Chapter 4
Prevention Strategy for Frailty

Hunkyung Kim and Tatsuro Ishizaki

Abstract Frailty is one of the most important concerns regarding our aging population. Frailty includes physical, social, oral, psychological, and cognitive aspects due to multisystem declines in physiologic reserve, rendering older adults vulnerable to increased risk of functional disability, falls, hospitalization, long-term care, morbidity, and mortality. Therefore, prevention and treatment of frailty is very important to prolong independence in elderly people. There are numerous factors that contribute to muscle weakness, slow walking speed, and loss of muscle mass in aging adults such as chronic disease, a sedentary lifestyle, and undernutrition, where some factors can be reversed with lifestyle changes and others need specific medications and cannot be reversed. Exercise and nutritional supplementation are among the beneficial treatments promoting healthy and independent lifestyles in the elderly. Evidence reveals that exercise targeted at reducing risk factors is an effective strategy for preventing and/or treating frailty in elderly people. Progressive and moderate-intensity exercise alone or combined with nutritional and hormone supplementation should be encouraged among elderly people to minimize the degenerative physical, psychological, social, and cognitive function that occurs with aging.

Keywords Frailty · Prevention · Treatment · Exercise · Nutrition

4.1 Introduction

Physical, psychological, cognitive, and social function changes occur with aging, and frailty is one of the most important concerns regarding our aging population.

Physical frailty due to multisystem declines in physiologic reserve is common among older adults, rendering them vulnerable to increased risk of functional disability, falls, hospitalization, long-term care, morbidity, and mortality [1–3].

Even though several operational definitions of frailty were proposed to help develop screening criteria, there is not yet a standardized and valid method of clini-

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cal screening for frailty. Despite a lack of international consensus on the definition of frailty, the most commonly used definitions of frailty are the frailty phenotype [3], the frailty index [4], the classification of frailty and vigorousness [5], and the Edmonton frail scale [6]. Among them, Fried's cardiovascular health study (CHS) criteria are the most widely used. Fried et al. proposed the frailty phenotype and described it based on five indicators of physical components: unintentional weight loss, muscle weakness, exhaustion, slow gait speed, and low physical activity. Subjects are considered robust (no criteria present), prefrail (one or two criteria present), or frail (three to five criteria present) [3]. Several other commonly used criteria have modified Fried's frailty phenotype including the Women's Health and Aging Studies (WHAS) [7] and the Japanese version of the CHS [8] (Table 4.1).

Table 4.1 Frailty-defining criteria: Women's Health and Aging Studies (WHAS), Cardiovascular Health Study (CHS), and Japanese version of CHS

Characteristics	CHS	WHAS	Japanese version of CHS
Weight loss	*Baseline*: Lost >10 pounds unintentionally in last year *Follow-up:* (weight in previous year-current weight)/(weight in previous year) ≥0.05 and the loss was unintentional	*Baseline: Either of:* (1) (weight at age 60 – weight at exam)/(weight at age 60) ≥0.1 (2) BMI at exam <18.5 *Follow-up: Either of:* (1) BMI at exam <18.5 (2) (weight in previous year-current weight)/(weight in previous year) ≥0.05 and the loss was unintentional	Have you lost 2 kg or more in the past 6 months? Yes = 1, No = 0
Exhaustion	*Self-report of either of:* (1) Felt that everything I did was an effort in the last week (2) Could not get going in the last week	*Self-report of any of:* (1) Low usual energy level 1 (≤3, range 0–10) (2) Felt unusually tired in the last 2 months (3) Felt unusually weak in the past 2 months	In the past 2 weeks, have you felt tired without a reason? Yes = 1, No = 0
Low physical activity	Based on the short version of Minnesota Leisure Time Activity questionnaire: *Women*: Those with Kcals per week < 270 are frail *Men*: Those with Kcals of physical activity per week < 383 are frail	Women: Kcal <90 on activity scale (6 items) Men: Kcal <128 on activity scale (6 items)	(1) Do you engage in moderate levels of physical exercise or sports aimed at health? (2) Do you engage in low levels of physical exercise aimed at health? "No" to both questions = 1, others = 0

Table 4.1 (continued)

Characteristics	CHS	WHAS	Japanese version of CHS
Slowness	Walk time, stratified by gender and height. Cutoff for Time to Walk 15 feet (4.57m) criteria for frailty *Women*: time >= 7 seconds for height <= 159 cm time >= 6 seconds for height > 159 cm *Men*: time >= 7 seconds for height <= 173 cm time >= 6 seconds for height > 173 cm	Walking 4 at usual pace *Women*: speed ≤4.57/7 meter/seconds for height ≤159 cm speed ≤4.57/6 meter/seconds for height >159 cm *Men*: speed ≤4.57/7 meter/seconds for height ≤173 cm speed ≤4.57/6 meter/seconds for height >173 cm	Gait speed <1.0 meter/seconds
Weakness	Grip strength, stratified by gender and BMI quartiles. Cutoff for grip strength criteria for frailty *Women:* <= 17 kg for BMI <= 23 <=17.3 kg for BMI 23.1–26 <= 18 kg for BMI 26.1–29 <= 21 kg for BMI > 29 *Men:* <= 29 kg for BMI <= 24 <= 30 kg for BMI 24.1–26 <= 30 kg for BMI 26.1–28 <= 32 kg for BMI > 28	Grip strength: Same as in CHS	Grip strength Men: <26 kg Women: <18 kg

Notes: *BMI* body mass index (kg/m^2)

Recently, there have been trends toward classifying frailty into physical, psychological, cognitive, and social aspects; however, a standardized definition has not been established (Fig. 4.1) [9]. The CHS criteria are technically used for physical frailty. In this chapter, the focus will be placed on definitions within the more established physical frailty.

