Effectiveness of non-pharmacological interventions on the management of sarcopenic obesity: a systematic review and meta-analysis

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Short Title: Effects of non-pharmacological interventions on sarcopenic obesity

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Abstract

Background: Sarcopenic obesity is a combination of both sarcopenia and obesity, which potentiate each other and maximize the negative influences of each, such as physical disability, morbidity, or even mortality.

Objectives: To describe the criteria used to identify people with sarcopenic obesity and the components of the non-pharmacological interventions used to manage it, and to evaluate the effectiveness of those interventions.

Methods: Randomized controlled trials (RCTs) in Cochrane Library, Scopus, EMBASE, PscyINFO, CINAHL and PubMed were searched. The risk of bias was examined using the Cochrane risk of bias tool. The template for intervention description and replication (TIDieR) checklist was used to summarize the intervention components. Meta-analyses were conducted using random-effect models to pool estimates of the effects of the non-pharmacological interventions on body composition, BMI, grip strength, and gait speed.

Results: Sixteen papers (12 RCTs) with 863 participants were included. Diverse diagnostic criteria were used in the studies. Four categories of interventions were used: exercise (aerobic exercises, resistance exercises and exercise machines), nutritional interventions (supplements or dietary control), combined intervention and electrical acupuncture. Intervention durations varied from 8 to 28 weeks. Meta-analyses revealed that exercise with or without nutritional interventions had significant effects on grip strength (exercise: mean difference (MD): 1.63 kg, 95% confidence interval (CI): 0.94, 2.32, P<0.00001; exercise + nutrition: MD: 1.24 kg, 95% CI: 0.48, 1.99, P=0.001) and gait speed (exercise: MD: 0.13 m/s, 95% CI: 0.08, 0.18, P<0.00001, I^2=0%; exercise + nutrition: MD: 0.04 m/s, 95% CI: 0.02, 0.06, P=0.0002). Exercise had significant effects on reducing the percentage of body fat (PBF) compared to usual care (MD: -1.08%, 95% CI: -1.99, -0.17, P=0.02), while exercise combined with nutritional interventions showed no superiority over exercise solely on decreasing PBF (P=0.49). Exercise combined with nutritional interventions had significant effects on increasing appendicular skeletal muscle mass (MD: 0.43 kg, 95% CI: 0.20, 0.66, P=0.0003). Low-caloric high-protein diets showed no superiority over low-caloric low-protein diets in increasing fat-free mass. Subgroup analyses showed that using different formulas to estimate the skeletal muscle mass index may lead to significant differences in determining the effects of exercise on grip strength.

Conclusion: The diagnostic criteria for sarcopenic obesity used in future studies should refer to the latest consensus definition. Exercise tended to be the most effective method of improving grip strength and physical performance (e.g. gait speed). The combined effects of exercise and nutritional interventions on muscle mass and muscle strength require further exploration.

1. Introduction

Sarcopenic obesity, a condition combining low muscle strength, low muscle quantity and quality, and high body fat, has emerged as an important health issue (Polyzos & Margioris, 2018). Compounding the effects of both sarcopenia and obesity, sarcopenic obesity has negative consequences on individuals, which can lead to metabolic problems, physical disability, poor quality of life, institutionalization, morbidity and mortality (Stenholm et al., 2008). Sarcopenia and obesity may even potentiate each other and maximize the negative effects of the conditions (Zamboni et al., 2008). One study revealed that compared to obese women without sarcopenia, women with sarcopenic obesity had lower levels of muscle strength and higher risks of developing cardiovascular diseases (da Cunha Nascimento et al., 2018).

A commonly accepted definition of sarcopenic obesity includes both sarcopenia and obesity (Goisser et al., 2015). An updated consensus on the definition of sarcopenia was proposed in 2018 by the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2018), and includes low muscle strength as the primary parameter, low muscle quantity or quality as the diagnostic criteria, and low physical performance as the diagnostic standard of severity. The definition of sarcopenia in Asia is similar to that of the EWGSOP. The only differences are in the cutoff values of the various parameters, due to racial differences (Chen et al., 2014a). Obesity is defined as the abundant accumulation of fat mass, which negatively affects health (WHO, 2000), and is always diagnosed by BMI, waist circumference, or percentage of body fat (PBF).

Depending on the chosen diagnostic criteria, the prevalence of sarcopenic obesity in China ranges from 3.2% to 20.4% in women and from 13.8 % to 27.0% in men (Chen et al., 2014b). In the USA, the prevalence is reported to range from 4% to 94% in women and 4% to 84% in men, and to increase with age (Batsis et al., 2013).

Although sarcopenic obesity is more common among elderly people, it is being diagnosed more and more often in people across the entire age spectrum (Johnson Stoklossa et al., 2017). Muscle mass and strength begin to decline gradually around the age of 30, accelerating after the age of 60 (Stenholm et al., 2008). This decline is believed to be related to insulin resistance, a decrease in growth hormones and testosterone, inflammation, oxidation, fat infiltration, and so on. (da Cunha Nascimento et al., 2018). A decrease in physical activity and metabolic rate also result a decrease in total energy consumption, leading to an increase in body fat and weight (Ryu et al., 2013).

Currently, there are no approved medications for treating sarcopenic obesity. The most commonly proposed treatments focus on lifestyle interventions, among which exercise and nutritional interventions play important roles (Goisser et al., 2015). Exercise and nutritional interventions have either been combined or solely performed in the form of different types of exercise, education on dietary patterns, or oral supplements (Poggiogalle et al., 2014).

A number of interventional studies have been conducted on sarcopenic obesity, but only a few systematic reviews have evaluated the effects of the interventions. One review only included two studies, one of which focused on sarcopenia rather than on sarcopenic obesity (Theodorakopoulos et al., 2017). Another two systematic reviews, both conducted by the same team, reported that exercise alone or combined with supplements may have beneficial effects on increasing muscle mass, grip strength and gait speed, but that the results of the various studies were often contradictory (Hita-Contreras et al., 2018; Martínez-Amat et al., 2018). One of the most recently conducted systematic reviews revealed that resistance exercise is essential to managing body composition and physical performance parameters among people with sarcopenic obesity, while nutritional interventions only impact body fat mass (Hsu et al., 2019). To date, no systematic reviews have evaluated the effectiveness of all available non-pharmacological interventions on sarcopenic obesity. Moreover, the diagnostic criteria for sarcopenic obesity have varied greatly in the previous studies, which may have affected the true effects of the interventions, due to the lack of representativeness of participants with sarcopenic obesity, and no systematic review has described this. Therefore, in this systematic review the aims are: (1) to describe the criteria used to identify people with sarcopenic obesity, (2) to describe the components of the non-pharmacological interventions used to treat sarcopenic obesity, and (3) to evaluate the effectiveness of the non-pharmacological interventions on parameters related to body composition, muscle strength and physical performance among people with sarcopenic obesity.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009) were followed in reporting this systematic review, and this review was registered at PROSPERO (CRD42019122452). The PRISMA checklist could be seen in the supplementary file (Appendix 1).

