ESCOLA SUPERIOR DE SAÚDE
INSTITUTO POLITÉCNICO DO PORTO

Vera Margarida Pequito

NON-PHARMACOLOGICAL INTERVENTIONS AIMED AT REDUCING THE SEVERITY OF FRAILTY AND ITS ADVERSE OUTCOMES IN ELDERLY PEOPLE: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Dissertação submetida à Escola Superior de Tecnologia a Saúde do Porto para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Terapia Ocupacional, realizada sob a orientação científica de Professor Doutor Tiago Filipe Mota Coelho, Professor Adjunto da Escola Superior de Tecnologia da Saúde do Instituto Politécnico do Porto e Professora Doutora Maria João Ribeiro Fernandes Trigueiro, Professora Adjunta da Escola Superior de Tecnologia da Saúde do Instituto Politécnico do Porto.

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Resumo **Introdução:** 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 inversão ou redução da fragilidade e os seus resultados adversos, tais como incapacidade em Atividades da Vida Diária (AVDs) e Atividades da Vida Diária Instrumentais (AVDIs), pobre qualidade de vida e quedas em idosos frágeis.

Métodos: A pesquisa bibliográfica foi realizada através das bases de dados da PubMed, Scopus e ISI Web of Knowledge. Os critérios de inclusão foram: Estudos Clínicos Randomizados Controlados; artigos com amostra igual ou superior a 65 anos; artigos com idosos classificados como frágeis; intervenções não farmacológicas que reduzam a fragilidade e os seus efeitos adversos; artigos escritos em inglês ou português. A *Physiotherapy Evidence Database* (escala PEDro) foi utilizada para avaliar a qualidade metodológica dos artigos selecionados.

Resultados: De 2248 artigos, 9 artigos foram incluídos nesta revisão sistemática. Três artigos focaram-se em intervenções multifatoriais e interdisciplinares, dois artigos propuseram intervenções combinadas (intervenção nutricional, cognitiva e exercício físico), dois artigos analisaram o efeito de um programa com exercícios multifatoriais e dois artigos testaram o impacto da atividade física em intervenção de contexto domiciliário. Cinco artigos investigaram os efeitos da intervenção sobre a fragilidade, sendo que todos eles obtiveram resultados estatisticamente significativos quanto à sua redução. Em relação aos resultados adversos, 7 artigos focaram-se sobre os efeitos da intervenção no desempenho das AVDs /AVDIs, 4 artigos mediram a qualidade de vida e as quedas foram examinadas em 3 artigos.

Conclusão: Esta revisão sistemática conclui que, para além da falta de consenso sobre a avaliação da fragilidade, existe também pouca evidência sobre o efeito de diferentes intervenções não farmacológicas a este nível. A heterogeneidade de intervenções propostas na literatura revela, efetivamente, que no futuro a investigação deve focar-se na determinação da melhor forma de prevenir/reduzir a fragilidade e os seus resultados adversos.

Palavras-chaves Fragilidade, Resultados adversos, Intervenções não farmacológicas, Revisão Sistemática, Estudo Clínico Randomizado Controlado

Abstract **Introduction:** 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 is to examine non-pharmacological interventions that allows reversing or reducing frailty, and its adverse outcomes, such as disability in ADLs and ADIs, lower quality of life and falls in elderly people.

Methods: The literature search involved databases such as PubMed, Scopus and ISI Web of Knowledge. The criteria for inclusion were: Randomized Controlled Trial; papers with subjects aged 65 or more; papers with older people classified as frail; non-pharmacological interventions to reduce frailty and adverse outcomes; and written in English or Portuguese. The Physiotherapy Evidence Database (PEDro scale) was used to assess the methodological quality of the selected papers.

Results: Out of 2248 papers, 9 papers was included in this systematic review. Three papers focused on multifactorial and interdisciplinary intervention, two papers proposed combination interventions (exercise, nutrition and cognitive intervention), two papers analyzed the effects of multicomponent exercise and two papers verified physical activity in home-based intervention. Five intervention papers investigated the effects on frailty outcome, all of them showed statistically significant results in reducing of this outcome. Regarding to adverse outcomes, seven papers focused on the effects of intervention in ADL/IADL disability, four papers measured the quality of life and the falls outcome was examined in three papers.

Conclusions: This systematic review concluded that, apart from the lack of consensus on how to evaluate the frailty, there is also a lack of evidence on 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 / reduce frailty and its adverse outcomes.

Keywords Frailty , Adverse Outcomes, Non-pharmacological Intervention, Systematic Review, Randomized Controlled Trial

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Lists of Symbols, Abbreviations or Other

ADLs - Activities of Daily Living

BMI - Body Mass Index

CONSORT - Consolidated Standards of Reporting Trials

CES-D - Centre for Epidemiological Studies-Depression Scale

CHAMPS – Community Health Activities Model Program for Seniors Questionnaire

CI - Confidence Interval

EFS- Edmonton frail scale

EN - Exercise and Nutritional Program

EQ- 5D - EuroQol 5-D scale

EQ-5D VAS - EuroQol 5-D Visual Analog Scale.

FI - Frailty Index

GARS - Groningen Activity Restriction Scale

GFI - Groningen Frailty Indicator

HOPE - Home-based Older People's Exercise

IADLs - Instrumental Activities of Daily Living

IPAQ-SF - Taiwan International Physical Activity Questionnaire Short Form

LIFE-P – Lifestyle Intervention and Independence for Elders Pilot

NEADL - Nottingham Extended Activities of Daily Living Index

OR - Odds Ratio

PA - Physical Activity Program

PEDro - Physiotherapy Evidence Database scale

PoC - Prevention of Care

PST - Problem Solving Therapy

RCTs - Randomized Controlled Trials

RM - Repetition Maximum

SA - Successful Aging Program

SD - Standard Deviation

Short FES-I - Short Falls Efficacy Scale

TFI - Tilburg Frailty Indicator

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Introduction

Frailty is a common geriatric syndrome, characterized by a decreased reserve and increased vulnerability to adverse outcomes, including falls, hospitalization, institutionalization and death. The care of frail individuals is difficult, due to complex comorbidities, vulnerability to deterioration and increased social needs [1-3].

The identification of older individuals who are frail or at risk of becoming frail with appropriate subsequent evaluation and intervention constitutes a cornerstone of geriatric medicine and quality care for the ever-growing elderly population[4]. Chen and colleagues [5] emphasize that while health care providers and researchers in the field of aging have long been aware of the term of "frailty", defining this syndrome proved to be elusive until recently. Impressive progress has been made in the past decade also, and the number of scientific publications on this topic has grown exponentially[5].

Also, it's important to emphasize, that frailty is often misconstrued to be part of the normal ageing process and older patients are treated on the basis of their medical condition/s alone, rather than accounting for their frailty status. This supports the idea that the frailty can be prevented [1, 6]. In other words, elderly people of the same chronological age demonstrate that there is a large heterogeneity in terms of biological age. Some are still fit and energetic while a relatively large number of elderly people have an accelerated decline in wellbeing and resilience [7, 8].

Currently, there are two main conceptualizations of frailty: the biological model[1] and the accumulated deficits model[9], being the first the most widely applied in clinical research. Based on these models, there are different conceptualizations but there is consensus on the prevention and reversibility of the syndrome, and consequently their results.

Clinical improvement from the frail state is possible and there is an urgent need for effective interventions to mitigate frailty [3, 10]. It is possible to identify frail older people in the clinical setting and to deliver an intervention program targeting the components of frailty, in accordance with the best available evidence for each problem identified at assessment and with interventions addressing multiple problems, in a population vulnerable to adverse outcomes [3].

Increasingly, given the expanding elderly population, the major impact on health and with the understanding of the biologic basis and the complexity of frailty, it's benefic for be developed more adequate and innovative interventions[4].

