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Physical Activity and Nutritional Supplementation to Reduce Frailty in Community – Dwelling Older Adults, Searching for Evidence: A Systematic Review of Randomized Controlled Trials

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Background

In the last decades, older people represent a quickly growing proportion of the world's population. In 2015, 8.5 percent (617 million) of people worldwide were aged 65 and over. According to recent data, this is expected to grow to 17 percent (1.6 billion) by 2050.[1] In developed countries, this percentage reaches higher levels, with a peak in Italy, where in 2016 elderly people accounted for the 22% of the resident population.[2] Ageing population represents one of the most significant transformations of the twenty-first century, with implication for nearly all sectors of society, such as housing, transportation and social protection.[3] Moreover, the increase in ageing represents many opportunities and several public health challenges to which the health systems needs to prepare for. Primary, a strong shift from hospital-based to community-based care is suggested to address the burden of multi-morbidity and its effects on adverse healthcare outcomes.[4] In fact, due to physiological aging, the elderly reveal a reduction of psycho-physical efficiency that sometimes results in a feature of a greater vulnerability, also called frailty.[5] Frailty in the elderly is defined as a clinical syndrome characterized by a decrease in energy reserve, strength, and performance, resulting in a cumulative decline in multiple physiological systems, leading to a state of greater vulnerability.[6]

There are several ways to approach to frailty.[7] The most known of these was introduced by Fried and collaborators in the 2001, the "frailty phenotype". It is based on the identification of frailty when 3 or more of these criteria are present: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity.[8] A different model of frailty was proposed by Rockwood and colleagues.[9] This approach defines frailty as a result of multiple interacting factors such as having difficulties in activities of daily living (ADL), psychological and social dimensions.[10] The most recent approach to frailty was proposed in 2010 by Gobbens and colleagues, which defined frailty as a multidimensional syndrome.[11] To date, a consensus on the exact definition of frailty is still lacking.[4] Clinically, frailty is a potentially reversible syndrome[12] that determines an increased risk of adverse health outcomes when exposed to a stressor.[13] Indeed, frailty represent a major risk factor for negative health-related events in the elderly, including disability, falls, the need of long term care, hospitalization and death.[14,15] Recent data suggest that the prevalence of frailty ranges between 4.0% to 17.0% (mean 9.9%) in the elderly, with higher percentage (13.6%) when psychosocial frailty was considered. This condition was increased in persons older than 80 and women had almost twice the risk of men (9.6% vs 5.2%) to be frail.[16]

Therefore, clinical identification of frailty may play an important role in its prevention.[14] Due to its reversible nature, preventive strategies can be considered able to modify the natural history of this syndrome, with remarkable differences among community-dwelling and hospitalized frail individuals.[17,18]

The positive impact of physical exercise and nutritional interventions on frailty have long been investigated,[19] with uncertain results; in fact, in recent literature, physical activity is considered one of the most effective intervention in frail older persons, while separate nutritional intervention doesn't show noteworthy improvements. Recent data seem to associate type of dietary with a higher or lower risk of frailty. Despite the wide literature about this topic, a very few studies examined the reduction of frailty as primary outcome, and more often the population study doesn't respond to an exact definition of frailty.

The aim of this study was to evaluate the most effective intervention in reducing the frailty status, considering both physical activity and nutritional intervention in community-dwelling older adults, for highlight the better strategy in reducing the prevalence of frail elderly.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was followed as a methodological guide.[20]

A systematic literature research was performed in November 2016 through PubMed and Cochrane Central Register of Controlled Trials, using the following keyword: frail elderly and frailty as MeSH terms, physical activity or nutritional, exercise or nutrition, training or protein, amino acids, supplementation in the title/abstract. The searching was restricted to clinical trials published in the last 10 years, written in English.

As showed in Table 1, reporting inclusion criteria, clinical trials were considered eligible if included both gender population

Table 1. Inclusion Criteria.

Inclusion criteria	
Participants	• Age ≥ 60 years old • Living in the community • Both genders cohorts • Without disabling diseases • Standardized frailty criteria (eg, Fried's criteria or Frailty Index)
Interventions	• Active physical exercises, nutritional supplementation, or any combination of these
Comparisons	• Presence of a control group
Outcomes	• Effects of intervention on standardized physical frailty criteria or specific physical performance-based parameters (scales or performance measurements) related to frailty
Study design	• Controlled trial with a randomized assignment in each group

of frail community-dwelling, 65 years old or more excepted for one study[21] that included people from 61-89 years, self-dependent and without disabling diseases.

A specific definition of frailty was mandatory for eligibility, according to standardized criteria (eg, Fried's criteria or Frailty Index).

Selected articles had to evaluate the effect of active physical exercise programs, nutritional supplementation, or both on frailty status. As secondary outcomes, selected studies had to evaluate the performance-based measures of physical function, in frail older adults. All the studies should have the presence of a control group and randomization in the assignment to each group (Table 1).