2.1 Search Strategy

The Cochrane Library, Scopus, EMBASE, PscyINFO, CINAHL and PubMed were searched for relevant studies published up to September 2019, using MeSH terms (Medical Subject Headings)

and free text. To avoid the overlooking of articles, no restrictions were placed on dates of publication. We limited the languages of the studies to Chinese and English. The search terms were "sarcopenic obesity," "sarcopenia or sarcopenic," "obesity or overweight or obese," and "adiposity or adipos*," and were combined with Boolean operators (OR/AND) (Supplementary file: Appendix 2). A manual search was made of the reference lists of published systematic reviews on sarcopenic obesity and of original studies. No search terms related to interventions were used because we did not want to exclude any potentially relevant studies on sarcopenic obesity.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were based on the "PICOS" (population, intervention, comparator, outcome, and study) approach (Schardt et al., 2007), and were as follows:

1. P: adults with sarcopenic obesity (the participants should have both sarcopenia and obesity; the diagnostic criteria for sarcopenia should at least include the diagnosis of muscle quantity or quality, while the diagnostic criteria for obesity should include either BMI or PBF or waist circumference). Since the cut-off values were always based on different ethical groups (Cruz-Jentoft et al., 2018; WHO, 2000), no exact cut-off values were required when selecting the studies, as long as the studies have followed the diagnostic criteria supported with authoritative evidence. There were also no restrictions as to age, gender, or setting (the community, nursing homes, or hospitals);
2. I: all kinds of non-pharmacological interventions, including, but not limited to, physical activities, nutritional interventions, psychosocial interventions, and multifactorial interventions;
3. C: all kinds of non-pharmacological interventions or a placebo or blank control;
4. O: outcomes that included body composition parameters (e.g., appendicular skeletal muscle mass, PBF, weight, BMI, waist circumference, etc.), muscle strength (e.g., grip strength, etc.) and physical performance (e.g., gait speed, etc.);
5. S: RCTs or cluster RCTs were considered when published as a journal article. Conference papers (but not conference abstracts) and theses were also considered during the literature search.

Studies were excluded if the criteria for the diagnosis of participants did not strictly target sarcopenic obesity, for example, if the target participants were in a co-morbid condition (i.e. sarcopenic obesity co-existing with other diseases such as cancer or diabetes.) The reason is that

those studies were aimed at evaluating the treatments for a comorbidity, not simply for sarcopenic obesity. Studies of interventions using pharmacological methods such as pills, injections, or other pharmaceuticals were also excluded.

2.3 Study Selection

Two reviewers (Y.Y.H., J.Y.W.L.), working independently, selected articles according to the title and abstract, and subjected them to a preliminary screening using the EndNote X8 software. Full-text articles were screened according to the selection criteria. Any disagreements between these two reviewers were discussed with a third reviewer to reach a consensus.

2.4 Data Extraction and Management

The characteristics of the studies were described according to a standardized format: author, title, demographic data (age, gender, settings), methodological data (sample size, blinding, group design, intervention duration, assessment tools and time points), and outcome data (primary outcomes, including body composition parameters such as PBF and skeletal muscle mass; and secondary outcomes, including muscle strength and physical performance parameters such as grip strength and gait speed, significances, and drop-out rates). The data extraction form was independently piloted by the two reviewers on one included study to ensure that all relevant information had been captured in the form. The mean value and standard deviation (SD) between the baseline and final measures of the outcomes were extracted, and calculations were performed with reference to the equations given in the Cochrane handbook (Higgins & Green, 2011) when SD was not reported. If one original study had been published in more than one paper, the information was described in the data extraction table as one study based on the study protocol number.

The diagnostic criteria for sarcopenic obesity used in each included study were extracted in a separate table. Details of the intervention components were extracted using the TIDieR checklist and guide (Hoffmann et al., 2014).

If clarifications were required for any of the data, or if information was missing, the authors of the primary studies were contacted. Another reviewer (J.Y.W.L) checked the accuracy and completeness of the data. Any divergences were solved through discussion, and another independent reviewer was consulted if the disagreement persisted.

2.5 Risk of Bias

The risk of bias in the selected studies was assessed by two authors independently, who referred to the Cochrane Collaboration's Risk of Bias Tool (Higgins et al., 2011). Studies were rated as: being at a high risk of selection bias because the allocation was not concealed; being at a high risk of performance bias because the participants were not blinded and potential contamination existed; and being at a high risk of attrition bias because the proportion of missing data was large (n=21, attrition rate=19.05%) and no appropriate method of managing the missing data was reported. Studies were rated as having an unclear risk of selection bias because randomization details were not reported clearly; an unclear risk of performance bias because insufficient information was provided; an unclear risk of detection bias because the blinding of outcome assessors was not revealed; and an unclear risk of attrition bias because the attrition details were not reported. A risk of bias graph was conducted using Review Manager (RevMan) version 5.3 (Cochrane Collaboration, 2019). The funnel plot was not conducted due to the insufficiency of study numbers.

2.6 Data Analysis and Synthesis

We pooled meta-analyses of the primary outcomes, including PBF, BMI, appendicular skeletal muscle mass (ASM), skeletal muscle mass index (SMI), fat-free mass; and the secondary outcomes, including grip strength and gait speed. Subgroup analyses were performed on the available data (SMI, grip strength and gait speed) according to the operationalization of sarcopenia in terms of different formulas for estimating the SMI. For those studies (Balachandran et al., 2014; Zhou et al., 2018) that were not included in the meta-analysis, we synthesized the outcomes narratively to nest with the meta-analysis (the outcomes included PBF, ASM, and parameters related to physical performance).

In the meta-analyses, we reported the effect size by the mean difference (MD) with 95% confidence intervals (95% CIs) for studies that used the same measuring methods, and the standardized mean difference (SMD) for those that measured the same outcome with different units for continuous outcomes. The meta-analyses only included the post-intervention data and left out the follow-up data, because there was insufficient follow-up data to conduct a meta-analysis. Random effect models were used to merge the data because of the unavoidable clinical heterogeneity. The RevMan 5.3 (Cochrane Collaboration, 2019) was used for the meta-analyses.

Heterogeneity was tested using a chi-square test (χ^2) and the I^2 statistic. A P-value of ≤ 0.1 for the chi-square test indicates the presence of heterogeneity (Higgins et al., 2003). I^2 values of 0-30%, 30%- 50%, and >50% represent a low, moderate or high level of heterogeneity, respectively.

A sensitivity analysis was conducted to test the Change SD with different correlation coefficients (r), such as 0.3, 0.5, 0.7 or 0.8. A conservative estimate (r=0.5) was employed.

2.7 Assessing the quality of the body of evidence

The quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (Schünemann et al., 2009), which was rated according to the following five categories: risk of bias, imprecision, inconsistency, indirectness, and other factors such as publication bias (Balshem et al., 2011).

3. Results

3.1 Study Selection

A total of 5092 articles were found during the literature search. After duplicates were removed, 2875 hits were left for further screening. After screening the title and abstract of each of these hits, a total of 29 articles were left for the full-text screening (Supplementary file: Appendix 3). In the end, 16 articles (including 12 studies) met the eligibility criteria (Balachandran et al., 2014; H. T. Chen et al., 2017; Gadelha et al., 2016; Kemmler et al., 2018; Kemmler et al., 2018; Kemmler et al., 2016; Kemmler et al., 2017; Kim et al., 2016; Liao et al., 2018; Liao et al., 2017; Muscariello et al., 2016; Nabuco et al., 2019; Park et al., 2017; Sammarco et al., 2017; Wittmann et al., 2016; Zhou et al., 2018). Ten studies were included in the meta-analysis. The selection process is shown in Figure. 1.