Depending on the frailty definition and evaluation tool, frailty prevalence ranges between 4.0% and 59.1% in community-dwelling people aged 65 years [10]. As the population ages, frailty represents increasingly important public health concerns and has an incremental effect on health expenditures [11]. Because of the major clinical, long-term care and economic burden, it is critical to find efficient, feasible, and cost-effective interventions to prevent or slow down frailty in order to avoid or diminish the adverse health outcomes, maintain or improve quality of life, and reduce disability and extended healthy life expectancy [12].

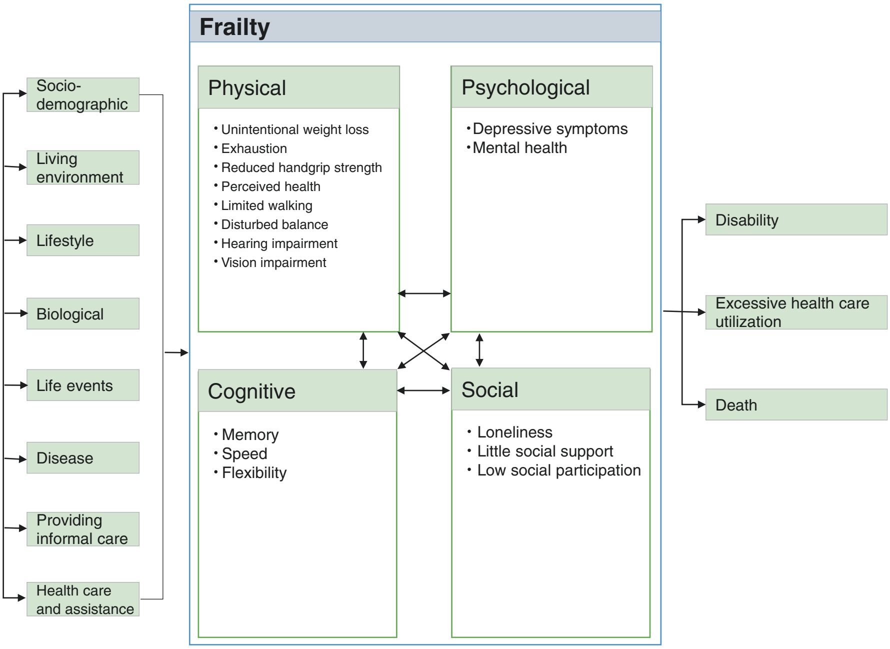

Fig. 4.1 Adapted version of integral conceptual model of frailty (cited from reference 9 published by BioMed Central)

4.2 Risk Factors

There are numerous factors that contribute to muscle weakness and loss of muscle mass in aging adults such as chronic disease, a sedentary lifestyle, and undernutrition, where some factors can be reversed with lifestyle changes and others need specific medications and cannot be reversed. Xue et al. hypothesized the cycle of frailty, as many of these factors can theoretically be unified into a cycle associated with decreasing energetics and functional reserve (Fig. 4.2). The core elements of this cycle, including weight loss, sarcopenia, decrease in strength and walking speed, as well as low activity, are commonly identified as clinical signs and symptoms of frailty [13].

4.3 Prevention Strategy

Declines in functional fitness such as walking speed and muscle strength and low physical activity in the elderly are strongly associated with the development of frailty. Hence, exercise and nutritional supplementation focusing on strength and mobility improvement, and physical activity increment even into advanced age, is usually offered as a strategy for the prevention and/or reduction of frailty in the elderly. Further, investigation into disability risk with each frailty criterion showed

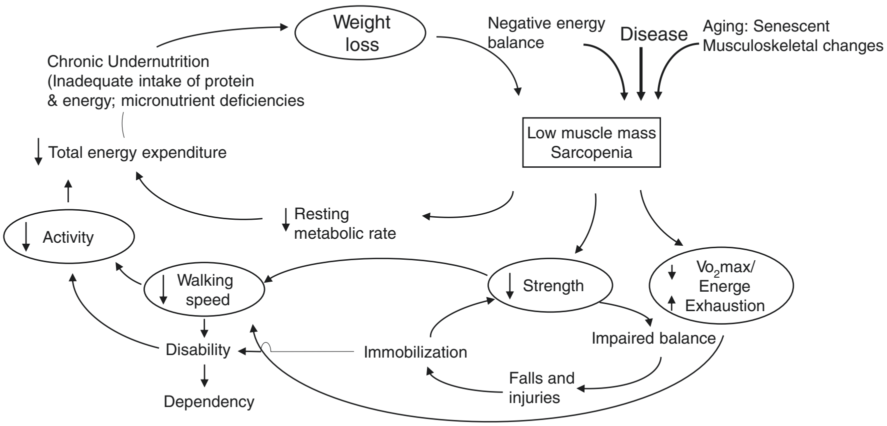

Fig. 4.2 Cycle of frailty [13] (Xue QL, Bandeen-Roche K, Varadhan R, Zhou J, & Fried LP (2008). Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, Vol 63A, No9, pp 984-990, by permission of Oxford University Press)

that declines in walking speed (HR = 2.32, 95% CI = 1.62–3.33), muscle strength decline (HR = 1.90, 95% CI = 1.35–2.68), and weight loss (HR = 1.61, 95% CI = 1.13–2.31) were most strongly associated with disability [14]. These findings show that frailty prevention should focus not only on walking ability and muscle strength but preventing unintentional weight loss as well. Out of many factors related with frailty, muscle disuse and nutritional deficiencies are potentially reversible or preventable through interventions and changes in lifestyle.

4.3.1 Nutritional Supplementation

Declines in muscle mass are related to declines in muscle protein synthesis rates in older adults. In order to resist and reverse the effects of muscle protein synthesis declines, protein or, more specifically, amino acids have been the focus of research. Investigators have found that leucine-enriched essential amino acid mixtures are primarily responsible for amino acid-induced muscle protein anabolism in the elderly. Amino acid supplementation can increase muscle mass in this population; however, an increase in muscle mass is not always accompanied by an increase in muscle strength [15]. Essential amino acid supplementation alone is probably insufficient in increasing muscle strength. Carbohydrate-rich supplements have also been examined for any effects on muscle strength and muscle mass. However, supplements rich in carbohydrates are inadequate for increasing muscle mass and strength [16]. There has been a peaked interest in other nutritional supplementations including protein, tea catechins, vitamin D, omega-3 fatty acids, and MFGM (milk fat globule membrane), as their efficacy in improving muscle mass and strength have been reported.

