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Review article

Interventions targeting geriatric frailty: A systemic review

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Geriatric frailty has drawn growing interest in recent years for its associations with multiple adverse outcomes. Previous studies showed that interventions may improve some aspects of frailty such as physical function. However, interventions targeting the entire frailty construct have not been systemically reviewed. We conducted a comprehensive search for randomized controlled trials targeting geriatric frailty. Only trials that measured outcomes based on their predefined frailty indicators were included. Of 98 articles, 11 met the inclusion criteria. Eight studies were classified as high quality. Of the six exercise-based interventions, five showed significant improvements on at least two of their frailty indicators. Hormone replacement therapy was not effective. Two of the three multifactorial interventions have not published their results, and the third did not show significant improvements. More studies with standardized definitions and measurements of frailty are needed to determine the effectiveness of interventions on geriatric frailty.

1. Introduction

Frailty is commonly referred to as a state of functional decline with increased vulnerability characterized by weakness and decreased physiologic reserve.[1] However, studies varied significantly on their operational definitions.[2] The Fried frailty criteria (FFC), which includes indicators such as shrinking, weakness, poor endurance, slowness, and low physical activity, is a widely used instrument for physical frailty in the research setting.[3] Others prefer a multidimensional approach by measuring biophysiologic, psychologic, and social aspects of frailty[2] such as the Edmonton frail scale[4] or the frailty index based on comprehensive geriatric assessment (CGA) results.[5] Lack of consistent operational definitions of frailty result in heterogeneous study populations and potential differential responses to interventions.[2]

A previous review showed that exercise training may improve balance, gait, and physical performance summary scores in frail older adults;[6] however, frailty was not clearly defined since studies were selected as long as the word "frail" appeared in the description of study populations. Another review examined the effects of 2 nutritional and 8 exercise interventions on disability of community dwelling frail elders.[7] Studies with at least one of the frailty indicators defined by Ferrucci and colleagues were included in the review.[8] However, the outcome of interest was disability, not changes in the frailty indicators. Also, both reviews did not include interventions other than nutritional or physical exercise programs. Another recent review on exercise interventions for management of frailty also pointed out that even all 47 studied enrolled "frail" older adults, validated operationalizations of frailty were only available for 3 studies.[9] None of the studies reviewed used frailty index as an outcome measure.[9]

The purpose of the this review was to examine current interventions specifically targeting geriatric frailty with focus on the dynamics of frailty status before and after interventions.

2. Method

Since frailty is not a MeSH term, we used "frailty" as the keyword to search PubMed and limited the results to English language publications and randomized control trials (RCTs). All manuscripts published before November 2011 were included. Ninety-eight articles were identified in the initial search. Articles that did not have a clear definition or measurements of "frailty"; or did not specify "frailty" as an outcome of interventions were

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excluded. Fifty were excluded after reading the abstracts .The remaining 48 articles underwent full text reading by 3 reviewers (Fig. 1). Among them, 6 did not have clear definition of frailty and 29 did not use frailty as an outcome.

Thirteen articles met the inclusion criteria. However, one was a 2003 reprint of a 1993 paper. Two were from the same study with one design paper and one outcome paper. The former was excluded. Eleven articles were presented (Fig. 1).[10–20] Two trials have not yet published their study outcomes as of November 2011; therefore, only the design papers were included.[10, 12] Differences of opinion were resolved by discussions among the reviewers.

All studies were evaluated for methodological quality by a scale[21] introduced in an earlier article.[6] For each item, 'yes' (= 1), 'no' (= 0) or 'unclear or not provided' (= 0) was recorded, with a possible score range from 0 to 9. A 'high quality' study was defined with a score of 5 or higher.[6] The result of quality assessment is summarized in Table 1.[11–20] Eight of the 11 studies were considered as high quality. For each study, the study population, frailty indicators, interventions, and outcomes were presented using a data-extracting table (Table 2).[11–20]

3. Results

3.1. Study population and frailty indicators

All participants in this review were aged 65 or older, and were recruited from either community or primary care clinics. Eight of the 11 studies used specific criteria to select "frail" participants, although these criteria were variously defined.[10–13,15,16,18,19] In the other three studies, two enrolled people only by age (>70 years)[17,20] and the remaining one enrolled frail or fractured older adults.[14] All studies agreed that decline in physiological reserves is an important component of frailty, although they operationalized the concept differently.