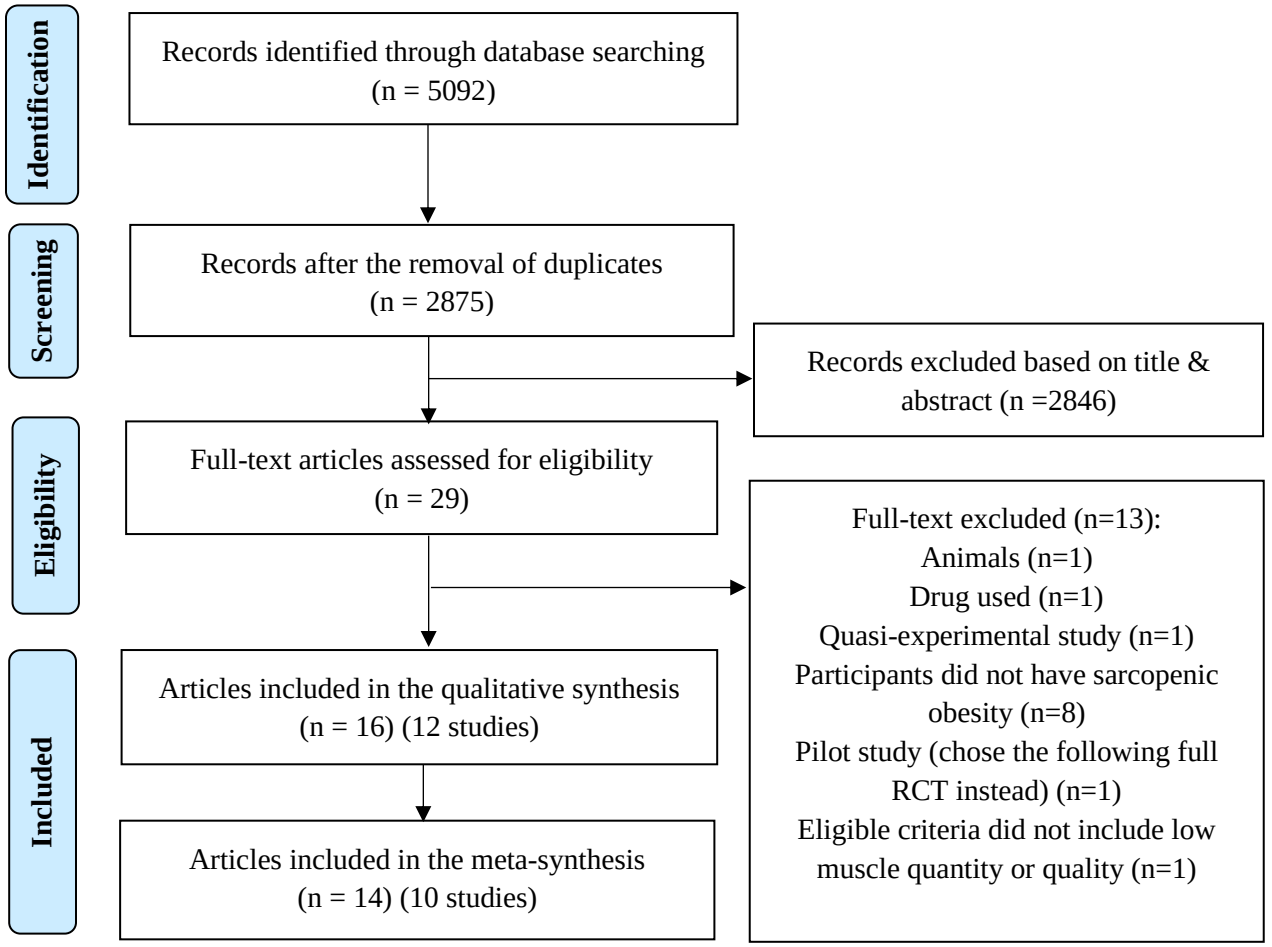


Fig. 1. PRISMA Flowchart showing the literature search and studies selection

3.2 Study Characteristics

All 12 RCTs (for a summary of the characteristics of the studies see Table 1) were conducted from 2014 to 2019 in Germany, Japan, the USA, Korea, Taiwan, Brazil, Italy and mainland China. The number of participants in the studies ranged from 18 to 139, with a total of 863 participants. The participants ranged in age from 41 to 90, and the average age was 72.01±7.76 years old. Two studies included only males, 8 studies included only females, and the remaining 2 studies included mixed populations. Two studies had four arms, 2 studies had three arms, and 8 studies were two-armed.

Table 1. Characteristics of the studies included in the review

Author, year	Country/Region	Setting & Intervention duration	Population (sample size) Mean age	Group design (number, age)	Compliance number & Attrition	Assessment time point	Outcomes
Kemmler et al., 2017	Germany	Community 16 weeks	≥70 years old men (N=100) 77.4±4.8	①Protein (n=33, 78.1±5.1) ②WBEMS&Protein (n=33, 77.1±4.3) ③CG (n=34, 76.9±5.1)	92 8%	Baseline, Week 16	Sarcopenia Z-Score, total body fat, ASM, SMI, grip strength, PBF
Kemmler et al., 2016	Germany	Community 26 weeks	≥70 years old women (N=75) 77.0±4.3	①WBEMS (n=25, 77.3 ± 4.9) ②WBEMS&Protein (n=25, 76.4±2.9) ③CG (n=25, 77.4 ± 4.9)	67 10.67%	Baseline, Week 26	Sarcopenia Z-Score total body fat, PBF, SMI, grip strength, gait speed
Kim et al., 2016	Japan	Community 3 months	≥70 years old women (N=139) 81.1±4.6	①Combined Exercise + Nutrition (n=36, 80.9±4.2) ②Combined Exercise (n=35, 81.4±4.3) ③Nutrition (n=34, 81.2±4.9) ④Health education (n=34, 81.1±5.1)	137 1.44%	Baseline 3-month	Muscle mass, body fat mass, PBF, ASM, SMI, grip strength, walking speed
Balachandran et al., 2014	USA	Community 15 weeks	60-90 years old people (N=21) 71.3±7.8	①Power circuit (HSC group, n=11, 71.6±7.8) ②Hypertrophy (SH group, n=10, 71±8.2)	17 19.05%	Baseline, Week 15	SPPB, SMI, PBF, IADL, grip strength
Chen et al., 2017	Taiwan	Community 8 weeks	65-75 years old people (N=93) 68.8±3.3	①Resistance (RT, n=22, 68.9±4.4) ②Aerobic (AT, n=24, 69.3±3.0) ③Combined exercise (CT, n=25, 68.5±2.7) ④CG (n=22, 68.6±3.1)	60 35.48%	Baseline, week 8, week 12	SMM, SMI, body fat mass, BMI, PBF, visceral fat area, grip strength, maximum back/knee extensor strength, maximum knee
Liao et al., 2018	Taiwan	Rehabilitation center 12 weeks	60-80 years older women (N=56) 67.3±5.2	①Elastic resistance group (n=33, 66.67±4.54) ②CG (n=23, 68.32±6.05)	50 12%	Baseline, 3-month, 9-month	FFM, LMI, TFM, PBF, SMI, grip strength, leg strength, upper extremity, lower extremity, gait speed, TUG
Gadelha et al., 2016	Brazil	Community 24 weeks	60-80 years old women (N=133) 67.0±5.2	①Resistance training group (n=69, 66.79±5.40) ②CG (n=64, 67.27±5.04)	133 0%	Baseline, Week 24	TFFM, PBF, AFFM, isokinetic peak torque