4.3.2 Exercise

There are several systematic reviews published on the benefits of exercise in frail elderly adults. Exercise in these individuals may potentially modify risk factors for age-associated reductions in muscle mass [17]. Research has shown that high-intensity resistance training is effective in counteracting muscle weakness and physical frailty in elderly people. Exercise interventions focusing on the major muscle groups that are crucial for performing functional activities are especially important for the reversal of muscle weakness.

Extensive research has confirmed that doing resistance training two to three times a week can improve physical function and functional limitations and also reduce disability and muscle weakness in older people. Resistance training in elderly people produces increases in strength from 9% to 15% [18] and about 1.1 kg in lean body mass [19]. More improvements are seen with high-intensity and high-volume resistance training. However, moderate-intensity exercises are also beneficial and are much safer for aging adults. Exercise prescriptions must be of a safe intensity, duration, and frequency to avoid further injury and complications [20].

4.3.3 Combination

Combinations of both exercise and nutritional supplementation have also been studied by researchers. Amino acid supplementations alone have beneficial effects such as increasing walking speed, and exercise, as we have previously seen, has beneficial effects of improving physical function as well. Exercise and amino acid supplementation together have significant effects in enhancing muscle mass, strength, and functional fitness [21]. The combination of high-resistance exercise and a high-carbohydrate mixture containing small amounts of soy protein is effective in the enhancement of muscle strength. High-resistance exercise alone increases both muscle mass and strength, while the carbohydrate supplementation alone does not [16]. In order to efficiently prevent frailty, more focus should be placed on eliminating variable factors within risk factors. Recent studies have shown that the combination of exercise and nutritional supplementation is more effective than exercise or nutrition alone.

4.4 Treatment Strategy

Exercise programs designed for frailty prevention and/or treatment in elderly people should address three major components – strength, gait, and muscle mass. People at high risk of frailty due to muscle weakness, gait deficit, and skeletal muscle mass decline should be instructed to perform low- or moderate-intensity exercise containing safe and simple movements at entry level.

In 2017, Dedyne et al. performed a systematic review to determine the effects of comprehensive intervention programs on the treatment of prefrailty and frailty [22]. A multi-domain intervention was defined as one that intervenes in at least two different domains, including exercise therapy, nutritional intervention (supplementation of proteins, vitamins, minerals, milk fat globule membrane, or nutritional advice), hormone supplementation, cognitive training, or psychosocial interventions. The review included 5500 studies published by September 14, 2016, with inclusion criteria as follows: (1) randomized controlled trials, quasi-experimental studies, or prospective or retrospective cohort studies with control groups, (2) testing of a multi-domain intervention to prevent or treat frailty in people aged, ≧65 years, (3) classification in terms of (pre)frailty status according to an operationalized definition, and (4) primary outcomes including one or more of the following – frailty status or score, muscle mass, strength or power, physical functioning, and cognitive or social outcomes. A total of 12 studies matched the criteria. On the other hand, Puts et al. discussed 14 studies found among 14,564 published between January 2000 and February 2016, in a coping review of frailty-related literature [23].

This chapter will provide an overview of some of the main studies within the 26 presented in the two aforementioned reviews (Table 4.2). However, because frailty criteria and main outcome variables differ depending on the publication, providing a comprehensive overview is difficult.

4.4.1 Intervention Characteristics

Although all studies labeled their participants as frail, there were subcategorizations including moderately frail, mild to moderate physical frail, risk of becoming frail, and prefrai1. Furthermore, many studies utilized one of the validated operational definitions of frailty: Fried's frailty phenotype [3], Speechley and Tinetti's classification of frailty and vigorousness [5], and Winograd's frailty scale [4]. In other studies, non-validated definitions of frailty were used. There are no standardized universal selection criteria used. These factors should be considered in the following summary of the interventions.

1. Frequency: The greater part of the exercise interventions was performed either twice or three times per week. Several studies increased the exercise frequency to five times or decrease to one time per week.
2. Intensity: In a few studies, the exercise intensity was evaluated using a perceived exertion scale. Most of the interventions that utilized a resistance training program reported intensity as three sets of eight repetitions at approximately 80% of the individual's one repetition maximum (1RM). Several resistance training programs compared low-intensity (20 and 40% 1RM) to high-intensity (80% 1RM) training and found that the changes in muscle strength and endurance were greater in the high-intensity group compared with low-intensity.

Table 4.2 Summary of study characteristics

Study	Country	Study participants	Intervention	Duration	Follow-up	Frequency	*N*	Frailty diagnostic tool
Chin A Paw et al. [32]	Netherlands	Frail, men and women, aged 78.7 (±5.6 yr)	Exercise: skill training Nutritional: fruit and daily products enriched with vitamin and minerals	17 weeks		2/week 45 min	157	Modified Chin A Paw frailty definition
Hennessey et al. [35]	USA	Moderately frail, men and women, aged 71.3 (±4.5) yr	Exercise: resistance training Growth hormone administration: 0.0025–0.0037 mg/kg/day	6 months		3/week 60 min	31	Physical performance test (PPT): score (12–28)/36
Rydwik et al. [27]	Sweden	Frail, men and women, aged 75+ (yr)	Exercise: aerobic, muscle strength, and balance training Nutritional: individual dietary counseling	12 weeks	6 months	2/week 60 min	96	Modified Chin A Paw frailty definition
Kenny et al. [25]	USA	(Pre) Frail, women, aged 76.6 (±6.0 yr)	Exercise: yoga or chair aerobics Nutritional: calcium and cholecalciferol Hormone: 50 mg/day DHEA	6 months		2/week 90 min	99	At least 1 of 5 Fried frailty criteria: population is at least prefrail
Tieland et al. [24]	Netherlands	(Pre)frail, men and women, aged 78 (±1.0 yr)	Exercise: resistance training Nutritional: 250 mL protein supplemented beverage with 15 g protein	24 weeks		2/week	62	1–2 (prefrail) or at least 3 (frail) of the Fried frailty phenotype criteria
Chan et al. [28]	Taiwan	(Pre)frail, men and women, aged 71.4 (±3.7 yr)	Exercise: resistance, postal control and balance training Nutritional: consultation	3 months	3, 9 months	3/week 60 min	117	3–6 on the Chinese-Canadian Study of Health and Aging Clinical Frailty Scale Telephone version and ≥1 of modified Fried frailty phenotype criteria
Cameron et al. [36]	Australia	Frail, men and women, aged 70+ (yr)	Exercise: home-based balance and mobility improvement training Nutritional: high-energy and high-protein supplements Encourage greater social engagement	3 months	9 months	3–5/week	241	The CHS criteria