Furthermore, the different conceptualization that converge the reversible potential of the syndrome, thus identification of frail people and subsequent interventions are very important. Therefore, this systematic review of randomized controlled trials (RCTs) aims to investigate non-pharmacological interventions allows reversing or reducing frailty, and its adverse outcomes, such as disability in ADLs and ADIs, quality of life and falls in elderly people. As so, this review develops the theoretical knowledge in the Chapter I, providing a literature review of the current state of knowledge about the frailty syndrome, particularly definitions, frailty models, pathogenesis, prevalence of frailty and therapeutic interventions. In Chapter II, the methods of this study are described, particularly regarding: search strategy, selection process, selection criteria and methodological quality of included studies. Results are presented in Chapter III, where the characterization of participants can be found, included studies, search and study selection and intervention characteristics. Also, in this chapter, are examined the outcome measurements and the methodological quality of evidence. Then, in Chapter IV, the results are discussed, with references to implications and limitations of the review, as well as directions for future studies. As a final matter, the conclusion summarizes the main evidence and implications.

I. Literature review

In our ageing society, older people are one of the greatest challenges in health [11]. According to the World Health Organization [12], 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[13].

These age-related changes, often are manifested by frailty, which can result in serious functional limitations and susceptibility to adverse outcomes. As Clegg et al. [4] suggested, frailty refers to a state of increased vulnerability to minor stressor events that arise from level of physical activity and nutritional factors, cumulative declines in many physiological systems throughout life, and increases risks of adverse health outcomes including falls, delirium and disability. The brain, endocrine system, immune system and skeletal muscle are intrinsically inter-related and are currently the organ systems best studied in the development of frailty. Loss of physiological reserve in other systems including the cardiovascular, respiratory and renal systems also contributes.

The biological causative mechanisms of frailty are different conceptually from ageing, disability, and co-morbidity although it is distinctly related to these factors [9, 14-16]. Frailty (multisystem dysregulation yielding decreased physiological reserves and increased vulnerability to stressors) has commonality to that of aging (loss of molecular/cellular functional properties yielding decreased adaptability to internal/external stress and increased vulnerability to disease and mortality). For both aging and frailty, have a basis in loss of homeostasis, though with aging the failure in hemodynamics is global whereas with frailty the failure in hemodynamics cycle around energy metabolism and neuromuscular changes [4]. As researchers have characterized frail elder populations, the observed changes in both functional performance and biomarker distribution are distinct from the corresponding age-related changes observed in the non-frail individuals[17].

Although frailty prevalence increases with age, it occurs independently from chronological age. There is a general agreement that the core feature of frailty is increased vulnerability to stressors due to impairments in multiple, inter-related systems that lead to

decline in homeostatic reserve and resiliency [18]. In other words, frailty occurs when not one, but multiple physiological systems decline [4, 16, 19, 20]: the more physiological systems that are in a diminished state, the greater the likelihood of frailty [21].

Other factors linked with frailty development are: sociodemographic influences, such as poverty, living alone, area deprivation and low education level [10, 16, 22, 23]; psychological factors, including depression [24]; nutritional issues such as malnutrition and poor oral health[4, 16, 24]; polypharmacy; diseases (cancer, endocrine disorders, dementia) and their associated complications ;and low physical activity [22].

Regarding the prevalence of frailty, a recent systematic review, incorporating 31 studies of frailty in persons 65 years or older, found a prevalence of 4.0% to 17.0% (mean 9.9%) of physical frailty, with a higher prevalence when psychosocial frailty was also included. Women (9.6%) were almost twice as likely as men (5.2%) to be frail. The prevalence of frailty is markedly increased in persons older than 80 [8]. Previous research showed that two different frailty models, such as biological model and cumulative deficit model had the same predictive value concerning adverse outcomes, such as falls, hip fracture, and death, although the results of this review suggest that the physical definition of frailty leads to a lower estimation of prevalence but is likely more easily comparable between studies that use a physical definition of frailty[17]. Thus, exist different operationalization of frailty status results in widely differing prevalence between studies, because the diversity in frailty criteria of broad frailty definitions appears to have contributed to the wide range of prevalence found in literature [8].

For clinical practice, several operational definitions have been proposed about the concept of frailty, in the past few years. Two approaches used to operationalize frailty have been widely applied, including the biological model and the cumulative deficit model [1, 4, 9]. The most well-known of these is the frailty phenotype (biological model), described by Fried et al [1], 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. Those with three or more of the five factors are judged to be frail, those with one or two factors as pre-frail, and those with no factors as not frail or robust elderly people[1]. Although the Fried frailty phenotype has been validated and modified for use in several published reports, limitations remain which challenge its generalizability and

usefulness in the clinical setting [25-28] . Other potentially important factors such as cognitive impairment, a highly prevalent condition associated with functional decline and disability, were not included as part of the phenotype [29].

On the other hand, the cumulative deficit model, developed by Rockwood et al. [9] 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 (FI). In other words, the FI is a simple calculation of the presence or absence of each variable as a proportion of the total (e.g. 20 deficits present out of a possible 92 gives a FI of 20/92 = 0.22). This model is clinically attractive because it allows frailty to be regarded as gradable, rather than present or absent. Moreover, exist a number of equally weighted deficits, as a measure of accumulated vulnerability, rather than particular clusters of deficits [4]. Importantly, a value of 0.67 appears to identify a level of frailty beyond which further deficit accumulation is not sustainable and death is likely to supervene [30]. The criteria for a variable to be considered as a deficit are that the variable needs to be acquired, age-associated, associated with an adverse outcome, and should not saturate too early. The last criterion means that the proportion of older adults who have the deficit should not be close to 100%, because the deficit is uninformative at that point [31]. These factors make the index very adaptable as a conceptual approach. Several studies that used the frailty index was strongly related to the risk of death and institutionalization [32, 33].

In contrast, multidimensional measures, such as the Edmonton Frail Scale (EFS) [34], the Groningen Frailty Indicator (GFI) [35] and the Tilburg Frailty Indicator (TFI) [36] have been developed as alternatives to the traditional physical operationalization.

EFS was elaborated by Rolfson and collaborators[34], whose approach measures bio-physiologic, psychological and social factors of frailty. The scale evaluates nine domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance, investigated through 11 items. The maximum score is 17, representing the highest level of frailty. Frailty analysis scores are: 0-4, no frailty; 5-6, apparently vulnerable; 7-8, mild frailty; 9-10, moderate frailty; 11 or more, severe frailty. The EFS has a good construct validity, reliability and acceptable internal consistency. A unique characteristic of the EFS as a clinical frailty instrument is its inclusion of the domain of social support, suggesting an endorsement of the dynamic model of frailty.

Thus, the EFS has the potential as a practical and clinically meaningful measure of frailty in a variety of settings.

The GFI is a questionnaire screens for self-reported limitations, that contains 15 dichotomous self-reported items, comprising of: physical factors (independence in shopping, walking, dressing, toileting; physical fitness, vision, hearing; weight loss and polypharmacy); a cognitive component (memory issues); social factors (emptiness, missing others, feeling abandoned); and a psychological component (feeling downhearted or sad; feeling nervous or anxious) [35, 37]. It's validated and with a score range from zero to fifteen, wherein higher scores indicate higher frailty levels and an increased need for integrated care[35].

Finally, the TFI is based on the integral model of frailty [38]. TFI is a brief self-report questionnaire for screening frail community-dwelling older adults, that consists of 2 parts: part A on determinants of frailty (1 question on multimorbidity and 9 questions on life-course determinants, namely sex, age, marital status, ethnicity, level of education, income, lifestyle, life events, and living environment) and part B on three domains of frailty such as physical domain (unexplained weight loss, difficulty in walking, strength in hands, physical tiredness, physical health, balance, vision problems and hearing problems), psychological domain (cognition, depressive symptoms, anxiety and coping) and social domain (living alone, social relations and social support)[36]. The TFI has good test-retest reliability, good construct validity, and good to excellent predictive validity for predicting the adverse outcomes disability, receiving personal care, receiving nursing and informal care, and mediocre validity for hospitalization and general practitioner [39].

The adverse outcomes are common clinical presentations of frailty and the reasons for admission to hospital and accelerate further decline [4, 33]. Frailty is a dynamic process but transition to a level of worse frailty is more common than is improvement in frailty, and the development of frailty often leads to a spiral of decline of increasing frailty and higher risk of worsening adverse outcomes [1, 26]. Based on multidimensional definition of frailty, well-known adverse outcomes of frailty are disability, health care utilization, falls, lower quality of life and premature death.

It's important to recognize frail elderly adults and to prevent adverse outcomes with special multidisciplinary treatments. To enable preventive interventions, it should be clear which frailty characteristics or underlying processes predict each outcome most accurately. Although numerous interventions have been developed to improve the outcomes of frail elderly people, a major obstacle found by researchers to success in such interventions has been the difficulty of comparing the studies retrieved, due to the lack of operationalization and differences in the diagnosis of frailty [40].

