Does the Combination of Resistance Training and A Nutritional Intervention Have A Synergic Effect on Muscle Mass, Strength, and Physical Function in Older Adults? A Systematic Review and Meta-Analysis

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Abstract

Background: Health-promoting interventions are important to prevent frailty and sarcopenia in older adults. However, there is limited evidence that nutritional interventions yield additional effects when combined with resistance training. This systematic review and meta-analysis aimed to compare the effectiveness of nutritional interventions with resistance training and that of resistance training only.

Methods: Randomized controlled trials published in peer-reviewed journals prior to July 2020 were retrieved from databases and other sources. The articles were screened according to the inclusion and exclusion criteria. The methodological quality of the included studies was assessed using Cochrane's risk of bias tool 2. A meta-analysis was performed using the RevMan 5.4 program.

Results: A total of 26 studies were included in the meta-analysis. The results of the meta-analysis showed no significant differences between groups in lean body mass, appendicular skeletal muscle mass, hand grip strength, knee extension, chair stand test results, or the timed up-and-go test results. In the subgroup analysis regarding the types of nutritional interventions, creatine showed significant effects on lean body mass (n=3, MD 2.96, CI 0.76 to 5.16). Regarding the other subgroup analyses, there were no significant differences in the mean age or sex of the participants, type of nutritional intervention, or duration of intervention.

Conclusions: This meta-analysis showed that the addition of nutritional interventions to resistance training has no additional effect on body composition, muscle strength, or physical function. Only creatine showed synergistic effects with resistance training on muscle mass.

Trial Registration

CRD42021224843

Background

Age-related conditions and chronic diseases increase the risk of disability and dependence, which are considered nearly irreversible conditions. Increasingly more older adults are becoming interested in 'active aging', which refers to the process of optimizing opportunities for health, participation, and security later in life [1]. A growing research interest is the identification of factors that increase the risk of negative events and the development of preventive interventions against disability. In this context, frailty and sarcopenia have increasingly emerged as research interests.

Although there is still no consensus on the definition and measurement of frailty for diagnosis, frailty is defined as a geriatric condition characterized by a cumulative decline in functioning and accompanied by increased vulnerability to stressors and dependency [2]. In 2001, Fried et al. [3] suggested the following criteria of frailty as a physical phenotype, focusing on physiological components: unintentional weight loss, exhaustion, decreased physical activity, a slow walking speed, and muscle weakness. Rockwood and Mitnitski [4] introduced a frailty index based on the accumulation of age-related deficits. A recent consensus suggested more broadly that frailty is a multidimensional syndrome including sensory limitations, cognitive decline, mood-related conditions, changes in the social environment, comorbidities and disability in addition to physical impairment [5]. The specific pathological pathway of frailty remains unclear, but frailty has a biological component resulting from inflammation and cumulative cellular damage over one's lifetime. Although it occurs independently of chronological age, frailty is more prevalent in people of an older age; females; those who are living alone; those with low educational and socioeconomic statuses, multimorbidity, malnourishment, depression, polypharmacy, cognitive impairment, and a low physical activity level; and those who smoke and drink alcohol regularly [6–8].

Sarcopenia is considered a muscle disorder associated with poor muscle function; low muscle mass is considered a principal determinant. Although sarcopenia occurs in people who are not elderly, muscle mass decreases with age [9]. There are several operational definitions of sarcopenia; for example, the European working group on sarcopenia in older people defines sarcopenia as a combination of low muscle mass and strength and/or poor physical function [10]. Inconsistency in the definition leads to a wide range of prevalence rates, ranging from 9.9–40.4% [11]. Although the concepts of both frailty and sarcopenia are still being developed, the physical phenotypes of frailty, including low grip strength and slow gait speed described by Fried et al. [3] overlap substantially with those of sarcopenia [12]. In addition, as the etiology of frailty, such as inflammation, cellular damage, and protein degradation, is also related to that of sarcopenia, as sarcopenia is an essential component of physical frailty. Frailty with sarcopenia can result in falls and fractures, a loss of independence, disability, morbidities, social isolation, institutionalization, and hospitalization [6, 13, 14], which lead to increases in healthcare costs and social burden [15]. Physical frailty and sarcopenia are transitional processes that increase individuals' vulnerability to reduced functional capacity and adverse health outcomes. Issues related to healthcare and support for frail and sarcopenic older adults are expected to increase with population aging [16].

Health-promoting behaviors are important to prevent disability and dependence and to reduce the need for care [17]. Physical inactivity and malnutrition are common conditions in older adults and are major modifiable risk factors for frailty and sarcopenia [18, 19]. An increasing amount of research has suggested that physical inactivity can lead to the loss of muscle mass, decreases in muscle strength and poor physical performance. Several evidence-based systematic reviews and meta-analyses of RCTs have shown that exercise affects muscle mass, strength, and physical performance [17, 20]. For optimal effects, multimodal exercise combined with moderate- to high-intensity progressive resistance training and functional balance and mobility training at least twice a week for 30–45 minutes per session is recommended [19, 21].

Several nutrients, such as protein and vitamins D and E, have been known to affect anabolic stimuli, lead to the synthesis of muscle proteins, and protect against oxidative damage and the loss of muscle mass [22]. Although nutrition plays a key role in the pathogenesis of physical frailty and sarcopenia, the

effects of nutritional interventions on muscle mass, strength and physical function are unclear. A systematic review showed that exercise training, when combined with dietary supplementation, has been shown to yield additional effects on muscle mass, strength and physical performance in some studies, but the existing evidence was inconsistent [23]. A more recent systematic review and meta-analysis by Hita-Contreras et al. showed that nutritional interventions do not provide additional or synergistic benefits when combined with resistance exercise in terms of muscle strength and mobility improvements among older adults with sarcopenic obesity [20].

There is evidence suggesting that there is an interaction effect between exercise and various nutritional factors, particularly protein and some multinutrient supplements, that can slow age-related decline and preserve muscle function in older adults. However, whether this effect is a meaningful preventive effect on frailty and sarcopenia remains unclear. Some previous reviews did not provide a quantitative synthesis, combined community-dwelling and institutionalized populations, or included and analyzed diverse types of interventions together [17, 23, 24], making it difficult to interpret the results. Thus, we focused on the primary prevention and synergistic effects of nutritional interventions, that is, the changes in muscle function after resistance training and nutritional interventions, in healthy community-dwelling older adults. The aim of this systematic review and meta-analysis was to compare the combination of resistance training and nutritional interventions with resistance training only. A PRISMA checklist is represented in Additional file 1.