Kim et al. [29]	Japan	Frail, women, aged 75+ (yr)	Exercise: comprehensive training Nutritional: milk fat globule membrane (1 g/day)	3 months	4 months	2/week 60 min	131	At least 3 of the modified Fried frailty phenotype criteria
Kwon et al. [33]	Japan	Prefrail, women, aged 70+ (yr)	Exercise: strength training Nutritional: education and cooking classes	3 months	6 months	1/week 60 min	89	Modified Fried frailty phenotype criteria
Ng et al. [34]	Singapore	(Pre)frail, men and women, aged 65+ (yr)	Exercise: home-based strength and balance training Nutritional: iron, folate, vitamin, and calcium supplement Cognitive: cognitive-enhancing activities	6 months	6 months	2/week 90 min	246	Fried frailty phenotype criteria
Luger et al. [38]	Austria	(Pre)frail, men and women, aged 65+ (yr)	Exercise: strength training Nutritional: dietary discussions, fluid intake, animal and plant protein intake, and energy intake	12 weeks		2/week 60 min	80	Prefrail or frail according to Frailty Instrument for Primary Care of the Survey of Health, Ageing, and Retirement in Europe
Tarazona-Santabalbina et al. [30]	Spain	Frail, men and women, aged 70+ (yr)	Exercise: multicomponent exercise (endurance, strength, coordination, balance and flexibility) Nutritional: nutritional information	24 weeks		2/week 60 min	100	Fried frailty phenotype criteria
Ikeda et al. [31]	Japan	(Pre)frail, men and women, aged 78.4 ± 7.8 yr and 80.4 ± 8.9 yr	Exercise: muscle strength and aerobic exercise Nutritional: 6-g amino acid	3 months		2/week	52	Fried frailty phenotype criteria

Notes: *yr* year, *PPT* physical performance test, *CHS* cardiovascular health study

However, improvements for functional ability were only marginally different between the two groups.

3. Duration: The duration of the interventions ranged from 3 to 12 months, and the most common duration was 3 months. The time per session ranged from 45 to 90 min, and the majority of the studies included interventions that lasted 60 min per session.
4. Type: Many of previous studies included multicomponent exercise intervention (usually focusing on resistance, balance, aerobic, and flexibility training), a few resistance training, and some other types of exercise interventions (walking exercise program, balance training, water exercise, tai chi, whole-body vibration exercise, and exercise using a horse-riding simulator).

4.4.2 Changes in the Components of the Frailty Phenotype

Fried et al. [3] described frailty in the Cardiovascular Health Study (CHS). More specifically, the Phenotypic Classification of Frailty (CHS-PCF) [3] includes five components: unintentional weight loss, muscle weakness, exhaustion, slow gait speed, and low physical activity. In the following sections, effects of exercise or nutrition supplementation trials in frail elderly on these components are described with detail.

4.4.2.1 Change in Muscle Mass (Unintentional Weight Loss)

Several studies examined muscle mass after an intervention (Table 4.3). Three studies observed treatment×time interactions. Tieland et al. [24] found that adding a protein and mineral supplementation to resistance exercise at increasing intensity significantly improved appendicular (exercise + protein, 20.1–21.0 kg; exercise + placebo, 19.3–19.1 kg, $P < 0.001$) and lean mass (exercise + protein, 47.2–48.5 kg; exercise + placebo, 45.7–45.4 kg, $P = 0.006$) post-intervention. Kenny et al. [25] found that adding a hormonal dehydroepiandrosterone intervention to an exercise and vitamin and mineral supplementation increased total lean mass post-intervention (exercise + DHEA, 39.6 ± 6.1 kg; exercise + placebo, 38.1 ± 5.2 kg, $P = 0.048$). However, there was no significant change in appendicular muscle mass. de Jong et al. [26] did not find significant changes in the comparison between all four groups, but a factorial analysis of the exercise group ($n = 75$; exercise alone and exercise + nutrition groups) and non-exercise group ($n = 68$; nutrition and control groups) showed significantly improved lean body mass in an exercise intervention combined with a protein, vitamin, and mineral supplementation intervention (+0.5 kg, $P = 0.02$) compared to no exercise or protein, vitamin, and mineral supplementation (−0.1 kg, $P = 0.60$). Several other studies also found significant improvements in within-group comparisons although significant interactions were not observed. Rydwik et al. [27] proposed that adding diet counseling and group session