Park et al., 2017	Korea	Community 24 weeks	≥65 years old women (N=50) 74.1±6.1	①Aerobic & resistance exercise group (n=25, 73.5±7.1) ②CG (n=25, 74.7±5.1)	50 0%	Baseline, Week 24	PBF, ASM, WC, gait speed, left and right grip strength, physical activity
Sammarco et al., 2017	Italy	Community 4 months	41-74 years old women (N=18) 55.0±9.6	①Hypocaloric diet plus placebo (n=9, 58±10) ②Hypocaloric high-protein diet (n=9, 53±8.9)	18 0%	Baseline, 4-month	Weight, fat mass, FFM, grip strength, SPPB
Zhou et al., 2018	China	Community pension center 28 weeks	60-80 years old men (N=48) 69.5±5.2	①Electrical acupuncture +Nutrition (n=23, 70.35±5.36) ②Nutrition (n=25, 68.8±5.08)	48 0%	Baseline, Week 4, Week 12, Week 20, Week 28	PBF, ASMM/Height^2
Muscariello et al., 2016	Italy	Community 3 months	>65 years old women (N=104) 66.7±4.9	①Normal protein intake hypocaloric diet (n=50, 66.4±4.5) ②High protein intake hypocaloric diet (n=54, 66.9±5.2)	104 N/A	Baseline, 3-month	MMI, FMI, FFM, FFMI, BMI, WC, grip strength
Nabuco et al., 2019	Brazil	Community 16 weeks	>60 years old women (N=26) 69.1±4.1	①Whey protein (n=13, 68.0±4.2) ②Placebo (n=13,70.1±3.9)	26 0%	Week 1, Week 2, Week 15, Week 16	WC, PBF, trunk/total fat mass, ALST, 1 RM tests, 10-m walk test, RSP

SMI: skeletal muscle mass index, ASM: appendicular skeletal muscle mass, PBF: Percentage of body fat, WBEMS: whole-body electromyostimulation, VFA: visceral fat area, FFM: fat-free mass, TSM: total skeletal muscle mass, MMI: muscle mass index, LLM: leg lean mass, TFM: total fat mass, TUG: time up and go test, IADL: instrumental activities of daily living, TFFM: total fat-free mass, AFFM: appendicular fat-free mass, WC: waist circumstance, SPPB: short physical performance battery, FMI: fat mass index, FFMI: Fat-free mass index, ALST: appendicular lean soft tissue, RSP: rising from the sitting position test

3.3 Description of the diagnostic criteria for sarcopenic obesity

The diagnostic criteria for sarcopenic obesity used in the studies varied greatly, especially the criteria for sarcopenia (for details, refer to Table 2). All of the studies measured the muscle quantity to identify sarcopenia, but only 2 studies included gait speed and grip strength as diagnostic criteria for sarcopenia. For the measurement of muscle quantity, 9 studies calculated the muscle mass with adjusted by height^2 or weight or BMI, and 3 studies that calculated the muscle quantity used different formulas. For the identification of obesity, 6 studies only used PBF, and 5 studies chose BMI; the remaining study used both PBF and visceral fat area (VFA≥100cm^2). The cut-off points for PBF ranged from 25% to 35%, and the cut-off points for BMI also varied (≥30 kg/m^2; ≥25 kg/m^2).

A bioelectrical impedance analysis was used in 9 studies to measure the muscle mass of the participants at the time of their recruitment (Balachandran et al., 2014; Chen et al., 2017; Kemmler et al., 2016; Kemmler et al., 2017; Liao et al., 2018; Muscariello et al., 2016; Park et al., 2017; Sammarco et al., 2017; Zhou et al., 2018); and in 8 studies (Balachandran et al., 2014; Chen et al., 2017; Kemmler et al., 2017; Kim et al., 2016; Muscariello et al., 2016; Park et al., 2017; Sammarco et al., 2017; Zhou et al., 2018) to assess the outcomes of the interventions. The remaining measurements were performed using dual energy X-ray absorptiometry.

Table 2. Diagnostic criteria for sarcopenic obesity used in the included studies

Studies	Measurement of body composition		Diagnostic criteria for sarcopenia						Diagnostic criteria for obesity		
	Recruit	Post-test	Low muscle strength	Low muscle mass				Low physical performance	BMI	PBF	Other criteria
				Adjusted by weight	Adjusted by height^2	Adjusted by BMI	Other criteria				
Kemmler et al., 2017	BIA	BIA				<0.789				>27%	
Kemmler et al., 2016	BIA	DXA			<5.75 kg/m^2					>35%	
Kim et al., 2016	DXA	BIA	Grip strength Women<17.0 kg		≤5.67 kg/m^2			Gait speed <1 m/s		≥32%	
Balachandran et al., 2014	BIA	BIA	Grip strength Men <30kg; Women<20 kg		Men: ≤10.76 kg/m^2 Women: ≤6.76 kg/m^2			Gait speed ≤1 m/s	>30 kg/m^2		
Chen et al., 2017	BIA	BIA		Men: ≤32.5% Women: ≤25.7%					≥25 kg/m^2		VFA ≥100cm^2
Liao et al., 2018	BIA	DXA		<27.6%						≥30%	
Gadelha et al., 2016	DXA	DXA					AFFM= -13,012 + 16,737× [Height (m)] + 0.07231× [FM (kg)]		≥30 kg/m^2		
Park et al., 2017	BIA	BIA		< 25.1%					≥25 kg/m^2		
Sammarco et al., 2017	BIA	BIA					<90% of subject's ideal FFM, (ideal FFM = 0,75 × ideal body weight + 0.25 × excess body weight)			>34.8%	
Zhou et al., 2018	BIA	BIA			≤ 7.0kg/m^2					≥25%	
Muscariello et al., 2016	BIA	BIA			≤7.3 kg/m^2				≥30 kg/m^2	≥35%	WC >88.0 cm FMI≥9.5kg/m^2
Nabuco et al., 2019	DXA	DXA					Appendicular lean soft tissue < 15.02 kg			≥35%	

BIA: bioelectrical impedance analysis; DXA: dual energy X-ray absorptiometry; BMI: body mass indxe; PBF: percentage of body fat; AFFM: appendicular fat-free mass; FFM: fat-free mass; VFA: visceral fat area; MMI: muscle mass index; WC: waist circumference; FMI: fat mass index

3.4 Description of interventions

Details of the interventions are presented in Table 3 in accordance with the TIDieR Checklist (Hoffmann et al., 2014). In 5 studies (Balachandran et al., 2014; Chen et al., 2017; Gadelha et al., 2016; Liao et al., 2018; Park et al., 2017) only exercises were used, in 2 studies (Muscariello et al., 2016; Sammarco et al., 2017) only nutritional interventions were conducted, in 4 studies (Kemmler et al., 2016; Kemmler et al., 2017; Kim et al., 2016; Nabuco et al., 2019) exercises were combined with nutritional interventions, and in 1 study (Zhou et al., 2018) electrical acupuncture was combined with nutritional interventions. We categorized the interventions into four groups: electrical acupuncture, exercise-based interventions, nutritional-based interventions and combined interventions.

The types of exercises consisted of resistance exercises, aerobic exercises, whole-body electromyostimulation (WB-EMS), and exercise using a hydraulic exercise machine. The duration of the interventions ranged from 8 to 26 weeks, and the time varied from 20 mins to 400 mins per week.

The nutritional interventions included the intake of supplements (i.e. protein, amino acids, tea catechin and vitamin-D) and dietary management. The durations of the nutritional interventions ranged from 12 weeks to 28 weeks. The protein intake amounts were 0.8–1.0g/kg body weight/day, 1.7–1.8g/kg body mass/day, 0.8 or 1.2 g/kg DBW/day, 40g/day or 35g/time, 3 times/week. The amino acids intake amounts were 3.0 g/day or 20g/day. The Vitamin-D intake amounts were 800 IU/day or 20 μg/day. In one study, the participants took 350 ml of tea fortified with 540g of catechin/day together with amino acid supplements. In the two studies that compared a low-caloric high-protein diet with a low-caloric normal-protein diet, high protein was defined as 1.2 g/kg desired body weight/day and 1.2–1.4 desired body weight/day. Low-caloric diet was defined as 20–25 kcal/kg desired body weight/day and 90% of daily metabolic rate, respectively. Adherence to the diet was monitored with a food diary.