Methods

Search Strategy

Electronic databases and the reference lists of related studies were searched by two investigators. First, for the electronic search, MEDLINE (PubMed), Cochrane CENTRAL, and EMBASE were searched for articles published prior to July 2020 by entering the following combinations of keywords: (“nutrition” OR “food” OR “diet”) OR (“exercise” OR “resistance training”) AND “aged” AND (“muscle mass” or “skeletal muscle” OR “muscle strength” OR “physical performance” OR “physical functional performance” OR “walking speed” OR “gait speed”). Second, the reference lists of related studies were searched to identify additional articles. The searches were limited to articles published in the English language, studies involving humans, and RCTs. Only peer-reviewed articles were included, and grey literature such as dissertations, proceedings, and government reports was excluded.

Study Selection

The inclusion criteria for this systematic review were as follows: (a) studies including community-dwelling healthy older adults aged 60 or above; (b) those including experimental groups that underwent resistance training and nutritional interventions; (c) those including comparison groups that underwent resistance training only with or without a placebo supplement; (d) studies that reported the outcome measures of muscle mass, muscle strength, and physical functional performance; and (e) randomized controlled parallel-group trials with at least one arm. We included only studies in healthy subjects to reduce the level of heterogeneity between studies. We accepted the various authors’ own definitions of ‘healthy’. The experimental interventions included any form of resistance training and nutritional (dietary) interventions that involved repeated practice during standardized programs for the purpose of enhancing muscle mass, muscle strength, and physical function. Resistance training included multimodal exercises, including aerobic and balance exercises along with resistance exercises as well as resistance exercises only. Nutritional interventions were defined as those that provided at least one nutrient through nutritional supplementation or whole food to obtain biologically beneficial effects. There was no minimum duration of follow-up. However, all included trials had to report outcomes at a minimum of one time point after the completion of the intervention.

Articles were excluded if (a) the participants had malignant tumors, severe chronic diseases, or levels of frailty and sarcopenia that limited their physical activity, diet, and level of independence in daily life; (b) the study was conducted in an animal model; (c) the experimental intervention was combined with any other form of interventions such as medication and hormone therapy; (d) the nutritional intervention was designed for calorie intake reduction and weight loss; (e) the study evaluated the effectiveness of experimental interventions by only examining inflammatory factors or biological markers related to muscle synthesis, or (f) the study had a non-RCT design such as case reports or cohort studies without a comparison group.

Studies were selected based on the inclusion and exclusion criteria by two independent researchers; these researchers screened the studies according to the titles and abstracts of all studies and then reviewed full texts of the remaining studies. Disagreements between researchers were resolved by discussion.

Data Extraction

Two independent researchers extracted key data from the included articles in a standardized Excel sheet, and the results were cross checked. For each article, data about (a) the article, including the authors, year of publication, and country; (b) characteristics of the study population, including the number of participants, mean age, sex, health status, and attrition rate; (c) characteristics of the experimental intervention, including the contents of resistance training, contents of nutritional intervention, delivery mode, amount, frequency and duration of intervention, and treatment for comparison group; and (d) outcome evaluation, including the follow-up period, method of measurement, and all outcome measured. As the aim of the study was to compare the effects of the combination of resistance training and nutritional interventions with those of resistance training only on muscle mass, strength, and physical performance, when more than two groups were present, only the data regarding the two groups we intended to compare were recorded.

Assessment of Study Quality (Assessment of Risk of Bias)

Methodological quality was assessed using Cochrane’s risk of bias 2 (RoB2) tool by two independent researchers. The RoB2 tool consists of five domains: the randomization process, deviation from intended intervention, missing outcome data, measurement of outcome, and selection of the reported result. The risk of bias for each domain is evaluated as a “low risk”, “some concerns”, or a “high risk” by an algorithm with several signaling questions. Overall,

“low risk of bias” was recorded when the study was judged to have a low risk of bias for all domains, “some concerns” was recorded when the study was judged to have some concerns in at least one domain, and “high risk of bias” was recorded when the study was judged to have a high risk of bias in at least one domain. This process was carried out by two independent researchers, and inconsistencies on items were resolved through discussion.

Data Synthesis and Statistical Analysis

The effect sizes of the combination of resistance training and a nutritional intervention were calculated using the mean difference (MD) or standardized MD (SMD) for continuous outcome data for muscle mass, muscle strength, and physical functional performance. When a study provided data on more than one outcome for the same construct (ex: timed up-and-go and 4 m walk tests for physical functional performance), the valid, reliable and commonly used measures for frailty and sarcopenia were selected by reviewing the associated literature and considering the frequencies of their use in the included studies. As a result, lean body mass and appendicular skeletal muscle mass were selected for muscle mass, grip strength and knee extension for muscle strength, and the chair stand and timed up-and-go tests for physical functional performance. Fat-free mass was included in the analysis when lean body mass was not available. Both isometric strength and isotonic strength in knee extension were included, and when both of them were measured in the same study, isotonic strength was selected.

In addition, if a study used different lengths of intervention and follow-up periods, we used the outcome values at the postintervention endpoint. When only the mean change scores and standard deviation (SD) of each group were available, they were used instead of the postintervention endpoint mean and SD for the mean difference. SMDs were used for studies using different units (scale) of the same measure (ex: kg and Nm for strength). If there were more than two groups that could be considered experimental groups in the study, the group corresponding to the treatment that was expected to be more effective under the hypothesis or the group with a higher intensity of intervention was included as an experimental group in the meta-analysis. Studies for which we could not identify the outcome data necessary for quantitative synthesis after contacting the authors were excluded from this meta-analysis.

Individual MDs and SMDs were pooled using random-effects models and the inverse variance method. The statistical significance of each effect size and overall effect size were checked using 95% confidence intervals. The chi-squared test and Higgin’s I^2 test were used to examine between-trial heterogeneity. When the p value for the chi-squared test was less than 0.1 and I^2 was greater than 50%, heterogeneity was considered present. Subgroup analysis was conducted by the nutritional intervention type (creatine, multinutrients, protein, and vitamin D), duration of intervention (< 16 weeks and ≥ 16 weeks), and participant type (< 70 years and ≥ 70 years; female, male, and mixed). All subgroup differences were tested regarding the significance of the effect sizes and heterogeneity. All analyses were conducted using Review Manager (RevMan) 5.4.