Studies were not included if anyone of the following participants' characteristics was present: people living in a health structure or senior facility (hospitals, long-term care), patients with outcome-related comorbidities (e.g. diabetes, cardiovascular diseases), relevant acute recent event (as post-stroke, post fracture, etc.), severe cognitive impairment, single gender cohort.

The primary outcome was the evaluation of frailty status before and after the intervention. Secondary outcomes were the evaluation of other parameters such as disability, depressive symptoms, health-related quality of life, nutritional status, cognitive status, social networking, biochemical markers, self-reported health status.

Methodological quality of all the selected studies was evaluated using the CONSORT (CONsolidated Standards of Reporting Trials) 2010 checklist for randomized trial.[22,23] One point was assigned for each respected item of the checklist. Quality evaluation was independently achieved by four authors (C.A., G.C., F.C., F. DG.).

Four authors (C.A., G.C., F.C., and F. DG.) independently screened in pairs the search results, performed data extraction and quality evaluation. Any discrepancies were resolved by consensus or consulting with a fifth author (L.M.).

Results

The two-database search identified 602 articles totally, and after duplicated removal, 324 were considered for selection about title and abstract. Through the reading of title and abstract, 225 articles were excluded, and 99 were retrieved for full-text assessment of eligibility. Eight studies met the inclusion criteria and were included in this review.

Details about selection workflow are shown in the Flowchart (Figure 1).

Eight studies satisfied eligibility criteria, for a sample of 1265 older people (64.6% women) with a mean age of 77.64 years. Two studies were conducted in Europe,[24,25] one in Australia/Oceania,[26] two in Asia[27,28,29] and two in North of America.[21,30] Follow-up measurements ranged from 3 to 12 months. Six selected articles were centered only on physical intervention, and

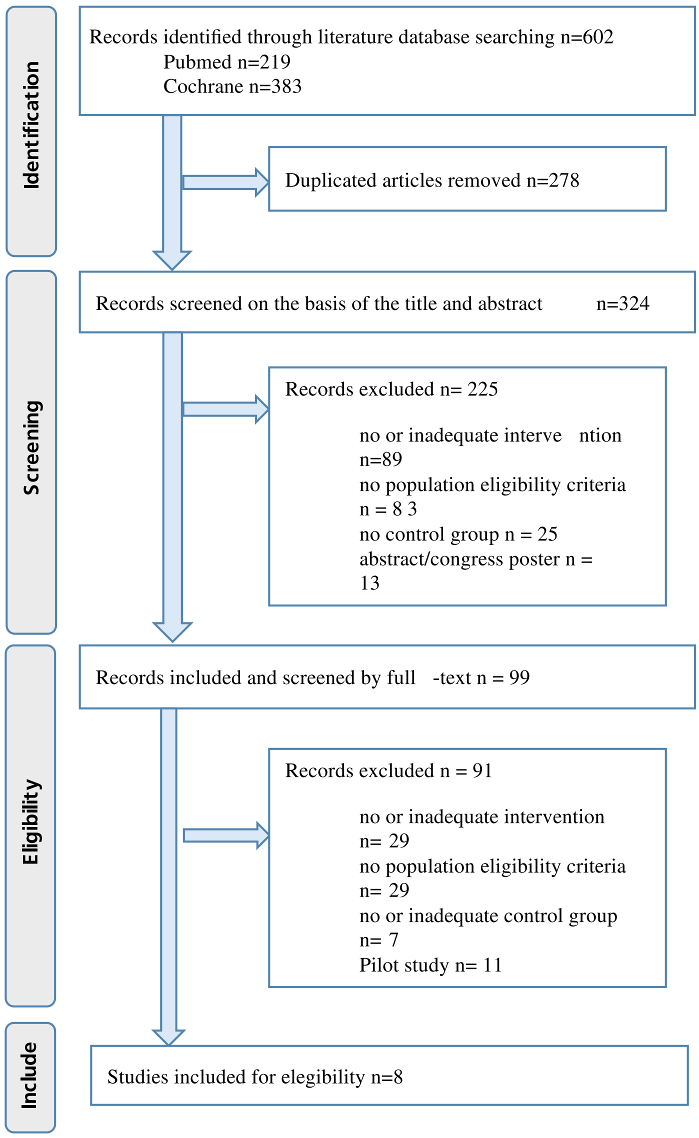

Figure 1. Flow Chart.

Table 2. Consort Rating.

Reference	Consort rating
Physical intervention	
Cameron et al. 2013	22/25
Cesari et al. 2015	16/25
Giné-Garriga et al. 2010	22/25
Tarazona-Santabalbina et al. 2016	21/25
Langlois et al. 2012	16/25
Zhang et al 2014	21/25
Physical and nutritional interventions	
Tze Pin et al. 2015	22/25
Chan et al. 2012	22/25

two were based on both physical and nutritional intervention. No studies regarding only nutritional intervention were included.