Table 3. Description of the interventions of the included studies (modified based on TIDieR checklist)

Author	Brief name	Category [a]	Materials and Procedures	Who provided and how	Where, when and how much	How well (adherence)	Comparison group
Kemmler et al., 2017	WB-EMS & Isolated protein supplementation	Exercise, Nutrition, Combined	①WB-EMS equipment (miha bodytec®). A session consisted of 10–14 dynamic exercises structured in one to two sets of eight repetitions performed without any additional weights in a standing position. ②Daily take of whey protein powder and vitamin-D individually based on a 4-day dietary protocol (3 weekdays, 1 weekend day) recorded immediately before and after the trial.	One instructor coached two applicants face to face while taking WB-EMS in a group.	Location N/A. *WB-EMS*: 1.5 times/ week for 20 min/time. *Protein*: daily intake of 1.7–1.8 g/kg/day body mass. The whey protein powder contains 80% of (whey) protein with a caloric value of 1526 kJ/100g (360 kcal/100g). *Vitamin-D*: daily dose of 800 IU. 16 weeks	Adherence was monitored biweekly either by personal interviews or by phone calls. Lost to follow: WBEMS&P: n=3, Protein: n=2, CG: n=3	Take vitamin-D 800 IU/day independently.
Kemmler et al., 2016	WB-EMS, Protein & vitamin-D supplementation	Exercise, Nutrition, Combined	①WB-EMS equipment (miha bodytec®): up to four participants performed a video guided WB-EMS program in a supine sitting/lying position with slight movements of the lower and upper limbs. ② Whey protein powder (FortiFit; Nutricia) & Cholecalciferol (vitamin-D): Supplements were provided on a monthly basis. Participants of the WB-EMS&P group were not supplemented with isolated vitamin D.	Instructors closely cooperate with participants face to face in groups to maintain the intensity of WBEMS training.	Location N/A. *WBEMS*: once a week for 20 min after 8 weeks. *Protein*: 40g/day including 635 kJ caloric, 21g whey protein. *Vitamin-D*: 800 IU/day. 26 weeks	The compliance with dietary supplements was monitored via monthly phone call. Lost to follow-up: WBEMS: n=1, WBEMS&P: n=4, CG: n=3	Health Consultation and Vitamin-D Graduate nutritionist gave one-hour group lecture and individual counselling, with a focus on energy balance and the importance of protein intake.
Kim et al., 2016	Exercise Supplements	Exercise, Nutrition	① Exercise (Resistance: chair, resistance band, hydraulic machine; Aerobic: stationary bicycle): each exercise session was divided into warm-up, weight/machine training, stationary bicycle aerobic exercise, and chair/standing exercise. ②Nutrition: take amino acid supplementation and tea catechin daily.	One instructor coached all four face-to-face exercise classes, three trainers present at every class to assist.	Location: Tokyo Metropolitan Institute of Gerontology. *Exercise*: twice per week. 60 mins per time. *Nutrition*: 3.0g essential amino acid and 20 μg vitamin D, 350 mL of tea fortified with 540g of catechin daily. *Health education*: once every 2 weeks, a total of six times. 3 months	Participants recorded supplements intake via diary logs every 2 weeks to monitor adherence along with empty packets and bottle caps. Lost to follow-up: Exercise: n=1, Nutrition: n=1	Only health education, no exercise or nutrition is included.
Balachandran et al., 2014	Power circuit training (HSC group) & Strength/Hypertrophy training (SH group)	Exercise	Pneumatic exercise machines (Keiser A420). The HSC group performed 3 sets of 10–12 repetitions on each machine. Participant moved to the next machine after each set with no recovery between sets. One circuit was completed when the participant completed one set on all 11 machines.	A minimum of two trainers (exercise physiology major) supervised the training face to face.	Location N/A Twice per week. HSC: 40-45 mins per time SH: 55-60mins per time 15 weeks	Adherence checking N/A. Lost to follow-up: HSC: n=3, SH: n=1	The SH group performed 3 sets of 10–12 repetitions using 70% of their 1RM on each machine before moving to the next exercise. A 1–2 min recovery was provided between sets. When participants could do 3 sets of 12 repetitions, the load was increased by 5% for the next workout session.

Chen et al., 2017	Resistance training (RT) Aerobic training (AT) Combined training (CT)	Exercise	Weight-training equipment ①RT: 3 sets of 8–12 repetitions with a 2–3 minutes rest between sets. The difficulty of the exercise was adjusted every 2 weeks in ascending order from simple to difficult. ② AT: 5–10 minutes of dynamic stretching and warm up, 40–45 minutes of the actual training, 10 minutes of closing and relaxation exercises. ③CT: performed each training mode once a week with the AT following 48 hours after the RT.	Qualified professional trainer supervised the training face to face.	Location N/A RT, AT: two 60-minute sessions per week. CT: each training once a week. 8 weeks	Adherence checking N/A. Lost to follow-up: AT: n=9, RT: n=7, CT: n=10, CG: n=7	Maintain day-to-day lifestyles and dietary habits, be prohibited from engaging in any exercises.
Liao et al., 2018	Elastic band resistance training	Exercise	Theraband products (Hygenic Co.,) Participants individually perform with elastic bands in small groups (less than 6 people). Each exercise session involved a 10-minute warm-up, followed by resistance training exercises (35–40mins), and finally a cool-down routine (5 mins). Types of exercise: shoulders, arms, lower limbs, chest and abdomen.	Licensed senior physical therapist supervised and trained the training sessions face to face.	Location: A group physical therapy classroom in hospital. 3 training sessions weekly, nearly 1 hour every session. 12 weeks	Adherence checking N/A. Lost to follow-up: EG: n=4 CG: n=5	A 40-minute lesson about sarcopenic obesity and the home exercise concept.
Gadelha et al.,2016	Resistance training program	Exercise	Materials N/A After a general warm up, resistance was then adjusted to an estimated 1-RM (repeated in four-week intervals). Three sets of each exercise, and one minute rest between sets. Progressive intensity increase (First 4 weeks: 60% of 1-RM; Second 4 weeks: 70%; Remaining 16 weeks: 80%); Decreased repetitions respectively: 12, 10, 8.	Capable professionals supervised all training sessions and 1-RM measurements face to face.	Location N/A 3 times per week 24 weeks	Adherence checking N/A. Lost to follow-up: n=0	Maintain usual activities.
Park et al., 2017	Combined aerobic and resistance exercises	Exercise	Elastic band (Thera-Band) ①Resistance exercises were performed with elastic band exercises for 8–15 repetitions per set (in weeks 1–12, 8–11 repetitions per set; in weeks 13–24, 12–15 repetitions per set), 2–3 sets (1 min rest between sets), 20–30 min per session for 3 days per week. ② Aerobic exercise involved various walking activities (sideways, backward, and forward walking and slow and fast indoor walking) for 30–50 min per session, 5 days per week, with a rating of perceived exertion (RPE) in the 13–17 range.	An exercise specialist supervised the exercise face to face.	Location: N/A 50-80 mins per time, 5 days per week 24 weeks	Adherence checking N/A. Lost to follow-up: n=0 (but mean attendance rate was 92%)	Maintain individual lifestyles