All 11 studies had specified frailty indicators. Three studies measured frailty according to Modified Physical Performance Test, peak O_2 consumption, and functional dependence scores.[11,18,19] Isometric grip strength and leg extensor power were used in one study.[16] Another used the short physical performance battery to evaluate effectiveness of frailty intervention.[10] One study specified the rapid-gait test, stand-up test, and Barthal index as its frailty indicators.[13] Another used a set of biomedical, functional, and psychological variables as their outcomes.[20] Four studies measured frailty scores according to the phenotype described by Fried et al.[1] However, only one study used original version of FFC.[14] In the other three, two modified the "low physical activity" criteria by measuring physical activity with different tools.[12,15] The remaining one study operationalized FFC with different tools to assess all five components.[17]

3.2. Interventions

Six studies introduced exercise as the main components of their interventions. Types of exercise include tai chi,[20] structured exercise training,[11,13,18,19] and telephone exercise counseling.[17] The frequency ranged from 3 times/week to daily practice. The intensity ranged from at least 150 minutes/week to 270 minutes/week. Most exercises were practiced on study sites[11,13,18–20] except one at home.[17] The durations of exercise training ranged from 15 weeks to 12 months.

Two studies evaluated the effect of hormone replacement therapy on frailty, with supplementation of transdermal testosterone in one study[14] and atamestane and/or dehydroepiandrosterone (DHEA) in the other.[16]

There were three multifactorial interventional studies.[10,12,15] Possible treatment strategies included exercise training, physical rehabilitation, medication adjustment, nutritional modification, specialty referral, and geriatric syndrome management. Interventions were tailored individually based on the CGA principles.

3.3. Outcomes

The six exercise intervention studies showed more favorable effects on frailty outcomes.[11,13,17–20] Telephone exercise counseling was not effective in decreasing frailty percentage.[17] Tai Chi improved hand grip and fear of falls but not the other frailty measurements.[20] A 1-year program on frail obese elderly improved all frailty measurements (modified physical performance test, functional status questionnaire and VO_2 peak) more in the 3

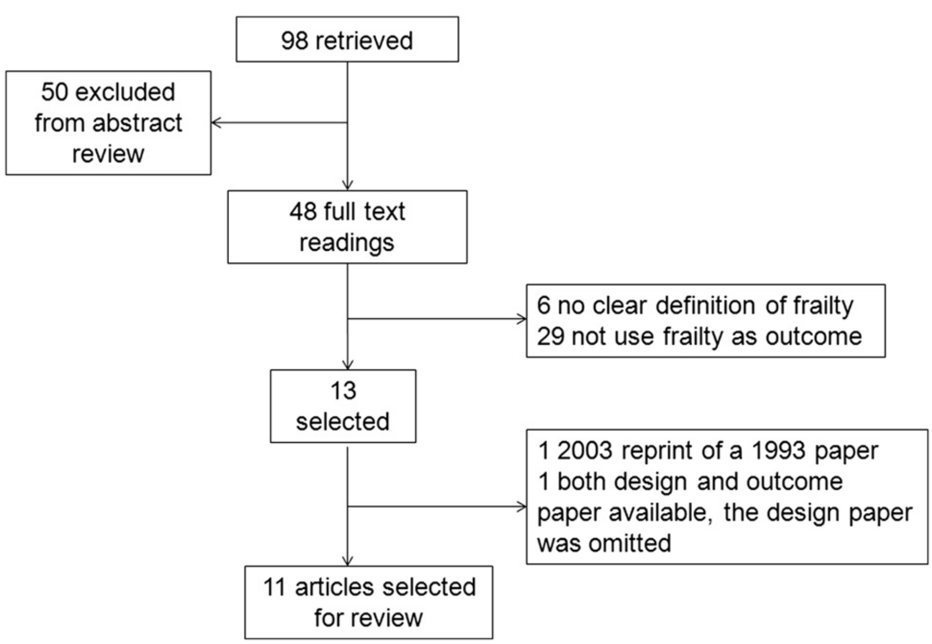

Fig. 1. Flowchart of search for relevant articles.

Table 1
Methodological quality of selected studies targeting to geriatric frailty.