Selected studies were of good quality, with a mean score of 20.25 out of 25, ranging from 16,[21,30] moderate quality, to 22 points,[24,26,28,29] excellent quality, as shown in Table 2. Assignment randomization methods were exhaustively described in six articles;[24,25,26,27,28,29] due to the nature of interventions, none of the studies had blinded participants. Regarding the evaluation of outcomes, articles were divided in two groups per type of intervention: only physical intervention[21,24,25,26,27,30] or both physical and nutritional intervention.[28,29]

A qualitative synthesis of the studies meeting the eligibility criteria or details about the data items are reported on Table 3.

Intervention Characteristics

The intervention characteristics are summarized in Table 2. In all the selected studies an exhaustive description of intervention program was reported. Six studies[21,24,25,26,27,30] were characterized only by physical interventions. In the study of Giné-Garriga et al.[24] population was submitted to a functional circuit training program, focusing on improvement of balance and lower body strength. Cameron et al.[26] conducted a multifactorial, interdisciplinary and individually tailored treatment intervention, targeted on better mobility and better balance, with a weight-bearing exercise program. Tarazona-Santalbina and collaborators[25] performed a multicomponent exercise program focused on improving balance, proprioception, and strength, adding nutritional information on optimal dietary intake. Cesari et al.[30] based their research on intervention including aerobic, strength, flexibility, and balance training. Langlois et al.[21] performed a physical training sessions including a warm-up session, a strength training and an aerobic workout that was individually increased to reach a moderate to hard intensity, followed by a set of cool down exercises. Zhang et al.[27] considered the whole-body vibration, which is a passive strong physical therapy, as the physical intervention, compared to a control group doing other kind of physical therapies and routine exercises.

Two studies[26,27] investigated the effects of both physical intervention and nutritional program, combined and individually, compared to a control group. In the study of Ng et al.[28] was performed a moderate physical exercise of 90 min/twice a week for 12 weeks in classes with a trainer, followed by 12 weeks of home-based exercises. Iron, folate, vitamin (B6, B12, D) and calcium supplement were administered daily for 24 weeks. Chan et al.[29] based the principal intervention (exercise and nutritional) in a structured exercise course 3 times a week for 3 months. Each section lasted about 1 h. The research team also inquired about the subjects' dietary compliance and responded to their dietary questions during the exercise sessions.

The interventions lasted 2 months in one study,[27] 3 months in three studies,[21,24,29] 6 months in two studies,[25,28] 12 months in the last two studies.[26,30]

The frequency of the interventions ranged from twice a week[24,28] to 5 times/week[25,27] for physical activity, while nutritional interventions were dispensed daily for all the time of the study.

Table three summarized in detail primary significant outcomes. A *p* value <0.05 or <0.001 were chosen as significance threshold level.

Outcomes

The primary outcome of this review was to investigate the potential reversibility power of a physical or combined physical and nutritional intervention program on frailty status.

Five of the included trials[25,26,28,29,30] evaluated the frailty status as an outcome and all the studies showed a significant improvement on specific frailty scores in the intervention group compared to the control one. Among the studies which investigated the effect of only physical intervention, both Cameron et al.[26] and Cesari et al.[30] evidenced an improvement of Fried-CHS criteria (p<0.01 at 12 months and p=0.01 at 12 months, respectively). Even Tarazona-Santabalbina et al.[25] evaluated the effect of a physical intervention alone, measuring Fried frailty criteria and Edmonton Frailty Scale at 24 weeks, showing a significant improvement of both frailty parameters (p<0.001), compared to the control group. Furthermore, Ng et al. and Ding-Cheng et al.,[28,29] evaluated the effect of a combined physical and nutritional intervention on frailty status. Ding Cheng et al.[29] showed a significant improvement of Fried-CHS score in a combined intervention group compared to the control (P=0.008 at 3 months); Ng et al.[28] observed a significant improvement in Fried Frailty Criteria at 12 months in the combined physical and nutritional intervention group (p<0.01), moreover showing a less but still significant positive effect on frailty status (p<0.05) of an only nutritional supplementation strategy.

Other relevant outcomes were observed, such as mobility, muscle strength, balance, quality of life, cognitive status and biochemical markers.

Mobility outcomes were investigated in all the trials evaluating the only physical intervention. Five authors[21,24,25,26,27] showed a statistically significant improvement in several mobility parameters: 6 minute walking test[21] (p=0.03 at 12 weeks), short physical performance battery (SPPB)[25,26] (p<0.001 at 12 months and p=0.007 at 24 weeks, respectively), lower extremity continuous summary performance score (LECSPS)[26] (p<0.001 at 12 months), physical performance test (p<0.001) and Tinetti scales (p<0.001),[25] time up and go and 30 second chair stand tests[27] (both p<0.05 at 8 weeks). Gine-Garriga et al.[24] evaluated a battery of several mobility tests, which almost all significantly improved at 36 weeks, such as stand up test (p=0.002), rapid gait

Table 3. Summary Of The Studies.