Results

Search Results

Figure 1 demonstrates the study selection process. After duplicates were removed, 3,638 articles remained. After 3,549 articles were excluded through title and abstract review, the full texts of 89 articles were reviewed. Sixty-two articles were additionally excluded, and consequently, 27 articles (26 RCTs in 27 papers) were included in this systematic review; among the 27 articles, two articles reported information from the same RCT [25, 26]. In some papers, the necessary values for meta-analysis could not be identified, so 26 articles were included in the quantitative synthesis.

Description of Included Studies

Table 1 shows the characteristics of the included studies. Six RCTs were conducted in Canada, six in Japan, three in Brazil, three in the UK, two in the Netherlands, and one each in Australia, Chile, Iceland, Norway, Sweden, and the USA; the studies were published between 2001 and 2020. The sample sizes ranged from 18 to 161. Six studies were conducted in males only, five studies were conducted in females only, and 15 studies were conducted in both males and females. There were 12 studies with a mean age of participants of less than 70 years and 14 studies with a mean age of more than 70 years.

Table 1
Summary of included study characteristics

First author (year), study location	Sample characteristics: n, mean age ± SD, sex (female ratio)	Intervention group		Control group†	Follow-up period (weeks)	Body composition assessment method	Muscle strength assessment method	Physical performance assessment method
		Exercise	Nutrition					
Aguiar (2013), Brazil	I: 9, 64 ± 4, female C: 9, 65 ± 6, female	Resistance training using machines, 60 min sessions, 3 times a week, for 24 weeks	5g Creatine monohydrate, once a day, for 12 weeks	Placebo: maltodextrin	24	Body mass Fat free mass Muscle mass	Bench press Biceps curl Knee extension	Chair stand
Aoki (2018), Japan	I: 43, 68.8 ± 5.3, mixed (74.4%) C: 45, 71.2 ± 6.8, mixed (75.6%)	Lower body resistance training, daily	25mcg vitamin D3 (1000 IU), divided into 3 times, daily	Usual diet	24	BMI Lower limb muscle mass	Hip flexion Knee extension	Chair stand Single leg stance Two step test Functional reach test
Arnarson (2013), Iceland	I: 83, 73.3 ± 6, mixed (*unknown*) C: 78, 74.6 ± 5.8, mixed (*unknown*)	Resistance training using machines, 3 times a week	20g of whey protein 3 times a week	Placebo: 250ml isocaloric carbohydrate drink	12	ASMM Lean body mass	Grip strength Knee extension	TUG 6-min walk
Bjørnsen (2016), Norway	I: 17, 69 ± 7, male C: 17, 67 ± 5, male	Free weight exercises, 3 times a week	500mg vitamin C and 117.5 mg vitamin E, twice a day	Placebo: cellulose and dicalsium phosphate	12	Lean body mass Muscle thickness	Biceps curl Knee extension Leg press	-
Bobeuf (2011), Canada	I: 14, 64.3 ± 3.8, mixed (50%) C: 17, 67 ± 3.7, mixed (52.9%)	Resistance training, 60 min sessions, 3 times a week	1000mg vitamin C ascorbate and vitamin E, once a day	Placebo: 100mg lactose	24	ASMM Muscle mass	-	-
Brose(2003), Canada	I: 14, 69.6 ± 5.4, mixed (42.8%) C: 14, 69.1 ± 4.8, mixed (50%)	Resistance training using machines, 3 times a week	5g creatine and 2g dextrose, once a day	Placebo: 7g dextrose	14	Fat free mass	Grip strength Knee extension Leg press	-
Bunout (2006), Chile	I: 24, 78 ± 4, mixed (91.6%) C:24, 76 ± 4, mixed (87.5%)	Multimodal exercise: strength, balance and aerobic training, 90 min sessions, biweekly	800mg calcium and vitamin D3 400IU, once a day	800mg calcium	36	-	Grip strength Knee extension Leg press	Body sway Romberg ratio SPPB TUG 12-min walk
Chrusch (2001), Canada	I:16, 70.4 ± 6.4, male C:14, 71.1 ± 6.7, male	Resistance training using machines, 3 times a week	Creatine supplement: 0.3g/kg/day for the first 5 days(loading phase) and 0.07g/kg/day thereafter, once a day, for 11 weeks	Placebo: sucrose-flour mixture	12	Lean body mass	Bench press Knee extension Leg press	-

†The resistance exercise of the control group applied in the same manner as in the experimental group.

† The duration of intervention in most studies were the same as the follow-up period.

‡ ASMM: appendicular skeletal muscle mass, BMI : body mass index, C: control group, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, I: intervention group, SMI; skeletal muscle massi index, SPPB: short physical performance battery, TUG: time up and go

First author (year), study location	Sample characteristics: n, mean age ± SD, sex (female ratio)	Intervention group		Control group†	Follow-up period (weeks)	Body composition assessment method	Muscle strength assessment method	Physical performance assessment method
		Exercise	Nutrition					
Cornish (2018), Canada	I:11, 71.4 ± 6.2, male C:12, 70.9 ± 5, male	Resistance training, 60 min sessions, 3 times a week	3.0g omega-3 fatty acid combined 1.98g EPA and 0.99g DHA, once a day	Placebo: 3.0g omega 3-6-9 blend	12	Body mass Lean body mass	Chest press Leg press	TUG 6-min walk
Da Boit (2017), UK	I: 27, 70.1 ± 4, mixed (48.1%) C: 23, 70.9 ± 4.2, mixed (43.4%)	Lower body resistance training, twice a week	3.0g omega–3 fatty acids containing 2.1g EPA and 0.6g DHA, once a day	Placebo: 3.0g safflower oil	18	Muscle anatomic cross-sectional area	Knee extension	Chair stand SPPB 4m walk
Dulac(2020), UK	I: 21, 68.3 ± 5.3, male C: 19, 70.7 ± 8.6, male	Resistance training with functional exercises, 60 min sessions, 3 times a week	Fast-whey protein: 10g milk proteins, 3 times a day	Placebo: isocaloric maltodextrin	12	Lean body mass Fat mass Lower limb lean mass	Grip strength	Chair stand Stair climb Standing balance TUG 4m walk
Edholom (2017), Sweden	I: 20, 67.2 ± 1.3, female C: 17, 67.9 ± 2.1, female	Resistance training, 60 min sessions, twice a week	Healthy diet : following a dietary consultation and a diet plan with the current dietary guidelines in Europe and US	Usual diet	24	Lean body mass	Knee extension Leg press	Chair stand Single leg stance Squat jump TUG
Formica (2020), Australia	I: 77, 71.2 ± 4.0, mixed (62%) C: 77, 70.3 ± 4.3, mixed (62%)	Multimodal exercise: aerobic, resistance, balance and mobility training, 60 ~ 75min sessions, 3 times a week	~ 220g of lean red meat or 160g of cooked red meat, twice a day-across 2 meals, 3 times a week	Usual diet	24	ASMM Lean body mass Lower limb lean mass Upper limb lean mass	Knee extension Leg press	Chair stand TUG 4m walk 4-square step test

†The resistance exercise of the control group applied in the same manner as in the experimental group.