Sammarco et al., 2017	Hypocaloric diet with protein supplementation	Nutrition	Low-calorie high-protein diet: – energy = basal metabolic rate-10% according to calorimetry; – protein intake: 1.2–1.4 g / kg body weight reference / day with 15 g of protein of high biological value for each main meal (breakfast, lunch and dinner); – essential amino acids < branched-chain amino acids < leucine equal to 15 g/day by administration of supplement; – carbohydrate: 60–65% of kcal complex; – fat: to satisfy the required amount of energy; 30% saturated; – report non-protein kcal/g nitrogen = 100/1; – sodium: less than 5 g/day in hypertensive subjects.	Participants conducted at home individually. Details were N/A.	Location: participant's home Dose referred to previous column. 4 months	Adherence to diets was evaluated by a 7-day dietary record at baseline and at week 4, 8, 12, 16, and was reinforced by the dietitians through counselling and phone calls every 2 weeks. Lost to follow-up: n=0	Low-calorie diet plus placebo: -- daily energy intake = metabolic rate-10% according to calorimetry; -- protein intake: 0.8–1 g / kg body weight reference / day; – carbohydrates: 60–65% of whole kcal; – fat: to supply the required amount of energy, with 30% saturated; – sodium: 5- 6 g/day, or less than 5 g / day in hypertensive subjects.
Zhou et al., 2018	Electrical acupuncture & Essential amino acid supplements	Electrical acupuncture	Sterile disposable acupuncture needles (CE-0197) ①Electrical Acupuncture: The acupuncture points (LI14 and LI11 pair, ST31 and ST34 pair) were punctured for 20 mins with a frequency of 5 Hz, wave duration of 1 ms, and strength of 1.5 mA. ②Essential amino acid were taken orally (20g in total, 10:00 AM and 5:00 PM). The breakfast, lunch, and dinner were scheduled at 7: 00 AM, 12: 00 noon, and 7: 00 PM. The total calories of the food were 1.58 × (13.5 × weight (kg) + 487). Those who take less than 80% total calories 5 times would be excluded from the study.	Two qualified acupuncture physicians conducted the acupuncture. Two cooks were responsible for the meal supply.	Location: community pension center Acupuncture: 20 mins per time, once every 3 days for 12 weeks; Amino acids: twice per day for 28 weeks. 28 weeks	Record the food intake. A reminder call for drug intake was made once every 7 days. Lost to follow-up: n=0	Only took the amino acid supplements.
Muscariello et al.,2016	Self-administered higher protein intake	Nutrition	① Every participant's calorie intake was approximately 20–25 kcal/kg DBW/day. ② Participants were treated with 1.2 g/kg DBW/day of proteins (breakfast 25%–30% g, lunch 35%–40% g, dinner 35%–40% g).	Participants conducted at home individually. Details were N/A.	Location: participant's home Dose referred to previous column. 3 months	Taking daily food diary, self-administered, and three reports of 24-hour recall every month during the follow-up. Lost to follow-up: N/A.	Participants were administered with 0.8 g/kg DBW/day of proteins (breakfast 25%–30% g, lunch 35%–40% g, dinner 35%–40% g).
Nabuco et al., 2019	Whey protein following resistance exercise	Exercise, Combined	①After each training session, participants took 35g whey protein (Lacprodan, Arla Foods). ② Resistance training sessions were conducted 3 times per week, including chest press, horizontal leg press, seated row, knee extension, etc.	Physical education professionals	Location: University training facility & participant's home 35 g whey protein per training session 16 weeks	24-h dietary recall was applied via Virtual Nutri Plus software. Lost to follow-up: n=0	Maltodextrin (New Millen, Brazil) was used as placebo, and mixed with non-caloric sugar-free drinks.

a. We classified the interventions into four categories: exercise, nutrition, combined exercise and nutrition, electrical acupuncture.
WB-EMS: whole-Body electromyostimulation

3.5 Effects of non-pharmacological interventions on primary outcomes

With regard to the body composition parameters, data were available from 8 studies (n=639) involving meta-analyses of exercise and nutritional interventions that measured PBF, 2 studies (n=193) that measured BMI, 2 studies (n=193) that measured body weight, 3 studies (n=255) that measured ASM, 5 studies (n=585) that measured SMI, and 2 studies (n=122) that measured fat-free mass. The quality of the evidence as assessed using GRADE was rated from very low to high (see Table 4).

Low-quality evidence suggested that there was a significant decrease in PBF with the exercise interventions compared to the usual care (MD: -1.08%, 95% CI: -1.99, -0.17, P=0.02, I^2=50%; Fig. 2). Exercise combined with nutritional interventions was not shown to have superior effects on PBF compared to exercise alone. The effects of the nutritional interventions with or without exercise on PBF compared to the usual care were also not statistically significant, but one individual study (Zhou et al., 2018) showed that electrical acupuncture combined with amino acids was effective at reducing PBF (P<0.001) after a 12-week intervention.

The overall effect of exercise on reducing BMI was not significant compared to the usual care (MD: -0.17 kg/m^2, 95% CI: -0.67, 0.33, P=0.50, I^2=0%; Fig. 3). However, in one individual study (Muscariello et al., 2016) a significant decrease in BMI values was found in the calorie control groups, both with or without protein intake (30.7±1.3 vs 32.0±2.3 kg/m^2, P<0.01; 30.3±0.9 vs 31.1±2.9 kg/m^2, P<0.01). The exercise interventions did not seem to have any significant effects on body weight (P=0.59, Fig. 4).

Exercise combined with nutritional interventions was shown to have significant effects on increasing ASM, with the evidence being of high-quality (MD: 0.41 kg, 95% CI: 0.10, 0.72, P=0.01, I^2=8%; Fig. 5). However, no significant effects on ASM were shown for exercise. Exercise and nutritional interventions, either solely performed or combined, had no significant effects on SMI (Fig. 6). Moreover, a significant difference ASM/Height^2 (P<0.001) after 12 weeks was seen in those who participated in the RCT using electrical acupuncture combined with amino acids.

In addition, low-quality evidence from 2 studies (n=122) suggested that a low-caloric high-protein diet had no statistically significant effects on fat-free mass compared with a low-caloric low-protein diet (MD: 0.37 kg, 95% CI: -0.60, 1.35, P=0.46, I^2=0%; Fig. 7).

Table 4. Summary of Findings for all comparisons among trials included in systematic review

GRADE Summary of Findings for all comparisons among trials included in systematic review

Outcomes	№ of RCTs	№ of participants	Anticipated absolute effects* (95% CI)	Certainty of the evidence (GRADE)	Certainty of the assessments				
			Risk with Intervention		Risk of bias	Inconsistency	Indirectness	imprecision	Publication bias
Exercise versus Usual care									
ASM follow up: range 3 months to 24 weeks	2	118	MD 0.25 higher (0.47 lower to 0.98 higher)	⊕⊕⊕◯ MODERATE [a,b]	Serious	Not serious	Not serious	Not serious	Undetected
SMI follow up: range 8 weeks to 26 weeks	4	234	SMD 0.37 higher (0.07 lower to 0.81 higher)	⊕◯◯◯ VERY LOW [a,c,d]	Serious	Serious	Not serious	Not serious	Strongly suspected
Grip strength follow up: range 8 weeks to 26 weeks	5	284	MD 1.63 higher (0.94 higher to 2.32 higher)	⊕⊕◯◯ LOW [a,d]	Serious	Not serious	Not serious	Not serious	Strongly suspected
Gait speed follow up: range 8 weeks to 26 weeks	4	224	MD 0.13 higher (0.08 higher to 0.18 higher)	⊕⊕⊕◯ MODERATE[a]	Serious	Not serious	Not serious	Not serious	Undetected
BMI follow up: range 8 weeks to 24 weeks	2	193	MD 0.17 lower (0.67 lower to 0.33 higher)	⊕⊕⊕◯ MODERATE[a]	Serious	Not serious	Not serious	Not serious	Undetected
Body weight follow up: range 8 weeks to 24 weeks	2	193	MD 0.31 lower (1.46 lower to 0.83 higher)	⊕⊕⊕◯ MODERATE[a]	Serious	Not serious	Not serious	Not serious	Undetected
PBF follow up: range 8 weeks to 26 weeks	6	417	MD 1.08 lower (1.99 lower to 0.17 lower)	⊕⊕◯◯ LOW [a,d]	Serious	Not serious	Not serious	Not serious	Strongly suspected
Nutrition versus usual care									
SMI - follow up: range 3 months to 16 weeks	2	134	SMD 0.32 SD higher (0.6 lower to 1.24 higher)	⊕⊕◯◯ LOW [a,e]	Serious	Serious	Not serious	Not serious	Undetected
Grip strength follow up: range 3 months to 16 weeks	2	134	MD 0.61 higher (0.49 lower to 1.7 higher)	⊕⊕⊕◯ MODERATE [a]	Serious	Not serious	Not serious	Not serious	Undetected
PBF follow up: range 3 months to 16 weeks	2	134	MD 1.03 lower (2.28 lower to 0.23 higher)	⊕⊕⊕◯ MODERATE [a]	Serious	Not serious	Not serious	Not serious	Undetected
Exercise + Nutrition versus usual care									