Intervention aims to improve physical, cognitive and social functioning and extend frail older individuals length of time in independence and self-management, living in their preferred setting. So, the type of intervention also includes psychosocial components, rather than only physical components, depending on the type of operationalization used. In addition, intervention aims to decrease vulnerability to adverse outcomes, in particular falls, injury, hospitalization and institutionalization. Most frail older people should be encouraged and supported to adhere to their intervention plan. It is important to recognize the needs of family and/or caregivers and engage with them, because regardless of the type of intervention that is proposed, depending on the definition of frailty, it is important that older people adhere to the programs and caregivers / families are involved. [3].

Despite the considerable academic interest in the frailty syndrome there is little research focusing on treating or at least ameliorating frailty. Efforts have been made to improve clinical outcomes for frail older people. However few interventions have been developed to specifically reverse the syndrome of frailty characterized by either an accepted phenotypic or accumulated deficits definition [6, 19].

Previous intervention studies targeting frailty have focused on using general interventions such as comprehensive geriatric assessment and rehabilitation models with inconclusive effects on functional ability and wellbeing [41, 42]. A large number of trials have demonstrated the positive impact of exercise intervention on key components of the frailty syndrome, including muscle strength and functional mobility [43]. Nutritional intervention is another non-pharmacological modality that may correct nutritional deficits, including micronutrients, and address weight loss of the frailty syndrome. However, there is a lack of evidence supporting its efficacy and a vigorous clinical evaluation is needed [44].

Chen and colleagues [5] emphasizes that another important area of interventions is to prevent biological, socioeconomic, and environmental stressors and improve clinical outcomes in elderly patients whose frailty. Preventive medicine is a core component of primary care and family medicine, and if frailty was understood to be amendable to preventive measures it could be incorporated into the existing preventive medicine framework. Prevention can be primary, secondary or tertiary, primary prevention refers to those actions taken to prevent frailty. In secondary prevention, attempts are made to identify frailty in the earliest stages and to control or reduce the impact on the individuals. Finally, tertiary prevention seeks reduce the impact of frailty and prevent adverse outcomes[45].

The overall objectives of the secondary and tertiary preventive interventions are the improvement of physical 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. The interdisciplinary assessment and care team elements usually consists of a geriatrician, a gerontologically trained nurse, a social worker, a pharmacist, and occupational and physical therapists[4, 5]. Multimodality strategies intervening in potential biological, socio-behavioral, and environmental stressors should be considered for the frail elderly. As the understanding of the biologic basis of frailty further improves, more effective interventional strategies that target specific physiologic systems and innovative geriatric care models are likely to be developed [4, 5, 46].

The main concern of Clegg et al. [4] is that the complex interventions based on comprehensive geriatric assessment and with most appropriate professionals, delivered to elderly people in the community, can increase the likelihood of continuing to live at home, mainly through a reduced need for care-home admission and fewer falls. However, the frailest patients seem to receive the least benefit, and few studies tested the effectiveness of interventions non-pharmacological for this effect.

Thus this systematic review of randomized controlled trials (RCTs) goal is to investigate the effects of non-pharmacological interventions in reversing or reducing frailty, and its adverse outcomes, such as disability in ADLs and IADLs, quality of life and falls in elderly people.

II. Methods

1. 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 ("Intervention 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 and ISI Web of Knowledge 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 15 years (January 2001–April 2016), because the first model that standardized and operationalized the definition of frailty was created in 2001 [1].

2. Selection process

The studies were screened and selected by two reviewers. 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 analyzing if the data that can be drawn respond to aim of the study.

3. Selection criteria

The criteria for inclusion were: Randomized Controlled Trials; papers with subjects aged 65 or more; papers with elderly classified as frail; non-pharmacological interventions to reduce the frailty and adverse outcomes (disability in ADLs and IADLs, quality of life and falls); and written in English or Portuguese.

Papers with unclear operational definition/measurement of frailty or that didn't mentioned the effects of non-pharmacological interventions in the frail elderly, with detailed information about the intervention were excluded. Although frailty usually interacts with

other chronic conditions, the purpose of this systematic review was to focus exclusively on frailty.

4. Methodological quality of included studies

Each Study was critically appraised for methodologic quality by using the Physiotherapy Evidence Database (PEDro) scale [47]. The PEDro scale is an instrument for the methodological quality assessment of RCTs in physical therapy and exercise studies. The items on the PEDro scale were derived from a Delphi consensus procedure [48], and there are 11 items that assess: eligibility criteria specified; random allocation; concealed allocation; groups similar at baseline; subject, therapist and assessor blinding; less than 15% dropouts; intention-to-treat analysis; between-group statistical comparisons; and point measures and variability data (the scale is presented in the table I). Each satisfied item (except for item 1, which, unlike other scale items, pertains to external validity) contributes one point to the total PEDro score (range 0 –10 points), with a higher score indicating better methodological quality. The reliability of this scale was evaluated with acceptable good results in intraclass correlation coefficients 0.56–0.91 [49, 50].

Table I *- PEDro Scale*

	No	**Yes**	**where**
1. Eligibility criteria were specified			
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)			
3. Allocation was concealed			
4. The groups were similar at baseline regarding the most important prognostic indicators			
5. There was blinding of all subjects			
6. There was blinding of all therapists who administered the therapy			
7. There was blinding of all assessors who measured at least one key outcome			
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to group			
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"			
10. The results of between-group statistical comparisons are reported for at least one key outcome			
11. The study provides both point measures and measures of variability for at least one key outcome			

III. Results

1. Search and study selection

A total of 2248 papers were identified using the search strategy and after duplicate's removal remained 1842. After reading the titles and abstracts, 1772 papers were excluded for the following reasons: 1375 with topic irrelevant for the paper; 51 with pharmacological interventions; 309 with not frail elderly; and 37 not randomized controlled trials. The remaining 70 papers were reviewed through full-text reading, where 6 were not written in English or Portuguese, 16 not randomized controlled trials, 17 had unclear criteria of frail elderly people, 10 had little information about the detailed intervention or the type of intervention was irrelevant and 12 was a study protocol. With this selection 9 papers was included in this systematic review. The flowchart of papers and causes of exclusion are presented in Figure I.