Table 4.3 Summary of intervention impact on muscle mass

Study	Intervention group	Outcome and method	Impact of intervention	
			Post-intervention	Follow-up
de Jong et al. [26]	Nutrition: 58 Exercise: 55 Combination: 60 Control: 44	Lean body mass (kg); DXA	Exercise (0.2 ± 1.4 kg, $P<0.05$): significantly improved compared to control group (−0.5±1.4 kg) Exercise ($n=75$) vs. no exercise ($n=68$): exercise (+0.5 ± 1.2 kg, $P=0.02$), significantly improved compared to no exercise (−0.1 kg)	Not available data
Rydwik et al. [27]	Exercise + nutrition: 25 Nutrition: 25 Exercise: 23 Control: 23	FFM (kg) = (weight−fat mass) (fat mass = four skin folds using prediction equations)	NS	Within-group comparison: Exercise = −0.9 kg (95% CI = −1.7 to −0.2, $P<0.05$)
Kenny et al. [25]	Aerobics + placebo: 25 Aerobics + DHEA: 24 Yoga + placebo: 25 Yoga + DHEA: 25	Total and regional lean tissue mass (kg); DXA	Appendicular skeletal muscle mass: NS Lean mass: exercise + DHEA ($n=43$, 39.6 ± 6.1 kg), exercise + placebo ($n = 44$, 38.1 ± 5.2 kg), significant differences between groups ($P = 0.048$)	Not available data
Tieland et al. [24]	Exercise + protein: 31 Exercise + placebo: 31	Lean mass (kg); DXA	Treatment × time interactions; Lean mass: exercise + protein (47.2–48.5 kg), exercise + placebo (45.7–45.4 kg), $P = 0.006$ Appendicular lean mass: exercise + protein (20.1–21.0 kg), exercise + placebo (19.3–19.1 kg), $P < 0.001$	Not available data

(continued)

Table 4.3 (continued)

Study	Intervention group	Outcome and method	Impact of intervention	
			Post-intervention	Follow-up
Chan et al. [28]	Exercise + nutrition + PST: 28 Exercise + nutrition: 27 PST: 29 Control: 33	FFM (kg); BIA	Not available data	FFM: exercise (−0.46 ± 1.36 kg, $P < 0.05$), Non-exercise (−0.62 ± 1.84 kg, $P < 0.001$)
Kim et al. [29]	Exercise + nutrition: 33 Exercise + placebo: 33 Nutrition: 32 Placebo: 33	Appendicular skeletal (AS) and leg muscle mass (kg); DXA	Appendicular skeletal muscle mass: NS Leg muscle mass: Exercise + nutrition 2.4% (95% CI = 1.3–3.5)	Within-group comparison: AS mass: NS Leg muscle mass: Exercise + nutrition 3.2% (95% CI = 1.1–5.4), Exercise + placebo 3.2% (95% CI = 1.2–5.3)
Tarazona-Santabalbina et al. [30]	Exercise: 51 Control: 49	Lean mass (kg); BIA	NS	Not available data

Note: *DXA* dual X-ray absorptiometry, *FFM* fat-free mass, *BIA* bioelectrical impedance analysis, *PST* problem-solving therapy, *DHEA* dehydroepiandrosterone, *NS* not significant, *CI* confidence interval

education to physical training did not increase FFM post-intervention. Chan et al. [28] showed FFM declines in the exercise group (−0.46 ± 1.36 kg, $P < 0.05$) less than the non-exercise group (−0.62 ± 1.84 kg, $P < 0.01$)). Kim et al. [29] reported that leg muscle mass significantly increased in the exercise + nutrition group post-intervention, but post follow-up increases were also seen in the exercise + nutrition group as well as the exercise + placebo groups. Furthermore, Tarazona-Santabalbina et al. [30] found that adding exercise to nutritional advice and vitamin and mineral supplementation intervention did not significantly improve lean mass.

4.4.2.2 Change in Muscle Strength (Weakness)

Muscle strength was examined in many studies and in many ways: combining exercise and MFGM [29], exercise and BCAA [31], exercise and enriched foods [32], exercise and protein [24], exercise and cooking practice [33], exercise and diet counseling [27], exercise + nutritional supplementation + cognitive training [34], exercise and DHEA [25], and exercise and growth hormone [35] (Table 4.4). Among them, three studies showed treatment×time interaction.

Ng et al. [34] found in exercise + nutrition + cognitive, exercise alone, and cognitive alone showed significantly improved knee strength both at 6 months (cognitive = 2.18 kg, 95% CI = 1.08; 3.27; exercise = 2.75 kg, 95% CI = 1.66; 3.83; exercise + nutrition + cognitive = 2.67 kg, 95% CI = 1.58; 3.76) and at 12-month fol-

Table 4.4 Summary of intervention on muscle strength

Study	Intervention group	Outcome	Impact of intervention	
			Post-intervention	Follow-up
Chin A Paw et al. [32]	Exercise + enriched foods: 42 Exercise: 39 Enriched foods: 39 Control: 37	Upper (grip strength) Lower (quadriceps strength)	NS	Not available data
Hennessey et al. [35]	Exercise + growth hormone: 8 Growth hormone: 7 Exercise: 8 Control: 8	Lower (knee extension)	Exercise + growth hormone (+55.6%, $P = 0.0004$), exercise (+47.8%, $P = 0.0005$) significantly improved compared to baseline	Not available data
Rydwik et al. [27]	Exercise + nutrition: 25 Nutrition: 25 Exercise: 23 Control: 23	Upper (dips, Pulldown) Lower (leg press)	Within-group comparison Dips: exercise + nutrition (1.7 kg, 95% CI = 0.04; 3.4) and exercise (1.8 kg, 95% CI = 0.8; 2.8) change significantly improved Pulldown: exercise (3.4 kg, 95% CI = 0.9; 5.8) change significantly improved Leg press: exercise + nutrition (9 kg, 95% CI = 1.8; 16.2) and exercise (11.9 kg, 95% CI = 6.3; 17.5): change significantly improved	Within-group comparison Dips: NS Pulldown: exercise (2.7 kg, 95% CI = 0.9; 4.6) change significantly improved
Kenny et al. [25]	Aerobics + placebo: 25 Aerobics + DHEA: 24 Yoga + placebo: 25 Yoga + DHEA: 25	Upper (grip strength) Lower (leg press)	Grip strength: NS Leg press: treatment × time interactions (P=0.015) Exercise + DHEA (459 ± 121 N to 484±147 N, P <0.05) significantly improved compared to Exercise + placebo (477 ± 186 to 447±128 N, P <0.05)	Not available data
Tieland et al. [24]	Exercise + protein: 31 Exercise + placebo: 31	Upper (grip strength) Lower (leg press, leg extension)	NS	Not available data