† The duration of intervention in most studies were the same as the follow-up period.

‡ ASMM: appendicular skeletal muscle mass, BMI : body mass index, C: control group, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, I: intervention group, SMI; skeletal muscle massi index, SPPB: short physical performance battery, TUG: time up and go

First author (year), study location	Sample characteristics: n, mean age ± SD, sex (female ratio)	Intervention group		Control group†	Follow-up period (weeks)	Body composition assessment method	Muscle strength assessment method	Physical performance assessment method
		Exercise	Nutrition					
Holwerda (2018), Netherlands	I: 21, 69 ± 4.6, male C: 20, 71 ± 4.5, male	Resistance exercise training, 3 times a week	21g leucine-enriched whey protein (3g total leucine), once a day	Placebo	12	ASMM BMI Body mass Fat mass Lean body mass	Knee extension Leg press	Chair stand SPPB 4m walk
Kawada (2013), Japan	I: 13, 67 ± 3, mixed (61.5%) C: 13, 70 ± 1, mixed (53.8%)	Low-intensity resistance training, twice a week	3.0g essential amino acid supplements with milk, twice a day	Placebo: 3g dextrin-contained powder with milk, once a day	24	Cross sectional area of Psoas major muscle	-	Gait speed Obstacle course walk 6-min walk
Kirk (2019), UK	I: 22, 69 ± 6, mixed (59.1%) C: 24, 66 ± 4, mixed (50%)	Resistance exercise and functional exercise with dancing, 50 min sessions, twice a week	Whey protein (0.5g/kg/meal) mixed with leucine(0.03g/kg/meal), 3 times a day	Usual diet	16	BMI	Leg press Chest press Biceps curl	Obstacle course walk SPPB 6-min walk
Kirk (2020), UK						Fat mass Muscle mass SMI	Grip strength Knee extension Knee flexion	-
Leenders (2013), Netherlands	I: 27,70.9 ± 5.4, mixed (44.4%) C: 26, 69.5 ± 3.6, mixed (46.2%)	Resistance training, 3 times a week	15g milk protein, once a day	Placebo: 7.13g lactose and 0.42g calcium only	24	BMI Lean body mass Lower limb lean mass	Grip strength Leg press	Chair stand
Mori (2018), Japan	I: 25, 70.6 ± 4.2, female C: 25, 70.6 ± 4.2, female	Resistance training, twice a week	25g leucine enriched whey protein, once a day	Usual diet	24	BMI Lower limb lean mass SMI Upper limb lean mass	Grip strength Knee extension	Gait speed
Nabuco (2018), Brazil	I: 23, 66.2 ± 9.4, female C: 23, 66.5 ± 7.2, female	Resistance training, 3 times a week	27.1g whey protein, 3 times a week	Placebo: maltodextrin drink	12	Lower limb lean mass Skeletal muscle mass Upper limb lean mass	Biceps curl Chest press Knee extension	Chair stand Gait speed

†The resistance exercise of the control group applied in the same manner as in the experimental group.

† The duration of intervention in most studies were the same as the follow-up period.

‡ ASMM: appendicular skeletal muscle mass, BMI : body mass index, C: control group, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, I: intervention group, SMI; skeletal muscle massi index, SPPB: short physical performance battery, TUG: time up and go

First author (year), study location	Sample characteristics: n, mean age ± SD, sex (female ratio)	Intervention group		Control group†	Follow-up period (weeks)	Body composition assessment method	Muscle strength assessment method	Physical performance assessment method
		Exercise	Nutrition					
Nagai (2019), Japan	I: 17, 72.7 ± 1.4, mixed (64.7%) C: 19, 73.5 ± 2.3, mixed (68.4%)	Latex band training, squat, and tai chi, 90 min sessions, once a week	60mg maslinic acid, once a day	Placebo: jelly without maslinic acid	12	BMI Body mass Fat mass Fat free mass Skeletal muscle mass Segmental muscle mass	Grip strength	Chair stand Gait speed
Nakayama (2020), Japan	I: 61, 71.4 ± 6.2, mixed (74%) C: 61, 70.4 ± 5.5, mixed (77%)	Body weight exercises and 5 medicine ball exercises, daily	Low-dose milk protein: 10.1 g protein, once a day	Placebo: Isocaloric carbohydrate	24	Body mass Fat mass Lean body mass	Grip strength Knee extension Knee flexion Push up	Chair stand Gait speed TUG
Nilsson (2020), Canada	I: 16, 77.4 ± 11.2, male C: 16, 74.4 ± 5.2, male	Home based resistance training with elastic bands, 3 times a week	Multi nutrients: 24g whey protein, 16g micellar casein contained 416 mg calcium, 3g creatine, vitamin D 1000IU, and omega-3 fish-oil containing 1.51g EPA and 0.95g DHA, once a day	Placebo: collagen and sunflower oil	12	ASMM Body mass BMI Lean body mass	Grip strength Knee extension Leg press	Chair stand SPPB Stair climb TUG 4m walk
Seino (2018), Japan	I: 40, 73.4 ± 4.3, mixed (85%) C: 40, 73.7 ± 4.3, mixed (82.5%)	Weight-bearing exercise and exercises using a resistance band and Pilates ball, 60min sessions, twice a week	Fortified milk containing 10.5 g total milk protein, 3.9 g fat, 9.3 g carbohydrate, and 337 mg calcium at lunch and micronutrient beverage at breakfast, daily	Usual diet	12	Body mass Lean body mass Lower limb lean mass SMI	Grip strength Knee extension	Chair stand Gait speed One leg standing with eyes open TUG
Stout (2013), USA	I: 24, 73 ± 4.9, mixed (54.2%) C: 24, 73 ± 4.9, mixed (54.2%)	Resistance exercise, three times a week for 21 weeks	1.5g calcium and 4g carbohydrate, twice a day	Placebo: 200mg calcium and 4g carbohydrate	24	Lean body mass Lower limb lean mass Upper limb lean mass	Grip strength	Chair stand
Sugihara (2018), Brazil	I: 15, 67.4 ± 4.1, female C: 16, 67.8 ± 4.1, female	Resistance training using a combination of free weights and machines, 45 ~ 50min sessions, 3 times a week	35g whey protein, immediately after each resistance training	Placebo: 35g maltodextrin	12	Body mass BMI Lower limb lean mass SMI Upper limb lean mass	Biceps curl Chest press Knee extension	-

†The resistance exercise of the control group applied in the same manner as in the experimental group.