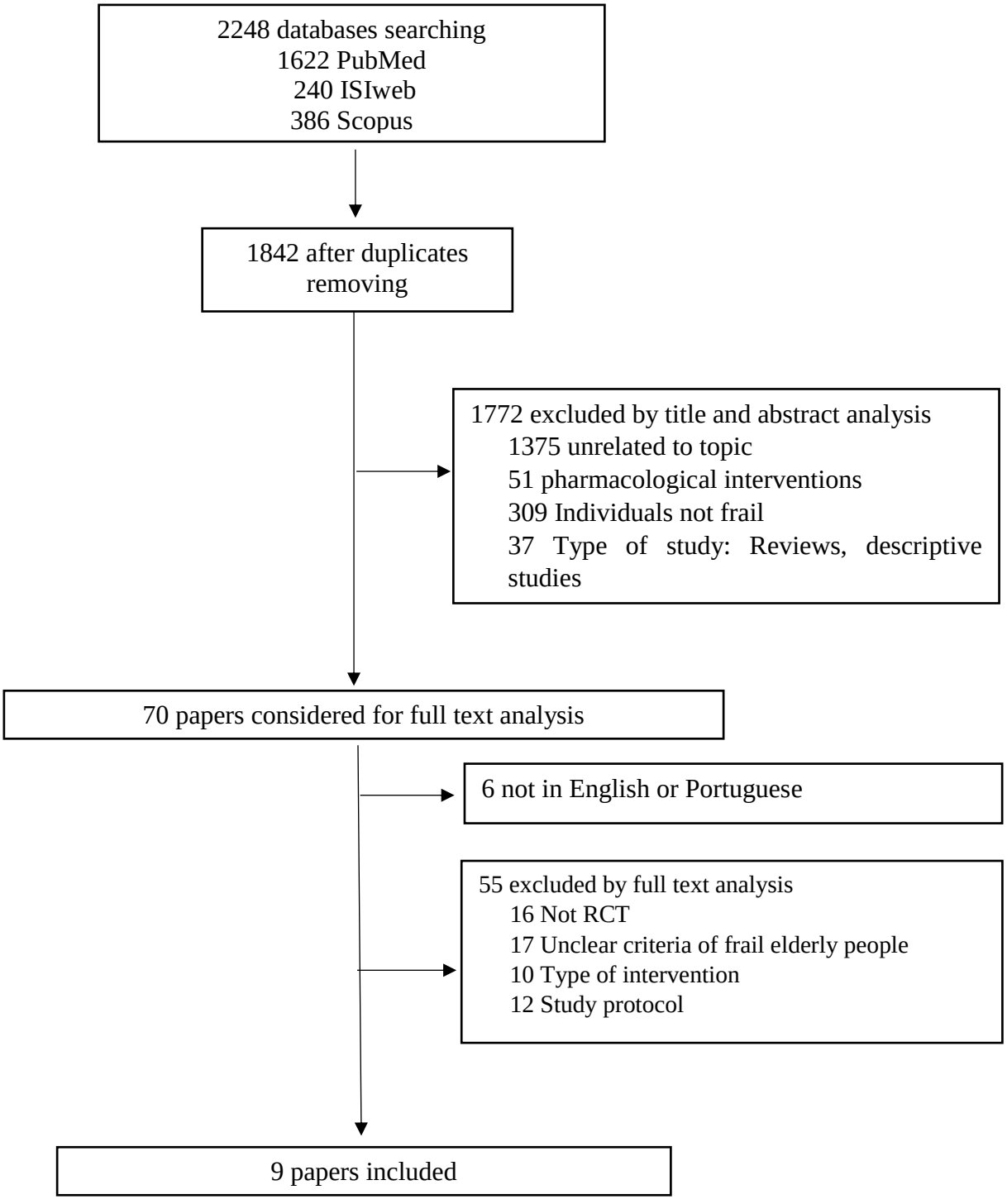

Figure I *- Flowchart of the selection process for this systematic review*

2. Participants and study characteristics

In Table III are shown of each paper: 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. The 9 papers that resulted in RCTs were published between 2012 and 2016.

The mean ages of the participants of the included studies were 79. 2 ± 5.1 (ranging from 70±4.7 to 91.9 ±4.1). The included papers encompassed a sample of 1823 older people, which were female (64.2 %). All papers, participants were community-dwelling elders (1799 participants), except in Cadore et al. [51] paper, where the participants lived in residential care (24 participants). Ng et al.[52], Cadore et al.[51], Cesari et al.[53], Tarazona-Santabalbina et al.[54], Cameron et al.[55], Fairhall et al.[56] and Chan et al. [57] identified the frailty in older people based on Fried's criteria, Clegg et al.[58] and Tarazona-Santabalbina et al.[54] used the Edmonton Frail Scale and Groningen Frailty Indicator was applied by Metzelthin et al.[59].

Fairhall et al.[56], Cameron et al.[55], Metzelthin et al.[59], Tarazona-Santabalbina et al.[54] and Clegg et al.[58] applied the non-pharmacological interventions only in frail elderly. On the other hand, Ng et al.[52], Chan et al. [57] and Cadore et al.[51] included pre-frail and frail older people and Cesari et al.[53] was the only one paper that included frail and non-frail older people.

Regarding the randomization of each paper, Fairhall et al.[56], Cameron et al.[55], Metzelthin et al.[59], Tarazona-Santabalbina et al.[54] and Clegg et al.[58] following simple randomization procedures randomly assigned intervention and control group. The control group didn't received training and they had the usual health care. Cesari et al.[53] and Cadore et al.[51] also defined the randomization with intervention and control group, however the first paper used the successful aging health education program serving as an active control group and, in the second paper the subjects in the control group performed mobility exercises 30 min per day, at 4 days per week, which consisted of small active and passive movements. In the paper of Chan et al. [57], randomization method was used with a permuted block (4persons/block) to ensure balanced assignments. The randomization code was generated from the off-site statistical center with a computer random number generator. Random group allocation was managed by a project manager not involved in assessment or intervention. In a 2 × 2 factorial

design, subjects were first randomly assigned to an exercise and nutritional program (EN) or non-EN group (control group). Within each group, subjects were further randomized to a problem solving therapy (PST) group or non-PST group (control group). Finally, in the Ng et al.[52] paper, participants were allocated randomly into one of 5 interventions: nutritional supplementation, cognitive training, physical training, combination treatment, and usual care control. A central computerized randomization procedure was used to randomly allocate. The randomization sequence was generated in permuted blocks (10 per block), and treatment was allocated by a project manager not involved in the enrollment, intervention, or assessment.

The blinding, for each paper is described in methodological quality that was used the PEDro scale.

3. Intervention characteristics

A summary of the interventions is shown in Table III. The types of intervention were (Figure II):

- 3 RCTs: Cameron et al. [55], Metzelthin et al. [59] and Fairhall et al. [56] - with **multifactorial and interdisciplinary intervention** include case management, exercise, nutritional and psychological management by an interdisciplinary team (e.g. geriatrician, practice nurse, occupational therapist, and physiotherapist);
- 2 RCTs: Ng et al. [52] and Chan et al. [57] - with **combination interventions** that contain physical, nutritional and cognitive intervention separately as well as combined;
- 2 RCTs: Cadore et al.[51] and Tarazona-Santabalbina et al.[54] - with **multicomponent exercise** is defined as a combined program of strength, balance, gait retraining, endurance, coordination and flexibility exercises;
- 2 RCTs: Clegg et al. [58], and Cesari et al. [53] - with **home-based physical activity** that included three levels or phases, respectively, with purpose to improve strength, flexibility, mobility, balance or aerobic capacity and their functionality.

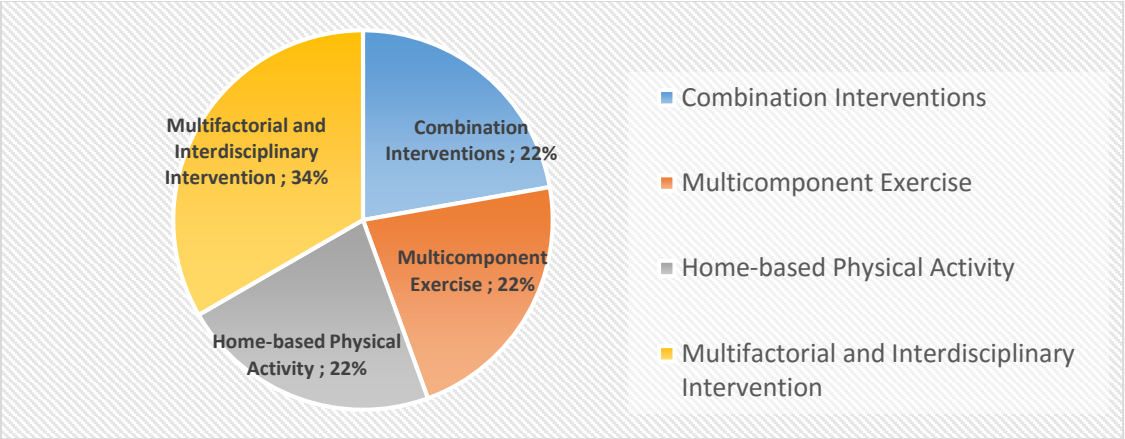

Figure II *- Interventions studied: Combination interventions from Ng et al. [52] and Chan et al. [57], Multicomponent exercise of Cadore et al. [51] and Tarazona-Santabalbina et al. [54] and home-based physical activity from Clegg et al. [58] and Cesari et al. [53] with 22%; and multifactorial and interdisciplinary intervention of Cameron et al. [55], Metzelthin et al. [59] and Fairhall et al. [56] with 34%.*

Three of the papers included the multifactorial and interdisciplinary interventions, Cameron et al. [55], Fairhall et al. [56] and Metzelthin et al. [59]. Interventions were coordinated by physiotherapists in the Cameron et al. [55] and Fairhall et al. [56] papers and nurses in the Metzelthin et al. [59] paper, and the other members of the interdisciplinary team were dieticians, geriatricians, rehabilitation physician, psychologist, pharmacist and occupational therapist in the three papers [55, 56, 59]. Cameron et al. [55] and Fairhall et al. [56] made a clinical evaluation of nutritional intake at home for participants that met the weight loss criterion for participants that met the weight loss criterion. In the same papers [55, 56], if the participant's body mass index was < 18.5, nutritional supplementation was offered using commercially available, high energy, high protein supplements. If the participant reports exhaustion and the Geriatric Depression Scale score was high, consideration was given for referral to a psychologist. Where the participant is socially isolated, options were identified to encourage greater social engagement, e.g. participation in day activity groups and telephone contact with a volunteer. Participants classified as having grip weakness, slow four meter walk time, or low physical activity level received up to ten home-based physiotherapy sessions and performs a home exercise program, over the course of one year. In addition, the participant's general health status was assessed. Methods to encourage compliance with medications, including education about the reasons for the medication, were provided to the participant and measures to encourage compliance with medication regimens (e.g. medication packaging in blister packs and reminder cards) was initiated or reinforced. In the other trial,

Metzelthin et al. [59], the intervention provided recommendations and guidelines for the execution of the treatment plan. For example, a toolbox of interventions was available that focused on five topics: “enhancing meaningful activities,” “daily physical activity,” “social network and social activities,” “adapting the environment, activities, or skills,” and “stimulating health".