References	Study design	Population (*included at baseline*) And setting	Identification of frailty	Intervention	Outcome	Findings
Physical intervention						
Cameron ID et al. 2013 [26]	RCT	N = 216 (68% F, 32% M), mean age was 83.3 years old (SD ± 5.9). From Division of Rehabilitation and Aged Care Services (DRACS) at Hornsby Ku-ring-gai Health Service (Sydney, Australia).	Adults aged 70 years or older if met three or more of the Cardiovascular Health Study (CHS) Frailty Phenotype criteria. Not usually living in a residential aged care facility; without moderate or severe cognitive impairment (defined with a MMSE).	A 12 months multifactorial, interdisciplinary treatment program individually tailored to each participant. Participants underwent 10 home-based physiotherapy sessions of 45-60 min each where conducted five times in 3 months and other 5 times in the next 9 months, targeting a participant-centered mobility goal, in association to a home-based strength, balance and endurance training regimen using the Weight-bearing for Better Balance (WEBB) program, 3-5 times/week. If BMI <18.5 kg/m2 or mid-upper arm circumference < 10th percentile, a high energy-protein nutritional supplementation was offered in the same period (29% N). The CG received usual health care.	Primary outcomes: - frailty: CHS criteria - mobility: Short Physical Performance Battery (SPPB) and lower extremity continuous summary performance score (LECSPS). Secondary outcomes: disability, depressive symptoms and health-related quality of life. Assessment at 0, 3 and 12 months.	Significant improvements between 3 and 12 months of primary outcomes: - CHS criteria (p<0.01) - Mobility SPPB (p<0.001) - LECSPS (p<0.001). No significant differences between the groups in secondary outcomes.
Cesari M et al. 2015 [30]	RCT	N = 424 mean Age 76.8 (SD 4.2) (68.9% W)	Frailty phenotype was measured by CHS – Fried Scale	The PA intervention lasted 12 months and included aerobic, strength, flexibility, and balance training. Control group received health education program	Primary outcomes (frailty measures): - Exhaustion - Involuntary weight loss - Sedentary behavior - Slow gate speed - Poor muscle strength	Significant improvements: - Number of frailty criteria at 6m between 2 groups (p=0.02) - Number of frailty criteria between 2 groups at 12m (p=0.01)

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Table 3. Summary Of The Studies. *(continued)*

References	Study design	Population (*included at baseline*) And setting	Identification of frailty	Intervention	Outcome	Findings
Giné-Garriga M et al. 2010 [24]	RCT	N = 51 (31 F, 20 M), mean age 84 years old (SD ± 2.9), community-dwelling. From one randomly selected primary health care center in the Barcelona area.	Two test of physical abilities: - required more than 10 seconds to perform a rapid-gait test - could not stand up five times from a seated position in a hardback chair with their arms folded. Two questions from the Center for Epidemiological Studies Depression Scale (CES-D).	A structured 12-week FCT (Functional Circuit Training) program, twice a week, which focused on a combination of functional balance and lower-body strength-based exercises. CG met once a week for health education meetings.	Measures at baseline, week 12 (end of training program), week 36 (follow-up). Primary measures: - 10 item version of Barthel Index - Rapid-Gait speed Test - Stand-up Test Secondary measures: Semitandem and Tandem Stands and Single-leg Balance, BMI, Modified Timed Up-and-Go Test, Normal-Gait speed, Maximal isometric quadriceps and hamstrings contraction strength.	Primary physical-frailty test: Barthel Index W0-W12 (p=0.001), W0-W36 (p=0.001), W12-W36 (p=0.049). Rapid-gait test W0-W12 (p<0.001), W0-W36 (p<0.001), W12-W36 (p=0.031). Stand-up Test W0-W12 (p<0.001), W0-W36 (p=0.002), W12-W36 (p<0.001). Secondary Balance: Semitandem W0-W12 (p<0.001), W0-W36 (p=0.021). Tandem W0-W12 (p<0.001), W0-W36 (p=0.001). Single leg W0-W12 (p<0.001), W12-W36 (p<0.001). Secondary gait Normal speed (m/s) W0-W12 (p<0.001), W0-W36 (p=0.003), W12-W36 (p=0.002). Fast speed (m/s) W0-W12 (p<0.001), W0-W36 (p=0.001). Secondary Timed up-and-go Questionnaire W0-W12 (p<0.001), W0-W36 (p=0.009), W12-W36 (p=0.001). Total time W0-W12 (p<0.001), W0-W36 (p=0.01), W12-W36 (p<0.001). Stand-up W0-W12 (p=0.001), W12-W36 (p=0.005). Kick 8 m W0-W12 (p<0.001), W12-W36 (p<0.001). Total time kick W0-W12 (p=0.001). Isometric dynamometry W0-W12 (p<0.001), W12-W36 (p=0.031).