† The duration of intervention in most studies were the same as the follow-up period.

‡ ASMM: appendicular skeletal muscle mass, BMI : body mass index, C: control group, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, I: intervention group, SMI; skeletal muscle massi index, SPPB: short physical performance battery, TUG: time up and go

First author (year), study location	Sample characteristics: n, mean age ± SD, sex (female ratio)	Intervention group		Control group†	Follow-up period (weeks)	Body composition assessment method	Muscle strength assessment method	Physical performance assessment method
		Exercise	Nutrition					
Tarnopolsky (2007), Canada	I: 21,70.7 ± 4.5, mixed (47.6%)	Resistance exercise using machines, twice a week	5g creatine monohydrate and 6g conjugated linoleic acid, once a day	Placebo: dextrose and safflower oil	24	Body mass BMI	Biceps curl Chest press	Chair stand Gait speed Stair climb Standing balance
	C: 18, 71.1 ± 5.5, mixed					Fat free mass	Knee extension Leg press	
	(55.6%)							
†The resistance exercise of the control group applied in the same manner as in the experimental group.								
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All of the studies administered supervised exercise programs except one study [27], which included a home-based exercise program with consistent encouragement. The exercise programs included resistance training in 21 studies and multimodal exercise including aerobic, balance, or functional training and resistance training in 5 studies. In almost all the studies, the exercise programs were performed twice (7 studies) or three times (15 studies) a week on nonconsecutive days; the exercise programs were performed daily in two studies, once a week in one study, and biweekly in one study.

The RCTs provided protein (ten studies), creatine (three studies), long chain n-3 polyunsaturated fatty acids (PUFA omega-3) (two studies), calcium (a study), maslinic acid (a study), vitamin D (two studies), vitamins C and E (two studies), linoleic acid and creatine (a study), and multinutrients containing more than three nutrients (four studies). Most studies provided nutritional supplements in pill, capsule, powder or drink forms. A study provided a diet with red meat [28], and another study provided a personalized and nutritionally balanced diet [29]. Most studies provided the control groups with an isocaloric placebo. Three studies provided the control groups with pills or capsules containing some nutrients, such as calcium or omega-3 [30–32]. The intervention period ranged between 12 and 36 weeks: 12 weeks in 12 studies, 14 weeks in one study, 16 weeks in one study, 18 weeks in one study, 24 weeks in ten studies, and 36 weeks in one study.

Risk of Bias

The risk of bias results for the 26 RCTs are demonstrated in Fig. 2. Regarding the randomization process, eight studies had a low risk of bias, 17 had some concerns, and one study had a high risk of bias because of a failure to conceal group allocation. Regarding deviation from the intended intervention, three had some concerns, and the others had a low risk of bias. As there were no studies in which missing values were judged to have an impact on the study results, all studies had a low risk of bias in the domain of missing outcome data. All studies had a low risk of bias in the domain of measurement of outcome, either because the outcome assessor was blinded or the outcome assessor's awareness of the group assignments was judged to not affect the measurement of muscle mass, strength, or physical function. In the fifth domain, the selection of the reported results, 11 studies had a low risk of bias, while the other 15 studies had some concerns because of the absence of a prespecified trial protocol. Overall, six RCTs had a low risk of bias, 19 RCTs had some concerns, and one study had a high risk of bias.

Effects of Resistance Training and Nutritional Interventions Compared with Those of Resistance Training Only on Muscle Mass, Muscle Strength, and Physical Functional Performance

The effect sizes and 95% confidence intervals (CIs) for individual studies and all studies are shown in Fig. 3. The results of the meta-analysis showed no significant effects on lean body mass (n = 13, MD 0.12, CI -0.46 to 0.7), appendicular skeletal muscle mass (n = 6, MD -0.01, CI -0.26 to 0.24), hand grip strength (n = 11, SMD 0.08, CI -0.09 to 0.24), knee extension strength (n = 16, SMD 0.08, CI -0.05 to 0.21), the chair stand test results (n = 7, MD -0.13, CI

-0.44 to 0.17), or the timed up-and-go test results (n = 9, MD zero, CI -0.17 to 0.17). The I^2 values for all outcomes except lean body mass were zero, indicating that heterogeneity was low for these outcomes and lean body mass had moderate heterogeneity (I^2 = 40%).

Subgroup Analysis According to the Characteristics of the Participants and Interventions

The results of the subgroup analyses are shown in Tables 2–4. The subgroup analyses for lean body mass showed significant differences between the types of nutritional interventions (Chi^2 = 9.02, p = .01). Among the nutritional interventions, only those with creatine showed significant effects on lean body mass (n = 3, MD 2.96, CI 0.76 to 5.16). Regarding the other subgroup analyses, there were no significant differences according to the mean age and sex of the participants, type of nutritional intervention, or duration of intervention.

Table 2
Summary of over effects and subgroup analyses results for muscle mass

Subgroups	Lean body mass					Appendicular skeletal muscle mass				
	n	MD	95% CI	I^2	Subgroup differences	n	MD	95% CI	I^2	Subgroup differences
Overall	13	0.12	-0.46 ~ 0.7	40%	-	6	-0.01	-0.26 ~ 0.24	0%	-
Participant mean age										
< 70	5	0.39	-1.58 ~ 2.35	57%	χ^2 = 0.07 (p = .79)	2	-0.89	-2.46 ~ 0.68	0%	χ^2 = 1.24 (p = .27)
≥ 70	8	0.11	-0.40 ~ 0.62	32%		4	0.01	-0.24 ~ 0.27	0%	
Participant sex										
Male	8	-0.42	-2.73 ~ 1.88	25%	χ^2 = 0.86 (p = .65)	2	-0.04	-2.27 ~ 2.19	65%	χ^2 = 0.00 (p = .97)
Female	3	0.89	-1.10 ~ 2.88	58%		0	-	-	-	
Mixed	4	0.03	-0.24 ~ 0.31	0%		4	-0.00	-0.26 ~ 0.26	0%	
Nutrition type										
Creatine	3	2.96	0.76 ~ 5.16	10%	χ^2 = 9.02 (p = .01)	-	-	-	-	χ^2 = 0.62 (p = .43)
Multi-nutrients	3	0.19	-0.16 ~ 0.55	0%		2	0.39	-0.68 ~ 1.45	0%	
Protein	5	-0.18	-0.54 ~ 0.17	0%		2	-0.20	-1.23 ~ 0.82	47%	
Duration of intervention										
≤ 14	10	0.47	-0.64 ~ 1.55	51%	χ^2 = 0.24 (p = .62)	4	0.08	-0.23 ~ 0.40	0%	χ^2 = 1.02 (p = .31)
≥ 16	3	0.18	-0.18 ~ 0.53	0%		2	-0.19	-0.63 ~ 0.24	0%	