Additionally, in the combination interventions from Ng et al. [52] and Chan et al. [57], all papers incorporated the physical and nutritional intervention, however in trial of Ng et al. [52] included cognitive training and the other trial from Chan et al. [57] included a problem solving therapy and training education booklet. The physical interventions, in the selected papers of Ng et al.[52] and Chan et al.[57] were focused on resistance exercises, strength and balance training and postural control. The frequency of these interventions ranged between 1 to 3 times per week, with duration between 60 to 90 minutes. The nutritional intervention was designed to increase protein-calorie and micronutrients intakes with supplements in the paper of Ng et al.[52] and Chan et al.[57] and healthy diets only in the paper of Chan et al.[57]. Regarding, the cognitive training was provided to stimulate short-term memory, and enhance attention and information-processing skills, and reasoning and problem solving abilities. The participants attended 2-hour weekly sessions for 12 weeks in the paper of Ng et al. [52]. In Chan et al.[57] implemented the problem solving therapy, and the subjects received 6 sessions. It taught people how to solve the “here-and-now” problems contributing to their mood-related conditions and helps increase their self-efficacy.

Cadore et al. [51] and Tarazona-Santabalbina et al. [54] used the multicomponent exercises, that involved progressive resistance exercise training: Tarazona-Santabalbina et al. [54] has used endurance, strength, coordination, balance and flexibility exercises that have the potential to impact a variety of functional performance measures; and Cadore et al. [51] has applied muscle power training combined with balance and gait retraining. The frequency of the training programs ranged from 2 times per week in Cadore et al. [51] paper and 5 times per week in Tarazona-Santabalbina et al. [54] paper. The length of each session, ranged from 40 to 65 min, respectively. In the paper from Cadore et al. [51], the participants started with an initial configuration of 8–10 repetitions of each exercise at 40-60% of their one-repetition maximum (1-RM), and in Tarazona-Santabalbina et al. [54] paper, the participants underwent a configuration initially at 25% of 1-RM to 75%.

Finally, the home-based physical activity, Clegg and colleagues [58] requested to the participants for perform five repetitions of each exercise of strength, mobility, balance or aerobic capacity in the routine. This progressed to 10 and then 15 repetitions as performance improves. The exercise routine took 15 min to complete, and participants were requested to complete the routine three times a day on 5 days of the week. Participants received weekly support from physiotherapists through five face-to-face home visits and seven telephone calls. Regarding the paper from Cesari et al. [53], the physical activity intervention as single-component has focused on aerobic, strength, flexibility, and balance training. The intervention was organized into the following three phases: Adoption (weeks 1–8): three center-based exercise sessions (40–60 minutes) per week conducted under supervision; Transition (weeks 9–24): two center-based exercise sessions per week and home-based endurance, strengthening, and flexibility exercises (at least three times per week); Maintenance (week 25 to the end of the study): home-based intervention with optional once-to-twice per week center-based sessions and monthly phone contacts. The intensity of training was gradually increased over the first 2–3 weeks. This paper comparing a physical activity intervention (PA) versus Successful aging group (SA - control group active) in frail and non-frail older people. Therefore, in SA group, participants were invited to meet once a week in small groups for the first 26 weeks of the study, and subsequently on a monthly basis. The topics presented at the meetings were relevant to older persons' health, including education on nutrition, medications, foot care, recommended preventive services. At the end of each meeting, a bout of gentle upper extremity stretching was conducted.

The duration of intervention each paper and follow-up are described in table III.

4. Methodological Quality

PEDro scores ranged from 5 to 10 points, with a mean score of 7.4. All of the selected studies scored 5 or more, indicating the high quality of the selected trials. All of the studies specified the eligibility criteria, the subjects were randomly allocated to groups, and six of them, Cadore et al. [51], Ng et al.[52], Fairhall et al. [56], Clegg et al. [58] and Metzelthin et al. [59] had concealment of allocation. Ng et al.[52], Tarazona-Santabalbina et al. [54], Cameron et al. [55], Fairhall et al. [56], Chan et al. [57] and Metzelthin et al. [59] papers showed the similarities at baseline. Two of the trials had blinded participants (Fairhall et al. [56] and Clegg et al. [58]) or therapists (Ng et al.[52] and Fairhall et al. [56]), and eight had blinded assessors (Cadore et al. [51], Ng et al.[52], Cesari et al. [53], Tarazona-Santabalbina et al. [54], Cameron et al. [55], Fairhall et al. [56], Chan et al. [57] and Metzelthin et al. [59]). Seven trials, such as Cadore et al. [51], Ng et al.[52], Tarazona-Santabalbina et al. [54], Cameron et al. [55], Fairhall et al. [56], Chan et al. [57] and Clegg et al. [58] papers, had retention rates of 85 % or greater, and all of the papers met the intention-to-treat analysis criteria. Also all of the papers applied statistical analysis to group differences, and reported point estimates and measurements of variability. No papers were excluded on the basis of their methodological quality (Table II).

Table II - *PEDro scale rating*

Reference	Eligibility criteria	Random allocation	Concealed allocation	Group similar at baseline	Blinded subjects	Blinded therapist	Blinded assessors	Less than 15% dropouts	Intention-to-treat analysis	Between-group comparisons	Point measure And variability	PEDro score
Ng, 2015 [52]	1	1	1	1	0	1	1	1	1	1	1	9
Cadore, 2014 [51]	1	1	1	0	0	0	1	1	1	1	1	7
Clegg, 2014 [58]	1	1	1	0	1	0	0	1	1	1	1	7
Tarazona-Santabalbina, 2016 [54]	1	1	0	1	0	0	1	1	1	1	1	7
Cesari, 2015 [53]	1	1	0	0	0	0	1	0	1	1	1	5
Cameron, 2013 [55]	1	1	0	1	0	0	1	1	1	1	1	7
Metzelthin, 2013 [59]	1	1	1	1	0	0	1	0	1	1	1	7
Fairhall, 2012 [56]	1	1	1	1	1	1	1	1	1	1	1	10
Chan, 2012 [57]	1	1	1	1	0	0	1	1	1	1	1	8

5. Outcome measurements

This review found five paper that examined the effects on frailty outcome, and in the adverse outcomes: seven measured the ADL/IADL disability; four investigated the quality of life; and three examined the falls.

i. Frailty status

Five intervention papers, Ng et al. [52], Cesari et al. [53], Tarazona-Santabalbina et al. [54], Cameron et al. [55] and Chan et al.[57], showed favorable effects on frailty outcomes. In the trial of Ng et al. [52], frailty score over 12 months were reduced in the nutritional, physical, cognitive, combination interventions and control group ,with significant main effect of time ($P < .001$). Over 12 months, 15% (7/46) of the control group participants showed reduction of frailty, but frailty reduction rates in the intervention groups were significantly higher (35.6% to 47.8%). Compared with the control group, nutritional intervention (OR 2.98) and cognition intervention (OR 2.89) were almost 3 times more likely to result in frailty reduction, whereas physical intervention (OR 4.05) was associated with 4 times higher odds of frailty reduction, and combination intervention was associated with the highest odds of frailty reduction (OR 5.0).