Selected studies	*Quality criteria*									Summing scores
	Randomization	Concealed allocation	Similar baseline	Eligibility criteria	Blinded assessor	Blinded trainer	Blinded subjects	Measures of variability	Intention-to-treat	
Studies with exercise-based intervention										
Wolf et al[20]	Y	?	Y	N	?	N	N	N	?	2
Binder et al[11]	Y	Y	Y	Y	Y	N	N	Y	Y	7
Villareal et al[18]	Y	Y	Y	Y	Y	N	N	Y	Y	7
Peterson et al[17]	Y	?	Y	N	?	N	N	N	?	2
Giné-Garriiga et al[13]	Y	Y	Y	Y	Y	N	N	Y	?	6
Villareal et al[19]	Y	?	Y	Y	?	?	?	Y	Y	5
Studies with hormone-based intervention										
Muller et al[16]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Kenny el al[14]	Y	Y	N	N	Y	Y	Y	N	Y	6
Studies with multifactorial interventions										
Bandineli et al[10]	Y	?	Y	Y	Y	N	N	?	?	4
Fairhall et al[12]	Y	Y	Y	Y	Y	N	N	?	Y	6
Li et al[15]	Y	?	?	Y	Y	N	N	Y	Y	5

Y = yes; N = no; ? = unclear or not provided.

intervention groups than the control group.[19] The exercise plus diet group showed most significant effect, followed by either exercise group or diet group alone. Two other studies with similar methodology also reported positive outcomes on nearly all frailty indicators.[11,18] A 3-month functional program with balance and lower body strength training improved all frailty indicators. Moreover, the group-by-time interactions remained significant even 6 months after program cessation.[13]

Hormone replacement, either with DHEA and atamestane or transdermal testosterone gel did not improve frailty.[14,16] Among the three multifactorial intervention studies, one reported favorable improvements without statistical significance,[15] while the other two have not published their results as of November 2011.[10,12]

4. Discussion

In this review of 11 RCTs targeting geriatric frailty, five of the six exercise programs improved frailty measurements. Hormone replacement therapy was not an effective intervention for frailty. The effectiveness of multifactorial interventions on frailty was uncertain, with results pending from two trials.

The finding that physical frailty indicators could be improved by exercise was consistent with previous reviews.[6,9] Our findings broaden current knowledge that exercise may also improve physical, psychological, social, and role function[11,13,18,19] as well as fear of falls.[20] However, the positive effect should be interpreted with caution. Nearly all studies in our review focused on physical frailty, which is more likely to improve after exercise training.[6] Growing evidence suggested that deficits in other domains such as mood or cognition should be important attributes of frailty as well.[22] The multidimensional frailty indicators such as those developed from the Canadian Study of Health and Ageing,[5,23] and the Edmonton Frail Scale[4] were not used in our review. Exercise has been shown to improve emotional health in depressed subjects,[24] and physical activity may be beneficial in preserving cognitive function.[25] It is possible that exercise training may also have positive impact when multidimensional measurements of frailty are used in future studies.

Our review found an increasing interest in multifactorial interventions aiming at optimizing the biophysiological, psychological and social functions of frail elders.[10,12,15] In a systemic review conducted by Beswick and colleagues, community-based multifactorial interventions could help older adults living independently at home with increased physical function and decreased fall rate.[26] In another review by Boult et al, outpatient CGA and geriatric evaluation and management may improve quality of care and quality of life[27]; however, the positive effect of multifactorial intervention was attenuated if participants were restricted to frail older adults. Furthermore, the two reviews did not mention the effect of these complex intervention models on the frailty status.

The multifactorial intervention study with published results in our review did not show significant improvement on the modified FFC after 6 months of intervention.[15] When the results of the two newer trials are published in the future,[10,12] the effects of multifactorial interventions on geriatric frailty may be clearer. However, the modified FFC and the SPPB used in the above 3 trials consisted of indicators mainly based on physical symptoms and signs. The true effects of multifactorial interventions could be underestimated when only biophysiological outcomes were measured. We felt that multidimensional definitions of frailty would be better indicators when these complex interventions were applied.