Table 3
Summary of over effects and subgroup analyses results for muscle strength

Subgroups	Hand grip strength					Knee extension strength				
	n	SMD	95% CI	I^2	Subgroup differences	n	SMD	95% CI	I^2	Subgroup differences
Overall	11	0.08	-0.09 ~ 0.24	0%	-	16	0.08	-0.05 ~ 0.21	0%	-
Participant mean age										
< 70	4	0.10	-0.21 ~ 0.41	0%	$\chi^2 = 0.02$ ($p = .88$)	7	0.07	-0.21 ~ 0.35	26%	$\chi^2 = 0.00$ ($p = .96$)
≥ 70	7	0.07	-0.13 ~ 0.27	0%		9	0.09	-0.06 ~ 0.25	0%	
Participant sex										
Male	5	0.08	-0.36 ~ 0.53	38%	$\chi^2 = 0.31$ ($p = .86$)	6	0.04	-0.27 ~ 0.35	0%	$\chi^2 = 0.80$ ($p = .67$)
Female	4	-0.06	-0.44 ~ 0.31	0%		6	0.20	-0.14 ~ 0.53	18%	
Mixed	5	0.04	-0.18 ~ 0.27	0%		7	0.06	-0.11 ~ 0.22	0%	
Nutrition type										
Multi-nutrients	2	-0.04	-0.48 ~ 0.40	21%	$\chi^2 = 0.10$ ($p = .75$)	2	0.05	-0.36 ~ 0.46	12%	$\chi^2 = 1.27$ ($p = 53$)
Protein	5	0.04	-0.19 ~ 0.26	0%		7	-0.02	-0.20 ~ 0.16	0%	
Vitamin D	-	-	-	-		2	0.20	-0.14 ~ 0.54	0%	
Duration of intervention										
≤ 14	5	0.14	-0.13 ~ 0.41	0%	$\chi^2 = 0.34$ ($p = .56$)	8	0.11	-0.08 ~ 0.31	4%	$\chi^2 = 0.17$ ($p = .68$)
≥ 16	6	0.04	-0.17 ~ 0.25	0%		8	0.06	-0.13 ~ 0.24	0%	

Table 4
Summary of over effects and subgroup analyses results for physical functional performance

Subgroups	Chair stand test					Timed up and go test				
	n	MD	95% CI	I^2	Subgroup differences	n	MD	95% CI	I^2	Subgroup differences
Overall	7	-0.13	-0.44 ~ 0.17	0%	-	9	0.00	-0.17 ~ 0.17	0%	-
Participant mean age										
< 70	2	-0.44	-1.08 ~ 0.20	0%	$\chi^2 = 1.11$ ($p = .29$)	1	0.01	-0.17 ~ 0.18	0%	$\chi^2 = 0.06$ ($p = .80$)
≥ 70	5	-0.05	-0.39 ~ 0.30	0%		8	0.00	-0.17 ~ 0.17	0%	
Participant sex										
Male	3	-0.35	-0.95 ~ 0.25	0%	$\chi^2 = 1.17$ ($p = .56$)	3	0.23	-0.25 ~ 0.72	0%	$\chi^2 = 1.00$ ($p = .32$)
Female	2	-0.39	-1.27 ~ 0.49	0%		0	-	-	-	
Mixed	3	-0.02	-0.40 ~ 0.35	0%		6	-0.03	-0.22 ~ 0.15	0%	
Nutrition type										
Multi-nutrients	2	0.15	-0.41 ~ 0.72	0%	$\chi^2 = 1.1$ ($p = .29$)	3	0.13	-0.25 ~ 0.52	9%	$\chi^2 = 0.73$ ($p = .39$)
Protein	3	-0.22	-0.63 ~ 0.19	0%		3	-0.06	-0.28 ~ 0.16	0%	
Duration of intervention										
≤ 14	4	-0.10	-0.53 ~ 0.32	0%	$\chi^2 = 0.04$ ($p = .84$)	5	0.07	-0.17 ~ 0.31	0%	$\chi^2 = 0.62$ ($p = .43$)
≥ 16	3	-0.16	-0.60 ~ 0.27	0%		4	-0.07	-0.31 ~ 0.17	0%	

Sensitivity Analysis

Sensitivity analysis was conducted to compare the effect sizes, CIs, and I^2 values by excluding three studies that provided some nutrients to control groups. There were no significant differences in lean body mass (n = 12, MD 0.15, CI -0.46 to 0.75), appendicular skeletal muscle mass (n = 5, MD 0.09, CI -0.23 to 0.40), hand grip strength (n = 9, MD 0.07, CI -0.11 to 0.25), knee extension (n = 14, MD 0.09, CI -0.04 to 0.23), chair stand test results (n = 11, MD -0.05, CI -0.2 to 0.1), or timed up-and-go test results (n = 6, MD zero, CI -0.18 to 0.18). The I^2 values for all outcomes except for lean body mass were zero, indicating that heterogeneity was low for these outcomes and lean body mass had moderate heterogeneity (I^2 = 44%).

Discussion

Nutrient-dense foods that ensure sufficient intake of energy, protein and micronutrients are important to prevent frailty and sarcopenia and promote physical activity. However, to date, the optimal type of nutritional intervention or supplementation is unclear for the prevention of frailty and sarcopenia. This study was conducted to compare the synergistic effect of nutritional interventions combined with resistance training with that of resistance training only. This study was conducted to provide insight into resource optimization and strategies to prevent frailty and sarcopenia.