Chan et al.[57] demonstrated that, exercise and nutritional intervention (EN) improvement rates were highest at the end of intervention (3-month) (45%), than in the problem solving therapy (PST) (44%). Afterwards, there were gradual declines of the improvement rates at 6 (42% EN group, 35% PST group) and 12 (40%, EN group, 35% PST group) months. On the other hands, the improvement rates of the non-EN, or non-PST group subjects were stable around 30%. Therefore, only the 3-month differences between EN and non-EN group (45% vs 27% $p = 0.008$) was significant. During the intervention period (baseline to 3-month), 33 (32.4%) of the pre-frail participants (n= 102) improved to robust, while 3 (20%) and 6(40%) of the frail (n = 15) participants improved to robust and pre-frail, respectively. During the 3-6 month follow up period, only 2 (22.2%) of frail individuals (n= 9) improved to pre-fail status, and only 12 (16.7%) of pre-frail individuals (n= 72) improved to robust status.

Concerning the multifactorial, interdisciplinary intervention of the Cameron et al. [55], the between-group differences in frailty were statistically significant at 12 months but not at 3

months. At 12 months, the average reduction in the number of frailty criteria was 0.80 (SD = 1.19) in the intervention group and 0.41 (SD = 1.02) in the control group (between-group difference 0.41; 95% CI= 0.14 - 0.68; P < 0.01).

The multicomponent exercise intervention, in Tarazona-Santabalbina et al. [54] paper was effective in reducing of the frailty status (P < 0.001). The statistical analysis showed that in 31.4% (95% CI= 20.3 - 45.0) of the intervention group, frailty was reversed after the exercise training program. No participant in the control group reversed frailty after the 6-month period. The relative risk to reverse frailty to robustness was 2.4 higher in the intervention group when compared with the control group.

In the last one, the paper from Cesari et al. [53] the physical activity intervention group decreased the mean number of frailty criteria (6 months: −0.43, 95% CI = −0.57, −0.29; 12 months: −0.48, 95% CI = −0.62, −0.33), more than the control group (successful aging) (6 months: −0.20, 95% CI = −0.33, −0.06; 12 months: −0.21, 95% CI = −0.35, −0.06). In frailty prevalence was observed at 12 month, a significant difference (p=0.01) in the intervention group (10%; 95% CI =6.5-15.1), relative to the control group (19.1%; 95% CI=13.9- 15.6). Sedentary behavior was the only frailty criterion showing a significant difference between randomized groups in prevalence over the follow-up (OR 2.37; 95% CI = 1.64-3.43; p < .001).

ii. Adverse health outcomes

Activities of daily living disability was measured in 7 papers. Tarazona-Santabalbina et al. [54], Cameron et al.[55], Chan et al.[57] and Clegg et al.[58] using Barthel Index; Fairhall et al. [56] assessed by means of Nottingham Extended Activities of Daily Living Index (NEADL); and Groningen Activity Restriction Scale (GARS) was using by Metzelthin et al. [59]. It was found that in the following six papers by Ng et al. [52], Cameron et al. [55], Fairhall et al. [56], Chan et al.[57], Clegg et al.[58] and Metzelthin et al. [59], non-pharmacological intervention showed non-significant differences in this outcome. Only in the Tarazona-Santabalbina et al. [54] paper, found a statistically significant improvement. More specifically, in the 3 papers, Ng et al. [52], Tarazona-Santabalbina et al. [54] (Lawton Scale) and Metzelthin et al. [59] (GARS - IADL scale), Instrumental Activities of daily living scales were used that in both subscales only in the Tarazona-Santabalbina et al. [54] papers reported significant improvements.

Quality of life was measured in Tarazona-Santabalbina et al. [54], Cameron et al. [55], Chan et al.[57] and Clegg et al.[58] papers, using the EQ- 5D questionnaire. Only in Tarazona-Santabalbina et al. [54] paper, showed that intervention causes a significant improvement in these parameters. Another paper, of the Chan et al.[57] reports that found improvements but the results were not statistically significant.

Regarding the falls, were examined in Cadore et al. [51], Ng et al. [52] and Metzelthin et al. [59] papers, by testing falls incident rates and fear of falling (Short Falls Efficacy Scale (Short FES-I)). After intervention, the incidence of falls was significantly lower in the intervention group with the control group ($P<0.001$) in the Cadore et al. [51] paper that measured this outcome. In other trials no significant differences were observed between the control group and found non-significant results by time interaction effects with the intervention group.

Table III *- 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	Outcome measures	Effect of the intervention
Ng et al. 2015 [52]	n=246 Age, mean ± SD: 70.0±4.7 61% women Pre-frail and frail older elderly Community dwelling	Fried's criteria: - BMI; - Fast gait speed test; - Knee extension; - SF-12 scale; - Self-reported 31-item longitudinal ageing physical activity questionnaire.	Combination Intervention	**Intervention groups** -Physical Interventions: Initial goal: <50% 1 RM involving 8-10 major muscle groups; Final goal: 8 to 15 RM, or 60% to 80% of 10 RM; Resistance Exercises integrated with functional tasks; and balance training exercises involving functional strength, sensory input, and attentional demands; -Nutritional Interventions: commercial formula: iron and folate supplement,	**Intervention groups:** 24 weeks Physical Interventions : 24 weeks (12 weeks conducted by a qualified Trainer; 12 weeks of home-based exercises); 2/week, 90 min/session; Nutritional Interventions : daily for 24 weeks Cognitive training: 24 weeks, 2-hour weekly sessions	During intervention: 0- 3 months End of intervention : 6 months After end of intervention : 12 months	**Frailty status:** 5 Fried's criteria **Adverse outcomes:** IADL/ADL dependency Self-reported falls	**Frailty score:** Significant main effect of time (P<.001), with the mean frailty score decreasing over the 12 months across all groups Over 12 months, 15% (7/46) of the control group participants showed reduction of frailty, but frailty reduction rates in the intervention groups were significantly higher (35.6% to 47.8%).

				vitamin B6 and vitamin B12 supplement and calcium and vitamin D supplement; -Cognitive training: 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; -Combination Interventions: Participants in this group underwent all 3 aforementioned interventions. **Control group** Usual care including primary and secondary level				Combination intervention was associated with the highest odds of frailty reduction (OR 5.0). **Adverse outcomes:** No significant differences vs control were observed.

				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.				
Cadore et al. 2014 [51]	n= 24 Age, mean ± SD: 91.9 ± 4.1 70 % women Pre-frail and frail elderly Institutional-ized	Fried's criteria	Multicomponent exercise	**Intervention group** Upper and lower body resistance training (8-10 repetitions, 40-60% 1-RM), combined with balance and gait retraining exercise that progressed in difficulty and functional exercises.	**Intervention group:** 12 weeks, 2/week, 40 min/session **Control group:** 30 min, 4 days/week	Before-after intervention	**Adverse outcomes:** Falls incidence (assessed retrospectively using questionnaires);	Incidence of falls was significantly lower in the intervention group compared with control group ($p<0.001$).

				Control group Mobility exercises (small active and passive movements applied as a series of stretches).				
Clegg et al. 2014 [58]	n=84 Age, mean ± SD: 79.0±9.2 71% women Frail elderly Community dwelling	EFS	Home-based 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: 1. 5 repetitions of each exercise in the routine. 2. 10 and then 15 repetitions as performance improves. The exercise routine	**Intervention group:** 12 weeks, 3/day, 5/week	Before-after intervention	**Adverse outcomes:** ADL: Barthel índex Quality of life: EQ-5D	There were no differences in ADL and quality of life outcomes (p>0, 05).