Hormonal replacement therapy in this review showed no benefit on frailty status even after 12 months of treatment. Testosterone supplementation may improve muscle mass, muscle strength and physical function in older adults with androgen insufficiency.[28,29] However, a recent RCT was terminated early because of increased cardiovascular adverse events associated with administration of testosterone gel.[30] Other potentially effective anabolic hormones included megestrol and growth hormone secretagogues. However, without concurrent exercise training, they tended to increase only muscle mass but not strength or function.[31] Statins could possibly be useful in the treatment or prevention of frailty, based on its anti-inflammatory effect.[31–33] A prospective cohort study found no difference in the incidence of frailty between current statin users and nonusers.[34] A low level of vitamin D was strongly associated with both prevalent and incident frailty in observational studies.[15,35] So far, no RCTs have been conducted to investigate the effect of vitamin D or statin on frailty status.

To our knowledge, this is the first review article specifically evaluating RCTs targeting interventions using “frailty” as an outcome. We were unable to pool data together for a meta-analysis because of considerable heterogeneity of the study design, population, interventions, and measurements. Three of the four studies that used FFC as frailty indicators modified the criteria to fit their study purposes. The validities of these modified instruments may have to be tested and the results can be difficult to compare across studies. Only English language papers were identified in our review. In addition, “frailty” was the only keyword used in our searching strategy; older relevant studies may not be included in the review as the term is a relatively new concept in medicine.

Table 2
Summary of the 11 selected studies targeting to geriatric frailty.