(continued)

Table 4.4 (continued)

Study	Intervention group	Outcome	Impact of intervention	
			Post-intervention	Follow-up
Kim et al. [29]	Exercise + nutrition: 33 Exercise + placebo: 33 Nutrition: 32 Placebo: 33	Upper (grip strength) Lower (knee extension)	NS	NS
Kwon et al. [33]	Exercise: 28 Exercise + nutrition: 30 Control: 31	Upper (grip strength)	Within-group comparison Exercise + nutrition: NS Exercise (2.3 ± 3.1 kg, P <0.05) significantly improved compared to baseline	Within-group comparison Exercise (−0.3 ± 2.2 kg): NS Exercise+ nutrition (−2.1 ± 5.0 kg, P <0.05) significantly declined compared to post-intervention
Ng et al. [34]	Nutrition: 49 Cognitive training: 50 Exercise: 48 Combination: 49 Control: 50	Lower (knee extension)	Treatment × time interactions ($P = 0.009$) Within-group comparison: Significantly improved change compared between baseline and 6 months (cognitive = 2.18 kg, 95% CI = 1.08; 3.27), (exercise = 2.75 kg, 95% CI = 1.66; 3.83), (combination = 2.67 kg, 95% CI = 1.58; 3.76)	Treatment × time interactions ($P = 0.009$) Within-group comparison: Significantly improved change compared between baseline and 12 months (cognitive = 1.98 kg, 95% CI = 0.87; 3.09), (exercise = 1.41 kg, 95% CI = 0.31; 2.51), (combination = 2.35 kg, 95% CI = 1.25; 3.44)
Ikeda et al. [31]	Exercise + BCAA: 27 Control: 25	Upper (grip strength, rowing) Lower (leg press, hip abduction, knee extension)	Between group comparison Grip strength and rowing: NS Leg press: exercise + BCAA (13.9 ± 36.0%) significantly improved ($P = 0.032$) compared to control (2.7 ± 12.5%) Knee extension: exercise + BCAA (9.5 ± 26.3%) significantly improved ($P = 0.008$) compared to control (−0.8 ± 18.2%). NS for hip abduction	Not available data

Notes: *DHEA* dehydroepiandrosterone, *NS* not significant, *CI* confidence interval, *BCAA* branched-chain amino acids low-up (cognitive = 1.98 kg, 95% CI =0.87; 3.09; exercise = 1.41 kg, 95% CI =0.31; 2.51; exercise + nutrition + cognitive = 2.35 kg, 95% CI =1.25; 3.44) compared to the nutrition-alone and control group. Kenny et al. [25] found that adding a dehydroepiandrosterone (DHEA) supplementation (50 mg/day) to yoga or chair aerobics significantly improved leg press in exercise + DHEA (459 ± 121 N to 484 ± 147 N, $P < 0.05$) compared to exercise + placebo (477 ± 186 to 447 ± 128 N, $P < 0.05$) but not grip strength. Also, Ikeda et al. [31] found that adding the 6 g amino acid supplement to a strength, balance, and aerobic exercise intervention significantly improved leg press strength (13.9 ± 36.0%, $P = 0.032$) and knee extension strength (9.5 ± 26.3%, $P = 0.008$), but not for hip abduction strength, grip strength, and rowing. While interactions were not observed in these three studies, significant within-group improvements were reported. Rydwik et al. [27] found significantly improved leg press in both exercise + dietary counseling and exercise-alone groups (exercise + dietary counseling = 9.0 kg, 95% CI = 1.8–16.2; exercise = 11.9 kg, 95% CI = 6.3–17.5) and dips (exercise + dietary counseling = 1.7 kg, 95% CI = 0.04–3.4; exercise = 1.8 kg, 95% CI = 0.8–2.8) compared to baseline, but not significant at follow-up. Kwon et al. [33] found in the exercise alone group a significantly increased grip strength (2.3 ± 3.1 kg, $P < 0.05$), but no post-intervention significant increase were seen in the exercise + cooking class group. At 6-month follow-up, they found significantly declined grip strength in the exercise + cooking class group (−2.1 ± 5.0 kg, $P < 0.05$) compared to the exercise and control group. Hennessey et al. [35] found in exercise + growth hormone (+55.6%, $P = 0.0004$) and exercise alone (+47.8%, $P = 0.0005$) groups a significantly increased right knee extension strength at post-intervention.Some studies found no significant differences between baseline and post-intervention or follow-up: there was no significant effect in adding a milk fat globule membrane (MFGM) [29] or 15 g protein supplementation [24] to an exercise intervention. Chin A Paw et al. [32] found no significantly improved grip strength and quadriceps strength by an exercise or exercise combined with vitamin and mineral supplementation intervention compared to no exercise or nutritional alone intervention.

4.4.2.3 Change in Exhaustion

Three studies examined the effect of an intervention on exhaustion. Adding an exercise intervention to a MFGM supplementation or not and MFGM alone significantly improved exhaustion at follow-up ($P = 0.007$) [29]. However, two studies found no significant effect on exhaustion of adding dietary advices and PST to exercise [28] and multifactorial exercise intervention [36], respectively.