				Participants receive weekly support from physiotherapists through 5 face-to-face home visits and 7 telephone calls. The HOPE program development process, including behavior change theory underpinning the intervention. **Control group** Usual care from the primary healthcare team.				
Tarazona-Santabalbina et al. 2016 [54]	n=100 Age, mean ± SD: 80.0 ±3.7 54% women Frail elderly	Fried's criteria and EFS	Multicomponent exercise	**Intervention group** Proprioception and balance exercises (10-15 minutes), aerobic training (initially at 40% of maximum heart rate increasing	**Intervention group:** 24 weeks, 5/week, 65min/session	Before-after intervention	**Frailty status:** EFS 5 Fried's criteria	**Frailty score:** The intervention group was effective in lowering of the frailty score assessed by Fried's

	Community dwelling			progressively to 65%), strength training (initially at 25% of 1 RM to 75%), and stretching. **Control group** Regular primary care program established.			**Adverse outcomes:** ADL: Barthel Index IADL: Lawton scale Quality of life: EQ-5D	criteria ($p<0.001$) and Edmonton ($p<0.001$). **-Adverse outcomes:** After intervention was observed significant improvement in performance in ADLs (trained group 91.6 SD 8.0 vs 82.0 SD 11.0 control group), as well as in IADLs (trained group 6.9 SD 0.9 vs 5.7 SD 2.0 control group), and in quality of life (trained group 8.2 SD 1.6 vs

								7.6 SD 1.3 control).
Cesari et al. 2015 [53]	n=424 Age, mean ± SD: 76.8 ±4.2 68,9% women Frail and non-frail elderly Community dwelling	Fried's criteria: - 2 questions from CES-D; - Unintentional weight loss; - CHAMPS questionnaire; - 4-m walk test; - Jamar handheld dynamometer.	Home-based exercise intervention	**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** SA health education group served as an active control group, including education on nutrition, medications, foot	**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	During intervention: 0 - 6 months End of intervention : 12 months	**Frailty status:** 5 Fried's criteria	The mean number of frailty criteria decreased in the intervention group (6 months: −0.43, 95% CI = −0.57, −0.29; 12 months: −0.48, 95% CI = −0.62, −0.33) as well as in the control group (6 months: −0.20, 95% CI = −0.33, −0.06; 12 months: −0.21, 95% CI = −0.35, −0.06).

				care, and recommended preventive services.				
Cameron et al. 2013 [55]	n=241 Age, mean ± SD: 83.3 ±5.9 68% women Frail elderly Community dwelling	Fried's criteria : - Unintentional weight loss; - Saehen Dynamometer; - 2 questions from CES-D; - 4-m walk test; - Questions about Low activity.	Multifactorial, 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;	**Intervention group :** 12 months	During intervention: 0 - 3 months End of intervention : 12 months	**Frailty status:** 5 Fried's criteria **Adverse outcomes:** ADL: Barthel Index Quality of life: EQ-5D VAS	**Frailty score:** In the intention-to-treat analysis, the between-group difference in frailty was 14.7% at 12 months (95% confidence interval: 2.4%, 27.0%; P = 0.02). **Adverse outcomes:** There were no major differences between the groups with respect to ADL and quality of life (p<0,05).

				-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).				
Metzelthin et al. 2013 [59]	n=346 Age, mean ± SD: 77.2 ±5.1 58% women Frail elderly Community dwelling	GFI	Multifactorial, interdisciplinary intervention	**Intervention group** Practices implemented the "Prevention of Care"(PoC) approach, in which frail older people received a multidimensional assessment and interdisciplinary care based on a tailor made treatment plan (Involving goals, strategies and responsibilities).	**Intervention group :** 24 months	During intervention: 0, 3, 6 and 12 months End of intervention : 24 months	**Adverse outcomes:** ADL:GARS ADL scale IADL: /GARS IADL scale Falls: -Short FES-I	No significant differences between the two groups with regard to ADL and falls ($p<0,05$).

				PoC Interventions protocol 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				
Fairhall et al. 2012 [56]	n=241 Age, mean ± SD: 83.3 ±5.9 68% women Frail elderly Community dwelling	Fried's criteria	Multifactorial, interdisciplinary intervention	**Intervention group** Targeting identified frailty components; Physiotherapy sessions and performed a targeted, goal-focused, home-based strength, balance, and endurance training regimen;	**Intervention group :** 12 months; 10 sessions; 3-5/week; 45-60min/session.	During intervention: 0 - 3 months End of intervention : 12 months	**-Adverse outcomes:** ADL: Nottingham Extended ADL Index	The difference between groups was small and not statistically significant (p=0.88) in the ADL outcome.

				Control group Usual care (medical management of health conditions).				
Chan et al. 2012 [57]	n=117 Age, mean ± SD: 71.4 ±3.7 59% women Pre-frail and frail older elderly Community dwelling	Fried's criteria: - Unintentional weight loss; - 2 questions from CES-D; - 5-m walk test; - Exact Hydraulic Hand Dynamometer; - IPAD-SF.	Combination Intervention	**Intervention group** -Education booklet**:** Healthy diets, exercise protocols, and self-coping strategies; EN or PST 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. -Exercise and nutritional group (EN): warm up (15 min; brisk walks, stretching; 5 repetitions each);	**Intervention group :** 3 months -Exercise and nutritional group (EN): 3months, 3/week, 60min/session; The problem solving therapy (PST): 6 sessions.	During intervention: 0 months End of intervention : 3 months After end of intervention : 6 and 12 months	**Frailty status:** 5 Fried's criteria **Adverse outcomes:** ADL: Barthel Index Quality of life: EQ-5D	**Frailty status:** The improvement rates were highest at the end of intervention (3-month) for EN (45%) and PST (44%) groups. Afterwards, there were gradual declines of the improvement rates at 6 (42% EN group, 35% PST group) and 12 (40%, EN group, 35% PST group) months.

				Resistance training (20-30 min; 10-15 repetitions for each); Postural control activities and balance training (10min); Cool down (5 min, relaxation movements). -The problem solving therapy group (PST): Evidence based psychotherapy **Control group** 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.				**Adverse outcomes:** ADL and quality of life were also improved in control groups (non-EN or non-PST). But there were no observable between group changes.

IV. Discussion

This systematic review, aimed to examine recent evidence about reversing or reducing frailty and its adverse outcomes in elderly people using non-pharmacological interventions. To our knowledge, this is the first systematic review that specifically includes this type of intervention. However, there are systematic reviews published on the benefits of physical activity in frail older adults and therapeutic interventions in frailty but include pharmacological interventions. In order to perform this review, we used strict criteria to define frailty in older people. This meant that there are recent trials that contribute to the research of intervention in frailty, but many didn't meet the inclusion criteria, therefore only 9 papers were included [51-59].

In the present study it was observed diversified interventions, even for similar frailty definitions. This different approaches meant a lack of evidence on the topic, therefore there is an urgent need for consensus on the definition of frailty among healthcare professionals, in order to make the screening and treatment of frailty more effective. Thus, the definition must be capable of serving, as a basis for the development of a measurement instrument, a frailty indicator. At the same time, the operational definition must include aspects on which interventions can be focused on [38]. Furthermore, research has demonstrated that the degree of frailty is a good predictor or selection criterion for intervention[37, 60].

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.[1] . However, a significant number of studies have proposed interventions implemented by interdisciplinary teams, corresponding to the complexity of the frailty syndrome. The multidimensional nature of the concept of frailty demands an integrated view of the human being and a multidisciplinary approach. 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[38].

It was also found in this study that most papers have chosen to analyze the effect of the interventions at the level of a specific measure of frailty, resulting all in Fried's criteria[1]. However, some studies choose to analyze the effect of the interventions associated to the frailty adverse outcomes, perhaps because there is no consensus about the measures of frailty, or the used frailty measures may not be considered sensitive enough[61].

In general, we concluded that exists significant benefits on the reduction of frailty in all of the papers that specified the "reduction of frailty" as an outcome. This supports the opinion that frailty unlike the ageing process, is in part reversible and amenable to interventions [62]. Often, frailty is misconstrued to be part of the normal ageing process and older patients are treated on the basis of their medical conditions alone, rather than accounting for their frailty status[63]. However, in most papers, there were no significant differences in ADLs / IADLs, quality of life and falls. This may be due to the fact, of the scales used being less sensitive to change, as is the case of the EQ-5D and Barthel index, measures that are likely to be insufficiently responsive, as mentioned in previous studies [64, 65].

Our study shows the multifactorial, interdisciplinary interventions among older people characterized as frail, using a specific frailty definition, were effective in reversing frailty [55, 56, 59]. In both of the papers in this study, Cameron et al.[55] and Fairhall et al. [56] (that used the same protocol intervention), included appropriate nutritional evaluation and supplementation, psychological treatment, social activities, and physical exercise. They reinforce the evidence that community-dwelling frail older people have the potential for functional improvement in both the participation and activity domains, through multifactorial intervention. This results didn't meet the evidence found in the systematic review of Lee and colleagues[66], which presented that in multifactorial intervention studies, the results on reducing frailty were uncertain, although some reports reported favorable improvements without statistical significance and there still pending results. This convergence of results may be due to the fact that, multidimensional frailty indicators might be better outcome measurements if multifactorial interventions are applied. To improve compatibilities of studies, a more standardized operationalization of frailty must be defined.