Author/population	Frailty indicator	Intervention	Outcome
Studies with exercise–based intervention			
Wolf et al, 1996[20] $n = 200$, 38 men, mean age: 76.2 Inclusion: Aged ≥70	1. Biomedical: strength, flexibility, cardiovascular endurance, and body composition 2. Functional: IADL 3. Psychosocial: CESDS, fear of falling, self–perception of health, mastery index	15 wk Tai chi (TC, $n = 72$) : 45 min/week at study site, 15 min twice/d at home Computerized balance training (BT, $n = 64$): 45 min/wk at study site CG ($n = 64$) : Usual exercise levels with weekly health–related educations	**Effective in some indicators** TC vs. BT vs. CG: Biomedical: grip strength: −0.4vs.−1.5vs.−1.6($p = 0.025$) Psychosocial: no fear of falling (TC vs. CG): +10% vs. −9% ($p = 0.046$) Dropouts: 20%, overall
Binder et al, 2002[11] $n = 115$, 55 men, mean age: 83 (4)[a] Inclusion: Aged ≥78 ≥2 of the 3 criteria: 1. MPPT[b] score: 18–32 2. VO_2 peak: 10–18 3. Dependency in 2 IADLs or 1 ADLs	1. MPPT 2. ADL performance: functional status questionnaire (FSQ) OARS ADL and IADL scale 3. VO_2 peak	9 mo IG ($n = 69$) 3 times/wk for 36 sessions, 3 phases: First phase: Focused on flexibility, balance, coordination and speed of reaction Second phase: Progressive resistance training Third phase: Endurance training CG ($n = 50$): Exercise at home 2–3 times/wk Monthly exercise at study site	**Effective on most indicators** IG vs. CG MPPT : +3.4 vs. +0.9 ($p = 0.02$) FSQ: +3.4 vs. +0.4 ($p = 0.01$) VO_2 peak: +2 vs. −0.4 ($p < 0.001$) Dropouts: 33.3% vs. 18%
Villareal et al, 2006[18] N = 27, 9 men, mean age 69.4(4.6)[a] in IG, 71.1(5.1) [a] in CG Inclusion: Aged ≥65 BMI ≥30 Others same as Binder et al, 2002, except VO_2 peak: 11–18	1. MPPT 2. FSQ 3. VO_2 peak	26 wk IG ($n = 17$): 1. Exercise: 3 times/wk, 90 min/time 2. Dietary: daily energy deficit 750 kcal, adjusted to meet 1.5% body weight loss/wk for a total 10 % 3. Group behavioral strategy CG ($n = 10$): Maintain usual diet and activities	**Effective on all indicators** IG vs. CG: MPPT: +2.5 vs. +0.1 ($p = 0.001$) FSQ: +2.9 vs. −0.2 ($p = 0.02$) VO_2 peak: +1.9 vs. +0.3 ($p = 0.02$) Body weight loss (kg): −8.2vs.+0.7($p = 0.001$) Dropouts: 12% vs. 10%
Peterson et al, 2007[17] $n = 81$, 81 men, mean age 78.4 (4.9) [a] Inclusion: Aged ≥70	Modified FFC: 1. BMI <18 2. 6-min walk <20% of norm.[36] 3. Chair stand <20% of norm.[36] 4. Gait velocity (m/s) height <173 cm, then <0.65 height >173 cm, then <0.76 5. CHAMPS <20% of study cohort	6 months IG ($n = 39$): 1. Physical activity: 30 min/day, at least 5 days/week 2. Telephone counseling CG ($n = 42$): Baseline counseling about exercise	**Not Effective** IG vs. CG Change in frailty percentage −18%(67–49%)vs.0%(69–69%) ($p = 0.08$) Dropouts: not provided
Gine–Garriga et al, 2011[13] $n = 51$, 20 men, mean age 84 (2.9) [a] Inclusion (at least 1): Rapid-gait test > 10 s Chair stand-up <5 times Positive to 2 questions from CESDS	1. Barthal index score 2. Rapid-gait test 3. Stand-up test	12 wk IG ($n = 26$): 45-min function-focused training twice a week with balance and lower body strength exercise CG ($n = 25$): Meet once a wk with health education sessions	**Effective on all indicators** IG vs. CG Barthal Index Score: +5.91 vs. −2.89 ($p < 0.001$) Rapid-gait test (s): −2.1vs.+0.52($p < 0.001$) Stand-up test(s): −4vs.−0.88($p < 0.001$) Dropouts: 15% vs. 24%
Villareal et al, 2011[19] N = 107, 40 men, mean age 69–70 (4) [a] Inclusion: Same as Villareal et al, 2006[18]	1. MPPT 2. FSQ 3. VO_2 peak	1 y Two interventions with four groups 1. Exercise (E): 3 times/week, 90 min/time with strength, resistance, flexibility and balance training 2. Dietary (D): Energy deficit 500–750 kcal for a goal of 10% weight loss, D+E ($n = 28$), E ($n = 26$), D ($n = 26$), CG ($n = 27$)	**Effective on all indicator** D+E, E, D, CG (all $p < 0.001$) MPPT:+5.4, +4.0, 3.1, 0.2 FSQ :+2.7, +1.8, +1.3, −0.2 VO_2 peak:+3.1, +1.4, +1.7, −0.9 Body weight loss (kg): −8.6,−0.5,−9.7,−0.1 Dropouts: 11%, 15%, 12%, 15%
Studies with hormone–based intervention			
Muller et al, 2006[16] $n = 100$, 100 men, mean age 78.4 Inclusion: Aged ≥70 IGS <30 kg LEP <100 Nm	1. IGS of nondominant hand 2. LEP 3. Physical performance: standing balance, walking speed, ability to rise from a chair	36 wk Dosage: atamestane: 100 mg/d, DHEA: 50 mg/d 1. Atamestane + DHEA ($n = 26$) 2. DHEA + placebo ($n = 25$) 3. Atamestane + placebo ($n = 25$) 4. 2 placebos ($n = 24$)	**Not effective** Dropouts: 17%
Kenny et al, 2011[14] $n = 131$ (men), mean age 77.1(7.6) [a] Inclusion: 1 + (2 or 3): 1. Low testosterone[c] 2. Age >50 +hip fracture 3. Age >60 + ≥1 FFC) + BMD <−2	FFC 1. Weight loss>10 pb or >5 % 2. Self reported exhaustion 3. Grip strength[d] 4. 15 feet walking[e] 5. Low activity: males < 383 kcals/wk females < 270 kcals/week	12 months Calcium intake 1500 mg/d + cholecalciferol 1000 IU/d IG ($n = 69$): 5 mg androgen gel/day CG ($n = 62$): Placebo gel	**Not effective** IG vs. CG Dropouts: 23% vs. 26%

Table 2 (*continued*)