Tarazona-Santabalbina FJ et al. 2016 [25]	RCT	N = 100 ≥ 70 years old, community-dwelling. 2 groups Intervention = 51 (29 F, 22 M), mean age 79.7 years old (SD ± 53.6). Control = 49 (25 F, 24 M), mean age 80.3 years old (SD ± 3.7). From 2 primary rural care centers of the same health department in Spain (Carcaixent and Sollana)	Frailty definition: - Fried Frailty Criteria (met at least 3) - Edmonton Frailty Scale Also considered as eligibility criteria: - Gait speed < 0.8 m/s Sedentary (< 3h/week physical activity)	Multicomponent exercise program (MEP) that included proprioception, balance exercises, aerobic and strength training and stretching exercises for 65 minutes, 5 days per week, for 24 weeks. Both groups received nutritional information of the optimal dietary energy-protein intake, with supplementation of calciferol when blood plasma calcidiol levels were ≤ 30 ng/mL, to reduce it as a confounding factor in the interpretation of the results.	Primary: - improvement of frailty definition criteria - functional measurements (SPPB, PPT, Barthel Index, Lawton, Tinetti, FAC, PAEE) Secondary: Falls, hospital visits. Cognitive, emotional status, social networking (MMSE, Duke social support, Yesavage, EQ-5D). Anthropometric characteristics and biochemical markers. Assessment 0 and 6 months.	Significant improvements W0-W24: Primary: Fried Frailty Criteria (p<0.001) Edmonton Frailty Scale (p<0.001) Functional measurements: SPPB (p=0.007) PPT (p<0.001) Barthel (p<0.001) Lawton (p=0.001) Tinetti (p=0.007) Tinetti Gait Test (p=0.002) PAEE (p<0.001) Secondary: N. hospital visits to PCP (p=0.021), MMSE (p=0.025), Duke Social Support (p<0.001), Yesavage (p=0.043), EQ-5D (p=0.045) Significant reduction observed also in fat mass and in one of the biochemical markers (protein carbonylation).
Zhang L et al. 2013 [27]	RCT	N = 39, 78-93 years old (mean 85.27±3.63). 2 groups Intervention (TG) = 19 (17M, 2F), mean age 85.84 ± 3.58. Control (CG) = 18 (15M, 3F), mean age 84.67 ± 3.68. Outpatients of the Department of Rehabilitation Medicine of Chinese PLA General Hospital. Excluded if cognitive impairment (MMSE ≤ 18) or any illness with a life expectancy of less than 12 months.	Frailty definition: Fried Frailty Criteria (met at least 3).	8 weeks treatment period TG: whole-body vibration exercise (commercial Galileo machine), 3-5 times per week. CG: usual care, physical therapy (phototherapy; ultrasound therapy; electrical stimulation; electromagnetic fields therapy, and manipulation therapy), and routine exercises (pedaling training with regular dosage).	Baseline (W0), 4 weeks (W4) and 8 weeks (W8) measurements: Primary: - Mobility: timed-up-and-go test (TUG), 30-second chair stand test (30SCS). - Knee extensor strength (KES, left & right). - Postural Balance function (surface area ellipse SAE, open and closed eyes). Secondary: - Activities-specific Balance Confidence (ABCs). - General health state (self-administered Short-form Health Survey Questionnaire SF-12, including a physical health component score PCS and a mental health component score MCS).	Significant improvements W0-W4-W8 (p<0.05): - W4 Outcomes (adjusted α) TG: TUG, KES left & right, SAE open & closed eyes, SF-12 PCS. CG: KES right. - W8 Outcomes (adjusted α) TG: TUG, KES left & right, SAE open & closed eyes, ABCs, SF-12 PCS & MCS. CG: KES left & right, SAE open & closed eyes, SF-12 MCS. Significant differences between TG & CG, W0-W8 (p<0.05): TUG, 30SCS, KES left & right, ABCs, SF-12 PCS & MCS.

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Table 3. Summary Of The Studies. *(continued)*