4.4.2.4 Change in Gait Speed

Eight studies measured gait speed (Table 4.5), and three found treatment×time interactions. Kim et al. [29] found that adding an exercise intervention to MFGM supplementation significantly improved usual walking speed (exercise + MFGM = 14.7 ± 4.1%,

Table 4.5 Summary of intervention on gait speed

Study	Intervention group	Outcome	Impact of intervention	
			Post-intervention	Follow-up
Chin A Paw et al. [32]	Exercise + enriched foods: 42 Exercise: 39 Enriched foods: 39 Control: 37	Usual walking speed	Exercise ($n = 81$, 0.06 ± 0.1 meter/seconds): significantly improved compared to no exercise ($n = 76$, 0.0 ± 0.04 meter/seconds, $P < 0.004$)	Not available data
Rydwik et al. [27]	Exercise + nutrition: 25 Nutrition: 25 Exercise: 23 Control: 23	Maximal walking speed	NS	NS
Kenny et al. [25]	Aerobics + placebo: 25 Aerobics + DHEA: 24 Yoga + placebo: 25 Yoga + DHEA: 25	Walking speed	NS	NS
Tieland et al. [24]	Exercise + protein: 31 Exercise + placebo: 31	Gait speed	NS	Not available data
Cameron et al. [36]	Multifactorial: 120 Control: 121	Gait speed	NS	Between group difference: intervention (−0.049 ± 0.183 meter/seconds) significantly improved compared to control (0.019 ± 0.230 meter/seconds), ($P = 0.02$)
Kwon et al. [33]	Exercise: 28 Exercise + nutrition: 30 Control: 31	Usual walking speed	NS	NS
Kim et al. [29]	Exercise + nutrition: 33 Exercise + placebo: 33 Nutrition: 32 Placebo: 33	Usual walking speed	Treatment × time interactions ($P = 0.005$) Exercise + nutrition (14.7 ± 4.1%, 95% CI = 6.4; 23.1) change significantly improved compared to nutrition (2.1 ± 1.9%, 95% CI = −1.8; 5.9) or placebo (3.6 ± 2.7%, 95% CI = −1.9; 9.1)	NS
Ng et al. [34]	Nutrition: 49 Cognitive training: 50 Exercise: 48 Combination: 49 Control: 50	Maximal walking speed	Treatment × time interactions: NS Within-group comparison: exercise (−1.29 m, 95% CI = −1.72; −0.85) significantly improved ($P<0.05$)	Treatment × time interactions: NS Within-group comparison, Exercise: 6 months (−1.10 m, 95% CI = −1.53; −0.67) and 12 months (−1.14 m, 95% CI = −1.58; −0.70) significantly improved ($P<0.05$)

Note: *DHEA* dehydroepiandrosterone, *NS* not significant, *CI* confidence interval

95% CI =6.4; 23.1) compared to MFGM (2.1 ± 1.9%, 95% CI = −1.8; 5.9) or placebo (3.6 ± 2.7%, 95% CI = −1.9; 9.1) ($P = 0.026$). Cameron et al. [36] did not find significant changes between baseline and 3 months. Baseline and 12-month comparisons showed that multifactorial interdisciplinary intervention (−0.049 ± 0.183 meter/seconds) significantly improved compared to control (0.019 ± 0.230 meter/seconds) ($P = 0.02$). Chin A Paw et al. [32] showed no significant changes when comparing four interventions. A two-factorial analysis between exercise ($n = 81$, exercise alone and exercise + enriched foods) and non-exercise ($n = 76$, enriched foods and control) revealed significant improvements in usual walking speed for exercise intervention (0.06 ± 0.1 meter/seconds) compared to no exercise (0.0 ± 0.04 meter/seconds, $P < 0.004$). In one study, although treatment × time interactions were not observed, within-group comparisons found significant changes. Ng et al. [34] found that while 3 months of strength and balance training significantly improved maximal walking speed (−1.29 m, 95% CI = −1.72; −0.85), there were no significant improvements in nutrition, cognitive, combined, and control groups. Further, only the exercise group significantly improved at the 6-month (−1.10 m, 95% CI = −1.53; −0.67) and 12-month (−1.14 m, 95% CI = −1.58; −0.70) follow-up. Adding nutritional advice and cooking class or protein supplementation to an exercise intervention showed no significant effect on gait speed, compared to exercise intervention alone [27, 33]. Also, adding a DHEA supplementation to yoga or chair aerobics exercise intervention showed no significant effect for walking speed [25].

4.4.2.5 Change in Physical Activity Level

Eight studies examined the effect interventions on physical activity level (Table 4.6). Adding an exercise intervention to nutritional advice and vitamin and mineral supplementation significantly improved low physical activity in exercise (485.6 ± 98.1) compared to the control (265.8 ± 46.1), $P < 0.001$ [30]. Low physical activity was also significantly improved by exercise alone or exercise combined with nutrition post-intervention and at 6-month follow-up. In addition, this increase remained in the exercise group compared to nutrition or control group [37]. Another three studies found no significant effect on physical activity level at post-intervention, but significantly increased physical activity level by a multifactorial exercise [36], exercise + MFGM [29], and nutrition-alone [34] intervention compared to the control group or baseline at follow-up. However, three studies found no significant effect on physical activity level of adding a hormone supplementation to exercise [25], adding dietary advices and PST to exercise [28], and adding a protein supplementation to exercise intervention Ikeda et al. [31], respectively.

Change in Frailty Status

Previous studies assessed the impact of a multi-domain intervention including exercise, nutritional supplementation, hormone supplementation, diet advice, cooking class, social support, and cognitive training on frailty status such as frail, prefrail, and robust (Table 4.7). Post-intervention, some studies found a significantly

Table 4.6 Summary of intervention on physical activity

Study	Intervention group	Outcome	Impact of intervention	
			Post-intervention	Follow-up
Rydwik et al. [37]	Exercise + nutrition: 25 Nutrition: 25 Exercise: 23 Control: 23	Classification of physical activity	Exercise and exercise + nutrition groups significantly increased compared to control group	Exercise group significantly improved compared to nutrition and control groups
Kenny et al. [25]	Aerobics + placebo: 25 Aerobics + DHEA: 24 Yoga + placebo: 25 Yoga + DHEA: 25	Physical activity scale (kcal/wk)	NS	Not available data
Chan et al. [28]	Exercise + nutrition + PST: 28 Exercise + nutrition: 27 PST: 29 Control: 33	International physical activity questionnaire short form Weekly energy expenditure	NS	NS
Cameron et al. [36]	Multifactorial: 120 Control: 121	Energy expenditure	NS	Low physical activity significantly improved in intervention (63%) compared to control (76%), and the between-group difference was 12.9% (95% CI = −25.2; −0.6, $P = 0.04$)
Kim et al. [29]	Exercise + nutrition: 33 Exercise + placebo: 33 Nutrition: 32 Placebo: 33	Three or more of the following activity: Regular walking, <once a week Regular exercise, no Hobbies activity, no Volunteering activity, no	NS	Low physical activity significantly improved in exercise + MFGM (36.4%) compared to exercise + placebo (9.1%), MFGM (9.4%), and control (9.1%) groups ($P = 0.004$)

