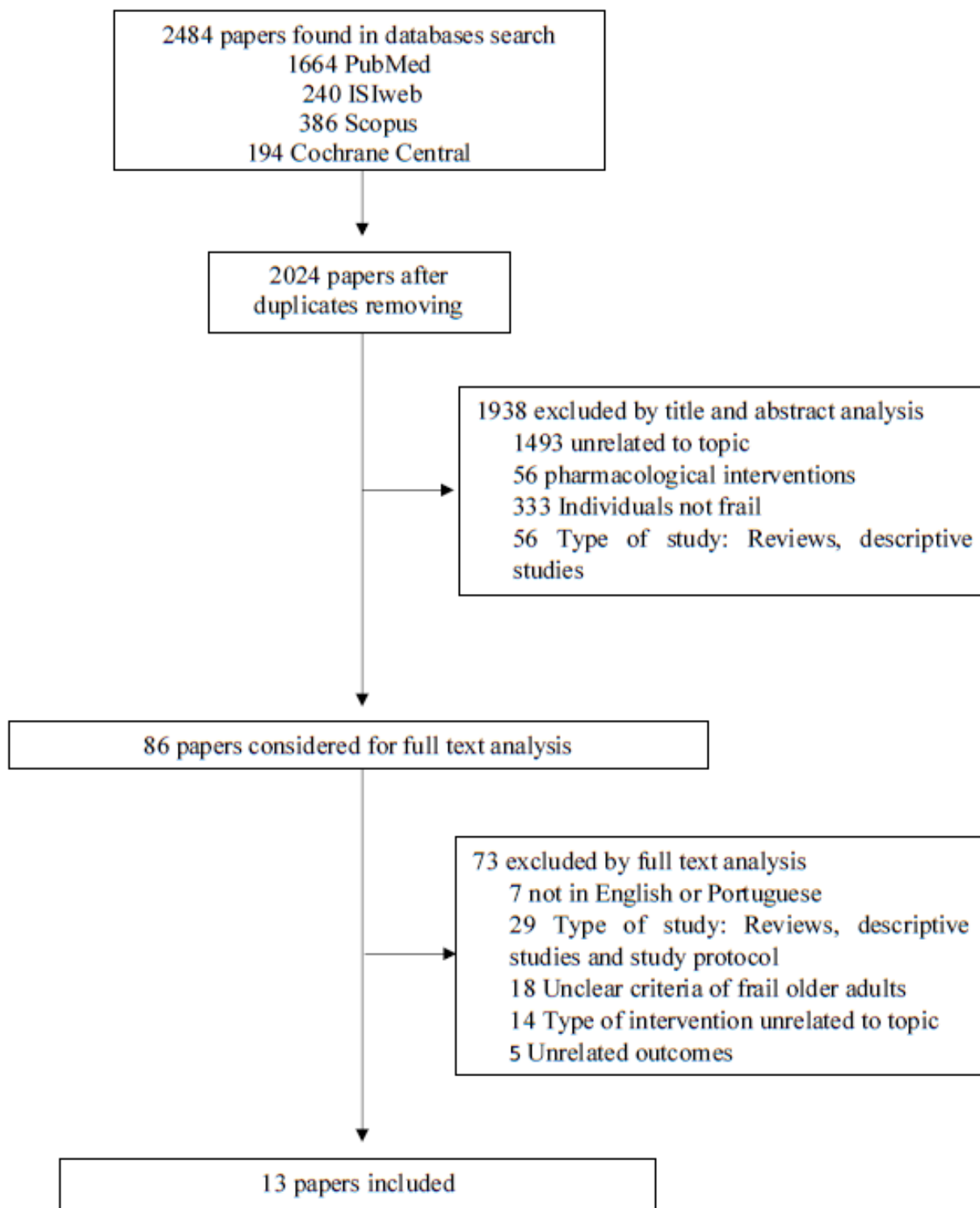


Fig. 1 - Flowchart of the selection process for this systematic review

Table 1 - Summary characteristics of the included papers

Reference	Sample	Identification of frailty	Type of Intervention	Intervention and control groups	Duration and frequency of intervention	Assessments and Follow-up
Ng et al. (2015)	n=246 Age, mean \pm SD: 70.0 \pm 4.7 61% women Pre-frail and frail older adults Community Dwelling	Fried's criteria	Multi-domain Intervention	<p>Intervention groups</p> <p><u>Physical Interventions:</u> Resistance Exercises integrated with functional tasks; and balance training exercises involving functional strength, sensory input, and attentional demands;</p> <p><u>Nutritional Interventions:</u> commercial formula: iron and folate supplement, vitamin B6 and vitamin B12 supplement and calcium and vitamin D supplement;</p> <p><u>Cognitive training:</u> stimulate short-term memory, and enhance attention and information-processing skills, reasoning and problem-solving abilities, learning strategies used to recall verbal and visual information;</p> <p><u>Combination Interventions:</u> Participants in this group underwent all 3 aforementioned interventions.</p> <p>Control group</p> <p>Usual care including primary and secondary level care from government or private clinics and hospitals, and community-based social, recreational, and day care rehabilitation services. They were given an equal volume of artificially sweetened, vanilla-flavored liquid, 2 capsules and 1 tablet.</p>	<p>Intervention groups: 24 weeks</p> <p><u>Physical Interventions:</u> 24 weeks (12 weeks conducted by a qualified Trainer; 12 weeks of home-based exercises); 2/week, 90 min/session;</p> <p><u>Nutritional Interventions:</u> daily for 24 weeks</p> <p><u>Cognitive training:</u> 24 weeks, 2-hour weekly sessions</p>	<p><u>During intervention:</u> 0-3 months</p> <p><u>End of intervention:</u> 6 months</p> <p><u>After end of intervention:</u> 12 months</p>
Chan et al. (2012)	n=117 Age, mean \pm SD: 71.4 \pm 3.7 59% women Pre-frail and frail older adults Community Dwelling	Fried's criteria	Multi-domain Intervention	<p>Intervention group</p> <p><u>Education booklet:</u> Healthy diets, exercise protocols, and self-coping strategies; groups were asked questions during their visits to the study sites for their designated programs, if they had read the booklet and how well they had complied with the suggested diet and exercise protocols.</p> <p><u>Exercise and nutritional group:</u> warm up (15 min; brisk walks, stretching; 5 repetitions each); Resistance training (20-30 min; 10-15 repetitions for each); Postural control activities and balance training (10min); Cool down (5 min, relaxation movements).</p> <p><u>The problem-solving therapy group:</u> Evidence based psychotherapy.</p> <p>Control group</p> <p>non- EN, non-PST groups were contacted monthly to check on how much they had read the booklet and how well they had complied with the suggested diet and exercise protocols.</p>	<p>Intervention group: 3 months</p> <p><u>Exercise and nutritional group:</u> 3months, 3/week, 60min/session;</p> <p><u>The problem-solving therapy:</u> 6 sessions.</p>	<p><u>Baseline:</u> 0 months</p> <p><u>End of intervention:</u> 3 months</p> <p><u>After end of intervention:</u> 6 and 12 months</p>