This systematic review and meta-analysis showed that there were no additional effects of nutritional interventions when combined with resistance training on muscle mass, strength, or physical function. Of note, in three studies, the control conditions included some nutrients that have biological benefits [30–32], which likely reduced the calculated effect size when the data for the control conditions were pooled. However, the findings of the sensitivity analysis showed little possibility of blunted effects. One of the possible reasons for this lack of significant results is that the analysis included studies of healthy older adults who might not have nutrient deficiencies with the usual diets [23]. Healthy diets provide a broad range of micronutrients and bioactive nonnutrients as well as macronutrients that might not be included in the experimental supplements in trials. In addition, since diets are patterned, isolating the effects of individual experimental supplements might not be possible without controlling the usual diet. Thus, the effects of nutritional interventions might be blunted among older adults who habitually consume sufficient nutrients. However, in previous studies that provided vitamin D-deficient and mobility-limited older adults with a protein mixture containing 20 g protein, 800 IU vitamin D, 350 mg calcium, and other minerals once a day for six months with an exercise program, there were no differences in muscle function parameters such as leg strength, gait speed, and short physical performance battery between this group and the exercise-only control group except in muscle density [33, 34]. In another study that also provided sarcopenic older adults who had low protein intake with multinutrient supplements containing 21 g protein, 800 IU vitamin D and other nutrients once a day for three months with an exercise program, there were no differences between the two groups, although both groups exhibited improved muscle function [33]. It is necessary to additionally consider the dose of the nutrient and duration of intervention and monitor dietary energy intake. Despite the lack of evidence, greater benefits of resistance training along with nutritional supplementation are expected in older adults who already have muscle failure or habitually have low nutrient intake.

In the subgroup analysis of the types of nutrients, only creatine showed significant effects on lean body mass. All three studies included in this meta-analysis administered 5 g creatine daily combined with resistance training 3 times a week for 12 weeks [35, 36] or twice a week for24 weeks [37]. Recent systematic reviews similarly identified the additive effect of creatine during resistance training on body composition, muscle strength, and physical function [38, 39]. As skeletal muscle has no capacity for creatine biosynthesis, the consumption of creatine-containing food or supplementation of creatine increases creatine and phosphocreatine levels in skeletal muscle and elevates phosphate resynthesis (energy buffer) during high-energy demanded exercise, such as repetitive resistance training [10, 40, 41]. Creatine helps to increase muscle mass and strength by indirectly increasing work capacity, and the combination of creatine supplementation and resistance training promotes muscle protein synthesis. Alternatively, creatine supplementation may enhance muscle protein synthesis stimulating signaling pathways (myogenic regulatory factors), which facilitate myosatellite cell proliferation and differentiation [42]. Controversy exists as to whether creatine stores and metabolism are affected by aging, but creatine supplements can account for dietary changes and reductions in physical activity with aging [39]. The effects sizes for variables other than lean body mass were not significant in this study. Additional meta-analyses including more experimental studies are needed to verify the effects of creatine on muscle mass and function in older adults.

As proteins provide amino acids that are essential for the muscle protein synthesis and act as anabolic stimuli, protein consumption increases muscle mass, and protein consumption following resistance training enhances net protein utilization, attenuating exercise-induced muscle protein breakdown [41, 43]. The combination of a nutritional intervention and exercise was expected to have a synergistic effect on muscle function, but the findings of this study did not support this hypothesis. On the other hand, in a previous meta-analysis, protein supplements for sarcopenic older adults along with exercise showed a larger effect size than did exercise alone and no intervention [25]. The previous meta-analysis was conducted in frail, sarcopenic, or mobility-limited older adults and included not only community-dwelling older adults but also institutionalized older adults. Individuals with existing nutritional deficiencies or muscle failure might have been shown to respond better to accompanying nutritional supplements than to exercise alone. Additional studies are needed to determine whether the inconsistency in findings resulted from the characteristics of the subjects.

Muscle protein synthesis through protein intake in older adults should be maximized with consideration of the frequency, distribution, and other nutritional components, such as creatine, vitamins, and fatty acids [22, 41]. It is recommended that older adults consume ≥ 0.4 g/kg per meal and 1.2–1.6 g/kg per day to induce muscle protein synthesis saturation to thus support muscle function [41]. Among the included studies, two studies provided an appropriate amount of protein (10 g milk protein and 0.5 g/kg whey protein) three times a day, taking into account frequency and distribution [21, 25, 26]. Other studies provided 10.1 g-25 g protein once a day [44–47] or 20 g ~ 35 g protein 3 times a week on the days exercise was performed [48–50]. A previous review showed that multi-ingredient protein supplements have the potential to increase the benefits of resistance training, but there were no differences in the effects on muscle mass and strength between multi-ingredient protein and single protein [51]. The impact of multiple nutrients is unclear, as there are complex interactions between food components inducing potential synergistic effects, so nutritional interventions involving dietary modifications with various and balanced nutrients or whole food approaches rather than a single specific nutrient can be effective in improving muscle mass and function [52]. Among the 26 RCTs, five provided multinutrients that were arbitrarily defined as containing three or more nutrients. Of the five studies, only two used a whole-food or whole-diet approach. The number of studies was too small to verify the effect of the whole-food or whole-diet approach.

Nutritional effects may not manifest following dietary interventions of short durations. Although this study showed that there were no differences in effect sizes according to the intervention period, a 6-year longitudinal study showed a positive relationship between daily protein intake and muscle strength [53]; nutritional contributions can be expected to be observed in the long term. Thus, despite the nonsignificant results, nutritional interventions may still be

beneficial for older adults who do not lack nutrients. With aging, muscle loss (breakdown) occurs more rapidly than does muscle synthesis, so additional supplements may be required. In addition, older adults experience declines in food intake because of changes in appetite and a lack of hunger, which is referred to as 'anorexia of aging' [54]. As consumed food is metabolized to synthesize energy for organ function, poor nourishment leads to body fat and muscle being catabolized to provide energy. Not only a lack of specific nutrients but also the consumption of an insufficient amount of food contributes to weight loss and declines in muscle mass, strength and physical function, which can lead to physical frailty and sarcopenia. Thus, the consumption of an adequate amount of food containing nutrients essential for muscle function is important to maintain muscle mass, strength, and physical function [22, 55]. Considering changes occur in various physiological functions as well as muscle function, interventions with a balanced diet are important in older people. As nutritional interventions have the advantages of low costs and high availability and accessibility, additional studies are necessary to determine whether they can be effective in preventing frailty and sarcopenia.