References	Study design	Population (*included at baseline*) And setting	Identification of frailty	Intervention	Outcome	Findings
Langlois F et al. 2013 [21]	RCT	N = 72, 61-89 years old Frailty (fr) + non frailty (nfr) participants randomly divided into 2 groups: Intervention (TG) = 19 nfr (5M, 14F) + 17 fr (5M, 12F); mean age 68.74 ± 5.52 nfr, 74.47 ± 6.99 fr. Control (CG) = 19 nfr (2M, 17F) + 17 fr (4M, 13F); mean age 70.95 ± 5.38 nfr, 75.41 ± 4.91 ± 6.99 fr. Excluded if limitations to undertake physical exercise program, or signs of dementia (<25 MMSE), or depression (>10 at the Geriatric depression scale).	Frailty definition, met at least 2 of the 3 following: - Fried Frailty Criteria (met at least 3). - Score of ≤28/36 on Modified Physical Performance Test (PPT; Binder et al., 2004). - Frail according to the Geriatrician's Judgment (mildly frail or worse on the clinical frailty scale) after assessing the 70 possible deficits of the frailty index (Rockwood et al., 2005). Non frail if not meeting anyone of the above criteria.	12 weeks treatment period TG: exercise-training program consisted of 12 weeks of 1-h exercise session 3 days a week (intensity and duration of aerobic exercises were increased individually, using the modified Borg Rating of Perceived Exertion scale to reach moderate to hard intensity. CG: participants were instructed to main- tain their current level of activity during the entire study period. w	1 week before intervention started (W-1) and 12 weeks (W12) measurements: Primary (physical assessment): - Modified PPT - Hand-grip strength (HGS) - Physical endurance (6-minute walk test 6MWT) - Timed Up and Go Test (TUG) - Gait speed Secondary (cognitive & quality of life assessment): - Cognitive (six cognitive domains) - Quality of life (achieve personal goals in 28 life domains)	Significant improvements primary outcomes TG vs CG (W-1) – (W12), p<0.05: - Modified PPT (p<0.001) - 6MWT (p=0.03) The group × frailty interaction was not significant, although improvement in functional capacity (PPT) was larger in frail than in non frail participants; improvement at the 6-MWT was equivalent in frail and nonfrail individuals. Significant improvements secondary outcomes TG vs CG (W-1) – (W12), p<0.05: significant main group effect, (particularly in 3/6 cognitive domains and in 5/28 life domains).
Physical and nutritional interventions						
Ng TP et al. 2015 [28]	RCT	N = 246, mean age 70.0 years (SD=4.7), women=61.4%, Community-dwelling (5 parallel group: physical training, nutritional supplementation, cognitive training, combination treatment, and usual care control)	- Fried's criteria - ≥65 years old - able to ambulate without personal assistance - living at home	Physical exercise moderate of 90 min/twice a week for 12 weeks, in classes with a trainer, followed by 12 weeks of home-based exercises. Iron, folate, vitamin (B6, B12, D) and calcium supplement taken daily for 24 weeks. Cognitive training for 2h/wk sessions for the first 12 weeks and for the subsequent 12 weeks fortnightly 2-hour "booster" sessions.	Primary outcomes: - frailty score - reduction of frailty - measures of frailty components Secondary outcomes: - self-reported hospitalization - self-reported falls - instrumental activities of daily living - activities of daily living (ADL) dependency	Significant improvements: Primary: Frailty score at 3m: TG. & TNG.: p<0.05 Frailty score at 6m: TG: p<0.01; TGN: p<0.05 Frailty score at 12m: N: p<0.05, TG & TGN: p<0.01 Frailty reduction ad 12m: N, TG, TGN: p<0.01 Secondary: Knee strength: TG & TGN: p<0.01 Physical activity: NG: p<0.01, Gait speed: TG: p<0.05 Energy: NG: p<0.05

Chan DC et al 2012 [29]	pRCT	N = 117 mean age 71.4 ± 3.7 yrs women=69 (59%) Community-dwelling older adults randomized into 4 groups: A: EN/PST B: EN/Non-PST C: PST/Non-EN D: Non-EN/Non-PST	CHS_PCF in 65 to 79 years old people	Education booklet: the educational booklet on frailty, healthy diets, exercise protocols, and self-coping strategies was given to all participants. Exercise and nutritional (EN) The EN group subjects were invited to take a structured exercise course three times a week for 3 months. Each section lasted about 1 h. The research team also inquired about the subjects' dietary compliance and responded to their dietary questions during the exer- cise sessions. Problem Solving Therapy (PST) The PST group subjects received 6 sessions therapy by trained case managers.	Primary outcomes: - Improvement of CHS_PCF Secondary outcomes: Interval changes of the following indicators: - Mini Mental Status Exam - Primary Care Evaluation of Mental Disorders - Barthel Index - BMI - Fat Free Mass - Left one-leg-stand time - Dominant leg-extension power - 25(OH)Vit.D Level	Significant improvements: Primary: Frailty status at 3m: EN Vs. Non-EN: p=0.008 Not statistically evaluated, but important findings: Pre-frail to robust at 3m: 33 (32.4%) Frail to robust at 3m: 3 (20%) and Frail to pre-frail at 3m: 6 (40%) Secondary: Dominant leg extension power at 6m and 12m in PST group: $p<0.05$ Increase of 25(OH)Vit.d EN vs Non-EN: p=0.006

Legend: RCT = Randomized Clinical Trial. IG = intervention group. CG = Control Group. TG: Training Group. NG: Nutritional Group. TGN: Combined Group. BMI = Body Mass Index. MMSE = Mini-Mental Sate Examination. ADL = Activities of Daily Living. pADL = personal Activities of Daily Living. iADL = instrumental Activities of Daily Living. NEADL = Nottingham Extended Activity of Daily Living Scale. NHHS = National Home Healthcare Services. PPT = Physical Performance Test. FAC = Functional Ambulation Categories. PAEE = Physical Activity Energetic Expenditure. EQ-5D = EuroQol quality-of-life scale.

test ($p<0.001$), normal speed ($p=0.003$), fast speed ($p=0.001$). In one of the trials evaluating a combined intervention,[28] a gait speed test was significantly improved ($p<0.05$) in the group undergoing an only physical training. Two authors[25,30] evaluated mobility indicators but they didn't found significant improvements. No mobility outcome was evaluated in one combined intervention trial.[29]