Reference	Sample	Identification of frailty	Type of Intervention	Intervention and control groups	Duration and frequency of intervention	Assessments and Follow-up
Serra-Prat et al. (2017)	n=172 Age, mean \pm SD: 78.3 \pm 4.5 57% women Pre-frail adults Community dwelling	Fried's criteria	Multi-domain Intervention	Intervention groups <u>Physical Interventions</u> : aerobic exercise and mixed strengthening, balance and coordination exercises; <u>Nutritional Interventions</u> : follow-up and the establishment of the usual dietary recommendations and corrective measures. Control group Usual care and recommendations.	Intervention groups 12 months <u>Physical Interventions</u> : -Aerobic exercise (30-45min/day; 4 days/week); Mixed exercises (20-25min/day; 4days/week).	<u>Baseline</u> : 0 months <u>Follow-up</u> : 12 months
Haider et al. (2017)	n= 80 Age, mean \pm SD: 82.8 \pm 8.0 84% women Pre-frail and frail adults Community dwelling	SHARE-FI	Multi-domain Intervention	Intervention group <u>Physical Intervention</u> : warm-up (mobilization exercises); strength exercises; <u>Nutritional intervention</u> : discussion of nutritional questions (focusing mainly on fluid, protein, and energy intake). (In this group, individuals also received social support) Control group <u>Social support group</u> : participation in conversation about social support or performed cognitive training with the help of a guidebook.	Intervention and control groups : Home visits: 12 weeks, 2/week, 60min/session	Before-after intervention
Chan et al. (2017)	n= 289 Age, mean \pm SD: 71.6 \pm 4.3 53% women Pre-frail and frail adults Community dwelling	Fried's criteria	Multi-domain Intervention	Intervention group The same educational course that the control group, <u>problem-solving therapy</u> and <u>physical exercise</u> . Control group Education course on frailty, sarcopenia, coping strategy, nutrition, and demonstration of study exercise program.	Intervention group 6 months; educational course (1 session, 2h), problem solving therapy (6 sessions) and physical exercise (48 sessions, 45min/session). Control group Educational course (1 session, 2h).	<u>Baseline</u> : 0 months <u>During intervention</u> : 3 months <u>Post-intervention</u> : 6 months <u>Follow-up</u> : 12 months
Cadore et al. (2014)	n= 24 Age, mean \pm SD: 91.9 \pm 4.1 70 % women Pre-frail and frail adults Institutionalized	Fried's criteria	Exercise Intervention	Intervention group Upper and lower body resistance training combined with balance and gait retraining exercise that progressed in difficulty and functional exercises. Control group Mobility exercises (small active and passive movements applied as a series of stretches).	Intervention group : 12 weeks, 2/week, 40 min/session Control group : 30 min, 4 days/week	Before-after intervention
Tarazona-Santabalbina et al. (2016)	n=100 Age, mean \pm SD: 80.0 \pm 3.7 54% women Frail older adults Community Dwelling	Fried's criteria and EFS		Intervention group Proprioception and balance exercises, aerobic training, strength and stretching. Control group Regular primary care program established.	Intervention group : 24 weeks, 5/week, 65min/session	Before-after intervention