ASM follow up: range 3 months to 16 weeks	2	137	MD 0.41 higher (0.1 higher to 0.72 higher)	⊕⊕⊕◯ MODERATE [a]	Serious	Not serious	Not serious	Not serious	Undetected
SMI follow up: range 3 months to 26 weeks	3	187	SMD 0.76 higher (0.08 lower to 1.6 higher)	⊕⊕◯◯ LOW [a,f]	Serious	Serious	Not serious	Not serious	Undetected
Grip strength follow up: range 3 months to 26 weeks	3	187	MD 1.24 higher (0.48 higher to 1.99 higher)	⊕⊕⊕◯ MODERATE [a]	Serious	Not serious	Not serious	Not serious	Undetected
Gait speed follow up: range 3 months to 26 weeks	3	187	MD 0.04 higher (0.02 higher to 0.06 higher)	⊕⊕⊕◯ MODERATE [a]	Serious	Not serious	Not serious	Not serious	Undetected
PBF follow up: range 3 months to 26 weeks	3	187	MD 1.04 lower (2.68 lower to 0.61 higher)	⊕⊕◯◯ LOW [a,g]	Serious	Serious	Not serious	Not serious	Undetected
Exercise + Nutrition versus Exercise									
PBF follow up: range 3 months to 26 weeks	3	146	MD 0.2 lower (0.77 lower to 0.37 higher)	⊕⊕⊕◯ MODERATE [a]	Serious	Not serious	Not serious	Not serious	Undetected
Low-caloric high-protein diet versus Low-caloric low-protein diet									
Grip strength follow up: range 3 months to 4 months	2	122	MD 5.54 higher (5.04 lower to 16.13 higher)	⊕◯◯◯ VERY LOW [a,h,i]	Serious	Serious	Not serious	Not serious	Strongly suspected
Fat-free mass follow up: range 3 months to 4 months	2	122	MD 0.37 higher (0.6 lower to 1.35 higher)	⊕⊕◯◯ LOW [a,i]	Serious	Not serious	Not serious	Not serious	Strongly suspected

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Selection bias, performance bias and detection bias exist in study.
b. Negative outcomes were also reported and the sample size were relatively big.
c. Heterogeneity test showed that P =0.04, I^2=56%.
d. Potential publication bias was existed.
e Heterogeneity test showed that P=0.008, I^2=86%.
f. Heterogeneity test showed that P=0.0005, I^2=87%.
g. Heterogeneity test showed that P=0.0004, I^2=87%.
h. Heterogeneity test showed P<0.00001, I^2 =97%.
i. Sample size were small in one study (n=18).

ASM: appendicular skeletal muscle mass; SMI: skeletal muscle mass; PBF: percentage of body fat; CI: Confidence interval; MD: Mean difference

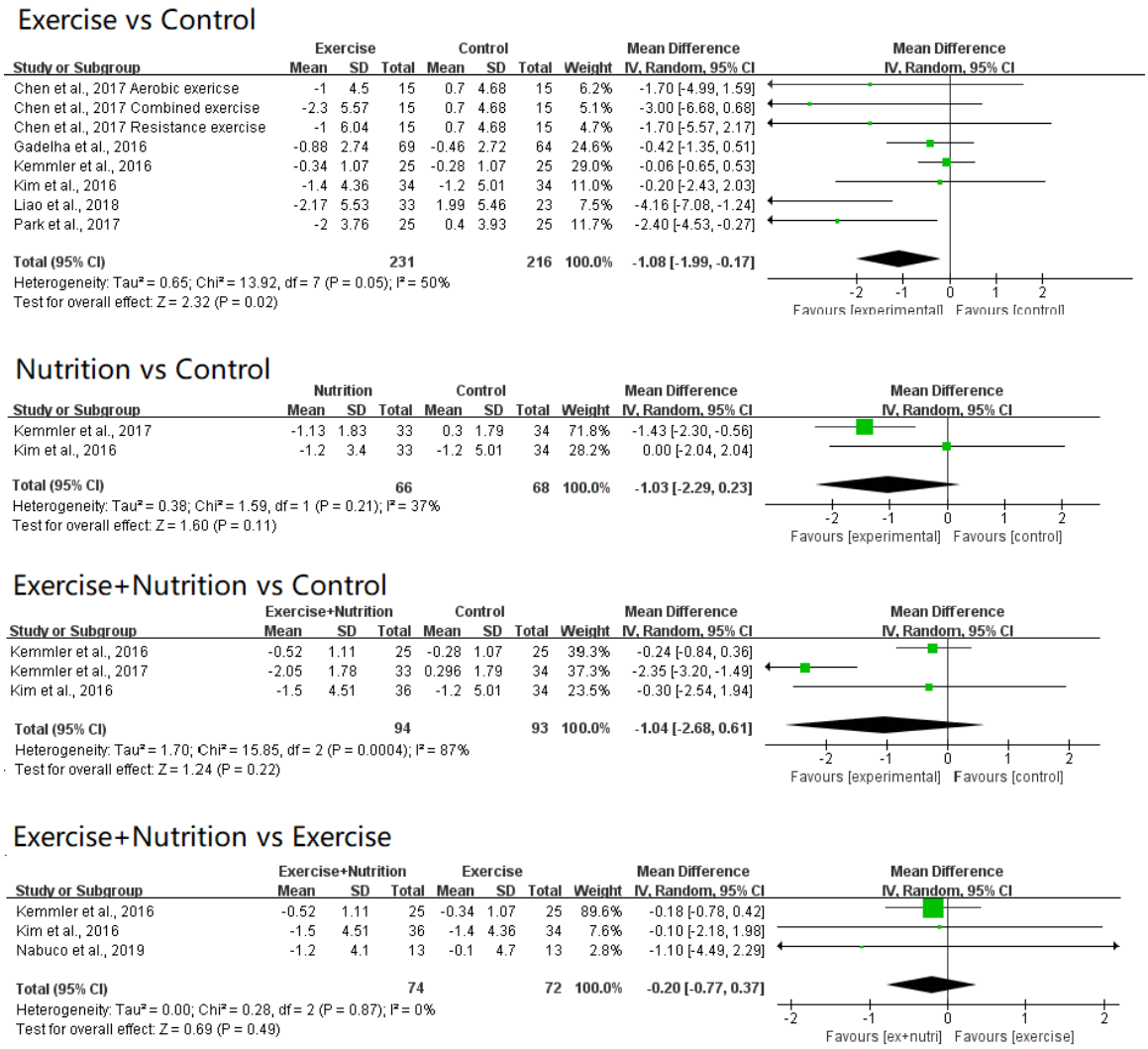


Fig. 2 Forest plot of the effectiveness of exercise and nutrition on the percentage of body fat