This study has several limitations. First, this meta-analysis included only retrievable RCTs that were published in English, which may have contributed to language bias. Second, this study in healthy older adults might not have demonstrated significant effects on muscle mass, muscle strength, and physical function due to the ceiling effect. Additional systematic reviews and meta-analyses are needed to identify the additional effects of nutritional interventions when combined with resistance training among dynapenic, sarcopenic, or frail older adults. Third, as mentioned above, the amount, frequency, and distribution of nutrients administered are important to consider to fully assess the effects of nutritional interventions; however, these factors were not assessed in the meta-analysis.

As the levels of variability in muscle mass and functional measurements are quite high in older adults, it is hard to obtain adequate statistical power to verify differences between groups in many studies on nutritional interventions. This meta-analysis showed that nutritional interventions have no additional effect on body composition, muscle strength, or physical function when combined with resistance training. Only creatine showed synergistic effects with resistance training on muscle mass. The enhanced effect of nutritional interventions for unhealthy older adults, such as frail, sarcopenic, nutritionally deficient older adults, needs to be investigated in future studies. The long-term effects of nutrition on muscle function also need to be studied. In addition, additional studies should be conducted to identify the dietary parameters that maximize nutritional effects on muscle protein synthesis, including dose, frequency, distribution, and recipes that take into account interactions with other nutrients. Health-promoting interventions such as exercise and diet are important for at-risk older adults to prevent clinically evident disability. This systematic review and meta-analysis provides a comprehensive synthesis of the experimental results available to date for health practitioners and researchers to establish intervention strategies or public health policies.

Abbreviations

CI: confidence interval; IU: international unit; MD: Mean difference; PUFA: Polyunsaturated fatty acid; RCT: Randomized controlled trial; RoB: Risk of bias; SD: Standard deviation; SMD Standardized mean difference; UK: United Kingdom; USA: United States of America

Declarations

Ethics Approval and Consent to Participate

This study was approved for a review exemption from the institutional review board of a university, Chuncheon, Korea (KWNUIRB-2020-07-006).

Consent for Publication

Not applicable.

Availability of Data and Materials

The authors can confirm that all relevant data are included in the article.

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Authors' Contributions

MK designed this study, collected and selected articles, extracted data from included studies, evaluated the risk of bias, performed meta-analyses, and draft the manuscript. HY performed data collection, selection of studies according to criteria, and data extraction. JY evaluated the risk of bias of included studies, checked the results of meta-analyses, helped to draft the manuscript. All authors read and approved the final manuscript.

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Supplementary

Due to technical limitations, Figure 3 is only available as a download in the Supplemental Files section.

Figures

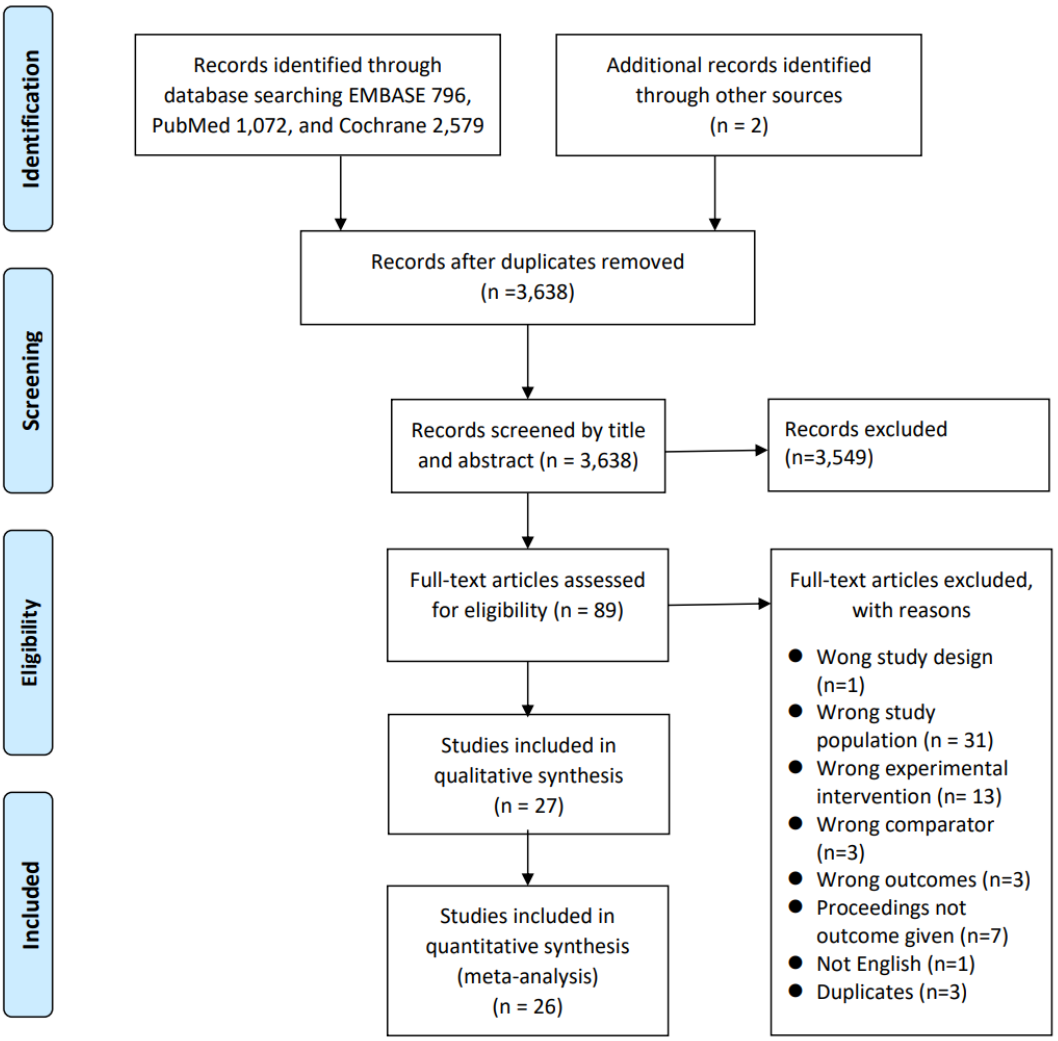

Figure 1

Flow diagram of the study selection process

Figure 2

Risk of bias of the included studies

Supplementary Files

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- Additionalfile.PRISMA2020checklist.docx
- Figure3Effectofresistancetrainingandnutritionalinterventiononmusclemassstrengthandphysicalfunctionalperformance.docx