Several muscle strength parameters were significantly improved in four trials[24,27,28,29] after intervention programs, while in two studies[21,30] intervention did not prove to have relevant effects. Ginè-Garriga et al.[24] detected an efficacy of physical intervention on isometric dynamometry performance at 12 weeks ($p<0.001$); Li et al.[27] measured the efficacy on knee extensor strength ($p<0.05$ at 8 weeks). Ng et al.[28] showed a knee extensor strength improvement in both physical and combined intervention groups ($p<0.01$ at 12 weeks), while no significant improvement was observed in the only nutritional supplementation group. Ding-Cheng et al.[29] evaluated the effect of combined intervention on dominant leg extension power, not showing any statistical improvement.

Balance scales were significantly improved in two articles[24,27] in which a physical intervention was performed. Ginè-Garriga et al.[24] evidenced at 36 weeks an improvement in tandem ($p<0.001$) and semitandem ($p=0.021$) tests, while single-leg test significantly improved ($p<0.001$) from 12 to 36 weeks. Li et al.[27] demonstrated the efficacy of a whole-body vibration training session on frail elderly's balance capacity at 8 weeks through an elliptic surface area walking ($p<0.05$). No balance scales were evaluated in the other included trials.

After his physical training program, Langlois et al.[21] measured an improvement of an Achieve Personal Goals in 28 life domains as a quality of life indicator ($p<0.05$). Physical exercise was effective in improving Barthel index in two studies[24,25] ($p=0.001$ at 36 weeks and $p<0.001$ at 24 weeks, respectively). Cameron et al.[26] and Ng et al.[28] evaluated a quality of life assessment with different scales with no statistically significant results at follow-up.

Anthropometric parameters, such as BMI, were measured as outcomes in three trials and did not show a significant benefit neither after a physical exercise program[24,25] nor after a combined physical and nutritional intervention.[29]

Physical and nutritional combined intervention, in Chan et al.,[29] showed to have significant effects on increasing in 25 (OH) vitamin D levels at 12 months ($p=0.006$); Tarazona-Santabalbina[25] evidenced a relevant improvement of another biochemical marker such as the plasma protein carbonyls levels at 24 weeks ($p=0.05$), performing only a physical program.

Different cognitive status scales were investigated in three trials[21,25,27] in which a significant better score was recorded after intervention, while in a combined intervention Chan et al.[29] did not observed any significant improvement in MMSE at follow-up. Langlois et al.[21] applied a cognitive domain survey which showed a significant score raising at 12 weeks ($p<0.05$); Tarazona-Santabalbina et al.[25] detected a significant improvement ($p=0.025$) of MMSE at 24 weeks; Li et al.[27] evaluated a Mental Health Component Score (MCS) which was significantly improvement at 8 weeks ($p<0.05$). Cameron et al.[26] recorded no statistically significant changes on a depression scale values during the follow-up in the intervention group.

Discussion

This systematic review highlighted that both interventions, physical activity alone or physical and nutritional combined, have undoubted positive effects on frailty status. Moreover, in all the studies based on physical activity intervention, it was observed an important and statistically significant improvement of physical parameters considered as frailty criteria. Furthermore, in articles that considered both physical and nutritional interventions, the improvement comprises also some chemical biomarker. Other frailty-related parameters, such as cognitive, balance and lower extremities performance indicators, Activity Daily Living and other generic quality of life indicators have been improved in the study populations compared to the control groups. All the trial included in our paper were of good quality, but probably the strictly inclusion criteria could have reduced the number of studies included, with a scarce prevalence of nutritional clinical trials. Nevertheless, in the last years several systematic reviews were published among the most effective interventions in frailty, but none, to date, exploring the combined effect of physical activity and nutritional implementation. The only review that affords this topic is a scoping review published in January 2017, where differences with our work are remarkable.[31]

The effects of physical activity on frailty are more studied. A heterogeneity of definitions, tools and results is the biggest challenge that researchers encountered. In fact, most studies reported in the literature, differ in terms of included participants (frailty diagnostic tools), intervention strategies (type, number and combination of interventions) and intervention duration.[32] As expected, also in our study physical exercise, with or without a nutritional intervention, improves frailty parameters, confirming the reversible nature of frailty syndrome and the importance of prevention or early intervention.