Author/population	Frailty indicator	Intervention	Outcome
Studies with multifactorial interventions			
Bandineli et al, 2006[10] $n = 251$, 74 men, mean age 76.4 (3.6) [a] in IG, 76.4 (3.4) [a] in CG Inclusion: Aged 70–85, Frailty: SSPB ≤9	SPPB (0–12 points, 4 for each item) 1. Walking speed over 4 m 2. Five times chair rises 3. Standing balance	12 mo IG ($n = 126$): 1. Multifactorial interventions 2. Exercise: 16 sessions (90 min/session) for 8 wk at a stretch, strength and balance CG ($n = 125$): Medical recommendations and follow-up	Baseline characteristics between IG and CG were similar. Between group comparisons for 12-mo follow up assessments were not available Dropouts of IG: 21.4%
Fairhall et al, 2008[12] $n = 230$, mean age and sex information not provided Inclusion: Aged ≥70 Modified FFC ≥ 3	Modified FFC: 1. Weight loss ≥4.5 kg or 5% 2. Self reported exhaustion 3. Grip strength < 30 kgw in men and 18 kgw in women 4. 4 m walk >6 s 5. Low physical activity[f]	12 mo IG: Multifactorial intervention based on FFC CG: Usual care for elderly from general practitioner and community services	No baseline data available. Only study design paper was published.
Li et al, 2010[15] $n = 310$, 162 men, mean age 78.4(8.2) [a] in IG, 79.3(8.2) [a] in CG Inclusion: Age ≥65 Modified FFC≥1	Modified FFC: 1. Weight loss>10 pb or >5 % 2. Self reported exhaustion 3. Grip strength [d] 4. 15 feet walking [e] 5. Low activities [g]: males < 383 kcals/wk females < 270 kcals/wk	6 mo IG ($n = 152$): Multifactorial intervention based on CGA: Medication adjustment, exercise instruction, nutrition support, physical rehabilitation, social worker consultation and specialty referrals CG ($n = 158$): Screening evaluation only	**Not effective** IG vs. CG: Improved frailty status: OR: 1.19 (95% CI: 0.48–3.04) Deteriorated frailty status: OR: 0.78 (95% CI: 0.34–1.79) Dropouts: 15% vs. 11% (p value not provided)

ADL = activities of daily living; BMI = body mass index; CESDS = center for epidemiologic studies depression scale; CG = control group; CGA = comprehensive geriatric assessment; CHAMPS = community healthy activities model program for seniors; CI = confidence interval; DHEA = dehydroepiandrosterone, FFC= Fried frailty criteria; IADL = instrumental activities of daily living; IG = intervention group; IGS = isometric grip strength; LEP = leg extensor power; OARS = older American resources and services; MPPT = modified physical performance test; SPPB = short physical performance battery; VO_2 peak = peak O_2 consumption (mL/min/kg).

[a] Age was expressed as mean (standard deviation) unless otherwise indicated.

[b] MPPT includes 7 timed tasks (50-foot floor walk, putting on and removing a laboratory coat, picking up a penny from the floor, standing up five times from a 16-inch chair, lifting a 7-pound book to a shelf, climbing one flight of stairs, and standing with feet in side-by-side, semi-tandem and full-tandem positions) and two additional tasks (climbing up and down four flights of stairs and performing a 360° turn).

[c] Testosterone <350 ng/dl or Bioavailable testosterone >1.5 SD lower.

[d] Cutoff for the grip strength criterion was as follows: Men: BMI ≤24: cutoff: ≤29 kgw, 24<BMI≤28: cutoff: ≤30 kgw, BMI >28: cutoff ≤32 kgw. Women: BMI ≤23: cutoff: ≤17 kgw, 23.1<BMI≤26: cutoff:≤17.3 kgw, 26.1<BMI≤29: cutoff: ≤18 kgw, BMI >29: cutoff ≤21 kgw.

[e] Cutoff for the criterion was ≥6 seconds if height >173 cm in men or height >159 in women, ≥7 s if height ≤173 cm in men or height ≤159 cm in women.

[f] The Criterion was modified as no weight–bearing activity for 3 months, spent >4 hours per day sitting, and short walk <1 per month.

[g] The Taiwan IPAQ–SF (International Physical Activity Questionnaire Short Form) instead of the Minnesota Leisure Time Physical Activity Questionnaire.

5. Conclusions

When frailty was served as an outcome of the interventions, most exercise-based interventions showed positive effects, while hormone replacement therapy was not effective. There were insufficient data to determine the effectiveness of multifactorial interventions on frailty. Multidimensional frailty indicators might be better outcome measurements if multifactorial interventions are applied. To improve compatibilities of studies, a more standardized operationalization of frailty is needed for future research.

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