Ng et al. [34]	Nutrition: 49 Cognitive training: 50 Exercise: 48 Combination: 49 Control: 50	31-item longitudinal aging physical activity questionnaire (self-reported)	NS	6 months: nutrition (mean change = 96.2, 95%Cl = 57.8; 134.7) significantly improved compared to baseline 12 months: nutrition (mean change = 110.1, 95%Cl = 71.9; 148.2) significantly improved compared to baseline
Ikeda et al. [31]	Exercise + BCAA: 27 Control: 25	Frenchay activities index	NS	Not available data
Tarazona-Santabalbina et al. [30]	Exercise: 51 Control: 49	Physical activity energetic expenditure	Exercise (485.6 ± 98.1) significantly improved compared to control group (265.8 ± 46.1), *P* <0.001.	Not available data

Notes: *NS* not significant, *BCAA* branched-chain amino acids, *CI* confidence interval, *MFGM* milk fat globule membrane

Table 4.7 Summary of intervention impact on frailty status

Study	Study participants	Intervention group	Outcome	Impact of intervention	
				Post-intervention	Follow-up
Cameron et al. [36]	Frail	Exercise (Multifactorial): 120 Control: 121	Frailty and mobility	NS	Frailty: Exercise (62%), Control (76%), % difference=14.7%, $P = 0.02$
Kim et al. [29]	Frail	Exercise + nutrition: 33 Exercise + placebo: 33 Nutrition: 32 Placebo: 33	Reversal rate of frailty status	Reversal rates: significantly higher in exercise + nutrition (57.6%) than nutrition (28.1%) or placebo (30.3%) groups, $P = 0.032$	Reversal rates: significantly higher in exercise + nutrition (45.5%) and exercise + placebo (39.4%) than placebo (15.2%) group, $P = 0.035$
Chan et al. [28]	Prefrail and frail	Exercise + nutrition + PST: 28 Exercise + nutrition: 27 PST: 29 Control: 33	Improvement of CHS criteria by at least one category	Improvement of one category: significantly higher in exercise + nutrition (45%) than non-exercise + non-nutrition (27%) group, $P = 0.008$	NS
Ng et al. [34]	Prefrail and frail	Nutrition: 49 Cognitive training: 50 Exercise: 48 Combination: 49 Control: 50	Reduction of frailty	Not available data	Frailty reduction: significantly higher in nutrition (35.6%), cognitive (35.6%), exercise (41.3%), and combination (47.8%) than control (15.2%) group, $P<0.01$
Luger et al. [38]	Prefrail and frail	Exercise + nutrition: 39 Social support: 41	Change of frailty prevalence	NS	Not available data

Note: *NS* not significant, *PST* problem-solving therapy, *CHS* cardiovascular health study improved frailty status or frailty criteria in the multi-domain intervention groups such as exercise + MFGM [29], exercise + nutrition + cognitive training [34], exercise + diet advices + PST [28], and exercise + diet advices + protein intake [37] compared to single-domain such as exercise-alone or nutrition-alone intervention groups or control group. The primary outcomes in two studies were frailty status reversal [29, 36], prefrail or frailty improvement in three studies [28, 34, 38], and, in one study, changes in frailty criteria [30].

Post-intervention results in one study showed significantly higher reversal rates in exercise + MFGM (57.6%) than MFGM alone (28.1%) or placebo (30.3%) groups ($P = 0.032$). Also, at 4-month follow-up, larger significant improvements were maintained in groups with an exercise intervention irrespective of their additional nutritional supplementation (exercise + MFGM = 45.5%, exercise + placebo = 39.4%) compared to placebo (15.2%) for frailty status ($P = 0.035$) [29]. In another study [36], participants of the multifactorial interdisciplinary intervention did not reverse frailty status at post-intervention. At 12-month follow-up, there was a lower prevalence of frailty in the intervention group (62%) compared with the control group (76%); the between-group difference in frailty was 14.7% (95% CI = 2.4–27.0, $P = 0.02$).

Chan et al. [28] found a significantly higher improvement of one category in exercise + diet advices group (45%) compared with non-exercise and nutrition group (27%) at post-intervention. But, participants of the exercise + diet advices + PST intervention did not maintain its significant larger improvement of frailty status at 6-month and 12-month follow-up compared to control or a PST intervention. Ng et al. [34], at 12-month follow-up, showed a significantly improved frailty status in nutrition (35.6%), cognitive (35.6%), exercise (41.3%), and combination (47.8%) than control (15.2%) group ($P < 0.01$).

At post-intervention, one study observed significantly lowering score assessed by Fried frailty criteria and Edmonton frailty scale in intervention groups compared to control group [30]. However, one study found no significant difference on frailty status between an exercise + nutrition (−17%) and a social support (−16%) intervention [38].

Overall, multi-domain interventions showed significantly larger improved frailty status and score compared to single-domain or control interventions.

4.5 Conclusion

Frailty is highly prevalent and associated with substantial morbidity and poor health outcomes. Various factors cause frailty in elderly people including chronic disease, lack of physical activity, malnutrition, and aging itself, some of which are unpreventable. Exercise and nutritional supplementation are among the beneficial treatments promoting healthy and independent lifestyles in the elderly. Evidence reveals that exercise targeted at reducing risk factors is an effective strategy for preventing and/or treating frailty in elderly people. Progressive and moderate-intensity exercise alone or combined with nutritional and hormone supplementation should be encouraged among elderly people to minimize the degenerative physical, psychological, social, and cognitive function that occurs with aging.

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