Fairhall and colleagues[56] , also mentioned that interventions reduce disability in the frail population, and have the potential to impact on morbidity, hospitalization and admission to

residential care facilities, along with the associated costs to government and society. This may happen because, regarding the systemic review conducted by Beswick and colleagues [43)], community-based multifactorial interventions help older adults living independently at home with increased physical function and decreased falls rate. On the other hand, Metzelthin and colleagues[59] emphasized that the benefit in the most of multifactorial and interdisciplinary interventions in frail older people is still not clear in an effort to reduce disability and prevent further functional decline. This may be related to the fact that the large number of participants were not eligible for this type of intervention, as they hardly had any disability in terms of ADLs and IADLs.

Cameron and colleagues[55] found that the benefit of multi-domain intervention was not evident at the 3-month follow-up and was apparent only at 12 months. This can indicate that an intervention treating frailty needs to be prolonged. This is in line with Giné-Garriga and colleagues[67] study, that suggested that the duration of interventions had also been an important contributing factor and, concluding that longer-duration programs are recommended. The results of Ng and colleagues [52] indicated that the benefit of 6 months duration of combined intervention was evident at 3 months and 6 months, and sustained at 12 months, indicating persisting benefit for at least 6 months.

The present study showed that the combined exercise, nutritional and cognitive intervention had significant effect in reducing frailty [52, 57]. Ng and colleagues[52], also demonstrated that a cognitive training program designed to stimulate short-term memory and enhance attention and information processing, as well as reasoning and problem-solving abilities, was effective in reducing frailty and, particularly, in improving lower limb strength [52]. As well as , in Chan et al.'s [57] paper, the subjects in the problem solving therapy had better improvement in frailty, but the differences didn't reach statistical significance, because the study sample size was relatively small. To our knowledge, there are no reviews that approach the cognitive intervention in reduction of frailty. However, one recent conceptual review on exercise and frailty concluded that physical activity is the only intervention found to consistently improve in cognitive performance [68].

In addition, Ng et al.'s [52] paper nutritional therapy group and combined therapy group intervention there was found no major differences in IADL-ADL dependency, and falls. This is supported by a review on protein and energy supplementation in malnourished elderly,

that reported evidence for weight gain, but found no evidence for positive effects on functional performance [69]. Another review, by Daniels and colleagues[70], emphasized that there is no evidence that nutritional interventions for frail older people, despite an observed effect on total energy intake and weight gain, resulting in positive effects on prevention of ADL/IADL disability in community-dwelling physically frail older persons.

This study found two trials that offer a multicomponent physical exercise program focusing on endurance, flexibility, balance and strength. This studies reported statistically significant effects on the reversion of frailty and adverse outcomes[51, 54]. Tarazona-Santabalbina et al. [54] concluded that a tailored multicomponent exercise training intervention can reverse frailty and improve physical function, cognitive, emotional, and social network determinations in community-dwelling frail individuals. Only in this multicomponent exercise program paper, resulted a significant improvement in performance in ADLs as well as in IADLs. They also found that an exercise intervention could improve individually the quality of life in frail individuals [54]. Our study is in agreement with the other systematic reviews, that the most common exercise protocol for frail older adults is a multicomponent training, which showed good evidence to support exercise training for improving function, but the evidence is not as strong for improving ADL disability [70, 71]. The study of Theou and colleagues [72] also corroborates the idea of multicomponent exercises having positive effects on the functional ability and adverting health consequences of frail people.

According to Cadore et al.'s [51] paper, advocate that multicomponent exercise intervention enhances their capacity to perform ADLs and reduce the incidence of falls. A possible explanation to the marked increase in the functional capacity in subjects, could be related to the improvements observed in the muscle cross-sectional area and power output. These results are relevant because a multicomponent exercise program that included muscle power training induced a positive stimulus to promote muscle hypertrophy, decrease fat muscle infiltration, enhance leg muscle power and functional capacity, and decrease the incidence of falls. A systematic review [73], that verify the effects of different exercise interventions on risk of falls, gait ability, and balance in physically frail older adults concluded that multicomponent exercise intervention program that consists of strength, endurance, and balance training appears to be the best strategy for improving gait, balance, and strength, as well as reducing the rate of falls in elderly individuals and consequently

maintaining their functional capacity during aging, and these results are in agreement with our study.

In regards to home-based physical activity for older people with frailty, the present study found a non-significant trend towards an improved ADL and quality of life. Indeed, this results are due to the relatively short duration of the trial, absence of long-term follow-up and lack of statistical power [58]. A recent systematic review [74] found that exercise positively influenced performance in ADLs in frail older adults. The improvement in ADLs might be associated with exercise type. Most of the included trials involving ADLs, either task-oriented or functional practice, were associated with findings that exercise is significantly beneficial. Researchers observed that the outcome of task-oriented ADLs training with repetitive practice could motivate subjects and, recommended that it should be performed often. It was also found that exercise training did not have a statistically significant impact on quality of life in frail older adults, these results are in line with the our study.

Continuing on the home-based interventions, it also reduced the presence of frailty especially in individuals at higher risk of disability. Our results suggest the existence of differences underlying each of the frailty criteria, this indicates the need for exploring the single components of frailty in separate analyses in order to understand the differential responsiveness of criteria to specific interventions or their underlying pathophysiological mechanisms [53].

Thus, a strong point of this analysis is that it is focused on a population of frail elderly people, with a clear theoretical or operational definition of frailty. Also, this review had restrictive inclusion of RCTs, which all of the types of nonpharmacological interventions and adverse outcomes included in frailty were assessed. All of the randomized controlled trials were considered to have sufficient 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 the type of intervention: multifactorial and interdisciplinary intervention; and home-based physical activity intervention. The description in the multifactorial and interdisciplinary interventions by the different intervening professionals is not detailed about the kind of work that they provide. Regarding the home-based physical activity, the plan of exercises is not detailed enough and

many times is not even detailed at all. Second, the included trials contained very limited information about the outcome measures. Also, the difficulty in blinding the participant and the therapist might have lowered the methodologic quality and may have led to insignificant findings. It's important to also refer, that according to our results, there is little evidence to guide interventions to reverse or reduce frailty in older people. The optimal intervention to improve these parameters in daily situations remains unclear. Studies should also follow Consolidated Standards of Reporting Trials (CONSORT) recommendations for non-pharmacologic trials [75] to report risk of bias with a total transparency, and make effective interventions reproducible in the clinical practice.

Our study could not do a meta-analysis because of the large variation and the large number of studies that did not report sufficient data. This great heterogeneity hinders the ability to draw conclusions about the appropriate design of the interventions program and, to some extent, the ability to quantify the effect of interventions.

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

V. 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.

Distinction of frail elderly people from those who are not frail should therefore be an essential part of the assessment for the creation of interventions with more effectiveness. The evidence reviewed demonstrates that there are limited data from RCTs to thoroughly explain the intervention on frailty. Furthermore, the range of the interventions being assessed is also limited, and remains focused on exercise and nutrition.

This review also demonstrates that frailty is not a steady state but rather a changeable result of complex interactions. Our study found an increasing interest in multifactorial interventions aimed at optimizing the physiological, psychological and social functions of frail elder. A better knowledge and comprehension of the concept of frailty, and what types of non-pharmacological interventions are more effective in reversing this syndrome is an increasingly and recurrent need felt across by health professionals. Based on an increasing construction of scientific knowledge, occupational therapy can increasingly respond in a more effective and targeted manner to the needs of people with frailty. The people with frailty are influenced by biological, behavioral and environmental factors that could increase the risk of falls, ADL/IADL disability and lower quality of life. Therefore, occupational therapy is an important intervenient in a frail population, for example in environment modifications for prevention of falls, reduces difficulties with ADLs/IADLs and mobility, and cognitive and behavioral intervention.

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 (type, duration, frequency, and intensity) 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 older frail people.

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