Reference	Sample	Identification of frailty	Type of Intervention	Intervention and control groups	Duration and frequency of intervention	Assessments and Follow-up
Clegg et al. (2014)	n=84 Age, mean \pm SD: 79.0 \pm 9.2 71% women Frail older adults Community dwelling	EFS	Exercise intervention	Intervention group Participants are stratified to the appropriate level. The exercises for each level of the program (Level 1, 2 and 3), their purpose to improve strength, mobility, balance or aerobic capacity and their functional relevance; Participants receive weekly support from physiotherapists through 5 face-to-face home visits and 7 telephone calls. The intervention development process, including behavior change theory underpinning the intervention. Control group Usual care from the primary healthcare team.	Intervention group: 12 weeks, 3/day, 5/week	Before-after intervention
Cesari et al. (2015)	n=424 Age, mean \pm SD: 76.8 \pm 4.2 68,9% women Frail and non-frail older adults Community dwelling	Fried's criteria		Intervention group Physical activity group: Adoption: center-based exercise sessions conducted under supervision; Transition: center-based exercise sessions and home-based endurance, strengthening, and flexibility exercises; Maintenance: home-based intervention and monthly phone contacts. Control group Successful aging group: Education group served as an active control group, including education on nutrition, medications, foot care, and recommended preventive services.	Intervention group: 12 months Adoption (weeks 1-8): 3/ week:40-60 min; Transition (weeks 9-24): 2/ week Maintenance (week 25 to the end of the study): 1-2/ week Control group: First 26 weeks of the study	<u>During intervention:</u> 0 - 6 months <u>End of intervention:</u> 12 months
Cameron et al. (2013)	n=241 Age, mean \pm SD: 83.3 \pm 5.9 68% women Frail older adults Community dwelling	Fried's criteria	Interdisciplinary intervention	Intervention group The interventions will be tailored to each participant, based on their frailty characteristics assessed at baseline: -Nutritional supplementation; -Referral to a psychiatrist or psychologist; -Participation in day activity groups and telephone contact with a volunteer; -10 home-based physiotherapy sessions and perform a home exercise program, over the course of one year; -Education about the reasons for the medication. Control group Usual care (general practitioner and medical specialist consultations, and nursing and allied health interventions as appropriate).	Intervention group: 12 months	<u>During intervention:</u> 0 - 3 months <u>End of intervention:</u> 12 months
Metzelthin et al. (2013)	n=346 Age, mean \pm SD: 77.2 \pm 5.1 58% women Frail older adults Community dwelling	GFI		Intervention group Multidimensional assessment and interdisciplinary care based on a tailor-made treatment plan (Involving goals, strategies and responsibilities); Interventions offers recommendation and guidelines for execution treatment plan (e.g. Meaningful activities; adapting environment, activities or skills; social network and social activities; daily physical activity; stimulating health). Control group Usual Care	Intervention group: 24 months	<u>During intervention:</u> 0, 3, 6 and 12 months <u>End of intervention:</u> 24 months

Reference	Sample	Identification of frailty	Type of Intervention	Intervention and control groups	Duration and frequency of intervention	Assessments and Follow-up
Fairhall et al. (2012)	n=241 Age, mean \pm SD: 83.3 \pm 5.9 68% women Frail older adults Community dwelling	Fried's criteria	Interdisciplinary intervention	Intervention group Targeting identified frailty components; Physiotherapy sessions and performed a targeted, goal-focused, home-based strength, balance, and endurance training regimen. Control group Usual care (medical management of health conditions).	Intervention group: 12 months; 10 sessions; 3-5/week; 45-60min/session.	<u>During intervention:</u> 0 - 3 months <u>End of intervention:</u> 12 months
Neumann et al. (2016)	n=2580 Age, mean \pm SD: 71 \pm 4.1 62.4% women Pre-frail and frail adults Community dwelling	Fried's criteria	Interdisciplinary intervention	Intervention group <u>Small group session and home visit:</u> Health promotion and prevention with physiotherapist, nutritionist and social worker. Control group Usual care.	Intervention group: 12 months;	<u>End of intervention:</u> 12 months <u>Follow-up:</u> 24 months

non- EN, non-Exercise and nutritional group; non-PST, non-the problem-solving therapy group; EFS, Edmonton Frail Scale; GFI, Groningen Frailty Indicator