In some recent systematic reviews,[33,34,35] the effects of exercise intervention in frail older people could promote an implement of physical functioning, but results showed great heterogeneity in terms of outcomes. De-Labra et al.[35] concluded that multi-component exercise interventions, including some type of resistance training, could promote better performance in the global function capacity of frail older adults. Chou et al. [34] showed a significant benefit of exercise in gait speed and in improving balance, but also great heterogeneity in results for the timed up and go test (TUG test) and performance in ADL. Giné-Garriga et al.[33] found moderate evidence to support exercise training for improving gait speed and combined performance measures such as SPPB in agreement with other authors,[34] but inconclusive findings about the effect of exercise training for improving functional mobility or balance, in contrast to other authors.[34,36] In conclusion, the exercise training has some benefit in frail older people, but uncertainty still exists regarding which exercise characteristics (type, frequency, duration) are most effective. According to our results, it seems that physical activity intervention itself could improve the frailty status, regardless of the type of exercise. In our revision, most of the beneficial effects of the physical intervention were observed also over time (12 months), highlighting the importance of this kind of intervention in improving quality of life and reducing the institutionalization and/or hospitalization of frail older adults. In fact, one of the utmost important consequences of frailty is the onset of disability. Ramon Daniels et al.[36] investigated how to prevent disability in frailty community-dwelling elderly through physical interventions. They were focused on disability outcome, where disability was defined as having trouble in performing activities in any domain of life. Exercise intervention seems to have a positive effect also on ADL and IADL in community-living people with a moderate physically disability.

Nutritional supplement doesn't seem to modify the frailty status, but it should attend more frequently on the metabolic aspect, improving the hematologic pattern, and the concentration of certain nutrients used as nutrition markers. Noteworthy, nutritional status is an important predictor marker of frailty. As reported by Yannakoulia M et al., all the frailty criteria are affected by poor eating habits.[37] They analyzed cross-sectional studies, prospective studies and intervention studies, assessed that not only a low level of energy intake is consistently associated with frailty, but also the daily distribution of dietary intake, the number of micronutrient deficiencies and the dietary patterns contribute to the syndrome. One important aspect that arises from this study is the correlation between the adherence to Mediterranean diet and the low risk of frailty in ageing, as many studies confirmed. As in our cases, their difficulty was to assess the correlation of frailty with poor dietary intake by randomized clinical trials. In fact, to date, it seems difficult to find randomized clinical trials that correlate nutritional supplementation and frailty itself. More often, nutritional interventions, based on administration of some micronutrients or proteins, were considered as part of combined intervention in clinical trials or studied in observational studies, therefore no cause-effect relationship was proven.[38,39,40,41,42,43,44]

Moreover, elderly people experiment the phenomenon called "anorexia of aging".[45,46,47] A significant number of older people fail to ingest sufficient food to meet their essential energy and nutrient needs. In the study of Tsutsumimoto and colleagues, in frail older people the anorexia of aging resulted in 21.2% respect to 7.9% in their robust counterparts, and was independently associated with frailty status, with slowness, exhaustion, and weight loss. Recent systematic reviews seem to confirm these results, such as Kelaiditi et al.,[48] that investigated whether nutrition intervention is important to postpone frailty. In contrast, Xu et al.[49] performed a systematic review and meta-analysis to assess the ability of protein or amino acid supplementation to augment lean body mass (LBM) or strength of leg muscles in elderly patients, but they did not found any differences in lean body mass gain and muscle strength more than placebo in frail elderly.

As previous said, available evidences are characterized by an overall heterogeneity in terms of objectives and methods, but mostly by the lack of randomized clinical trial performed with certain criteria for frailty definition and inclusion participants. Moreover, the combined interventions found in our revision, did not seem to improve the frailty status more than physical exercise alone, so future study need to be assessed to establish the role of nutrition in the syndrome.

Limits

The most important limit that author encountered in this systematic review, was the scarce prevalence of randomized clinical trials conducted according to univocal criteria for the identification of frailty. Moreover, in most cases trials were conducted including both frail and pre-frail population or institutionalized older adults. The strictly inclusion criteria chosen by the authors were mandatory for the study, but this probably has reduced the number of included studies, reducing the evidence strength. Another important limit was the heterogeneity of interventions, in terms of type, duration and population. These limits, despite a massive literature present in the scientific database, have reduced the quality of randomized clinical trials until now, resulting in the few number of articles comprises in this systematic review.

Conclusion

This systematic review showed that physical intervention alone or combined with nutritional supplementation should improve the frailty status. Furthermore, the role of nutritional intervention alone or in combination is still uncertain and recent data suggest that rather than making interventions based on the supplement of some nutrients, it should be more appropriate a global approach based on a healthy diet. Establishing which exercise program could be more effective to contrast frailty is a challenge for the future. In the meanwhile, one of the most important goal is standardize the screening tools to identify community-dwelling frail people who might benefit from prevention strategy or early interventions.

Therefore, an early identification of people at risk of being frail could significantly reduce the adverse outcomes of the syndrome and improve both the performance of healthcare systems and older people quality of life. Moreover, targeting people who are at risk for frailty, could also lead to economic advantages.

In conclusion this systematic review, although including a small number of articles, confirmed the benefits of physical exercise in reducing the frailty status, but more studies are needed to understand which is the best approach to achieve lasting results. More studies are also auspicial to understand the role of nutrition in the frailty syndrome and its treatment. The authors are convinced of the usefulness of this type of intervention, both isolated and in support of physical activity, so we hope that future studies will focus on this topic.

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