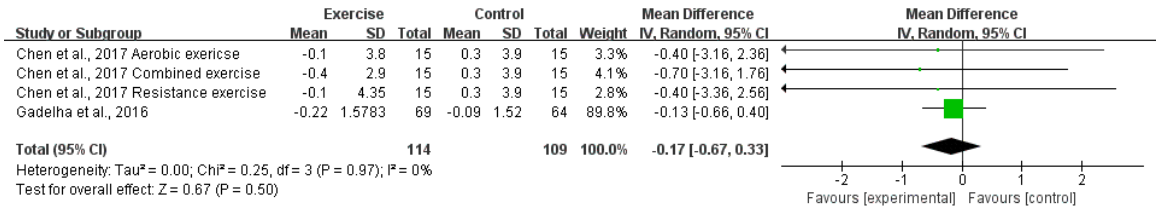


Fig. 3 Forest plot of the effectiveness of exercise on BMI

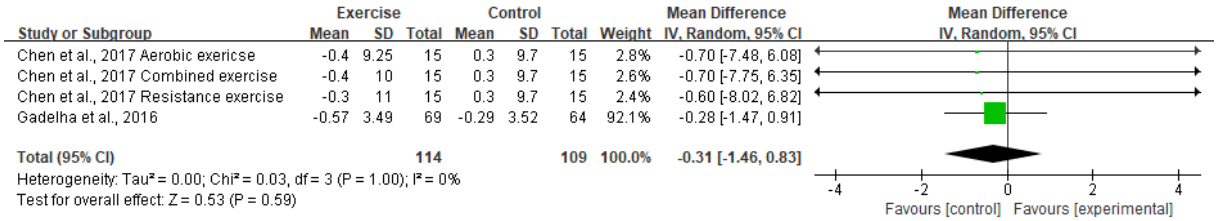


Fig. 4 Forest plot of the effectiveness of exercise on body weight

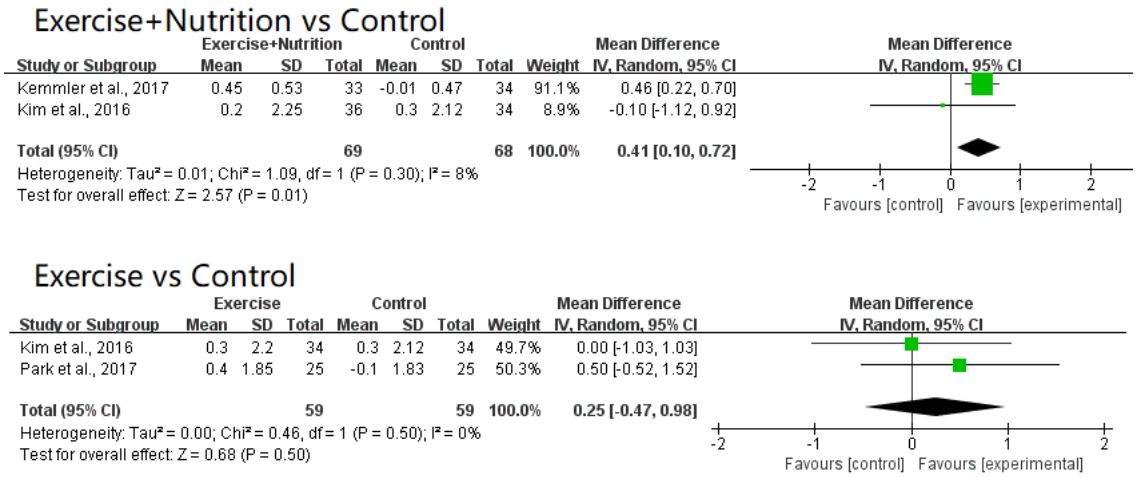


Fig. 5 Forest plot of the effectiveness of exercise and nutrition on appendicular skeletal muscle

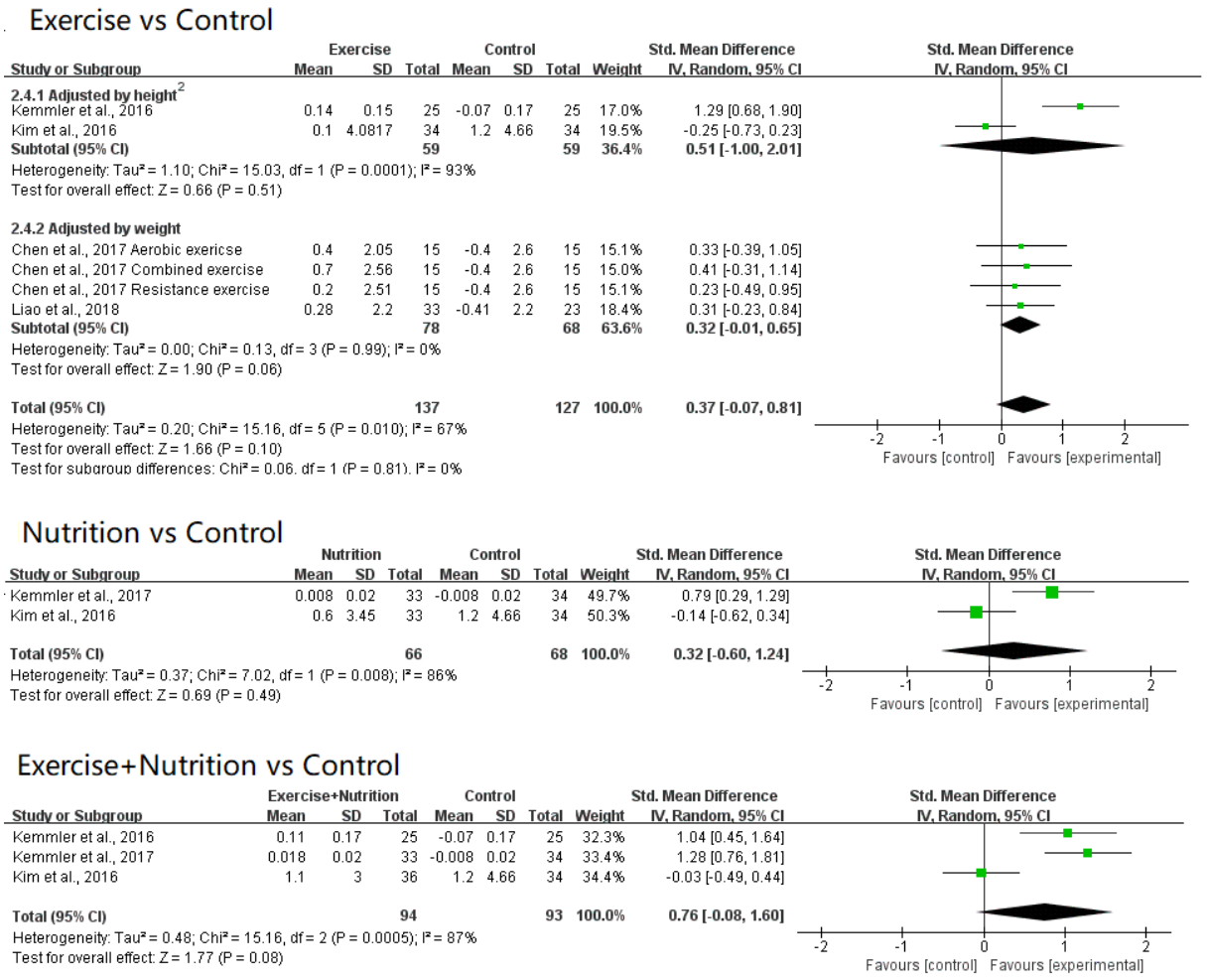


Fig. 6 Forest plot of the effectiveness of exercise and nutrition on skeletal muscle mass index

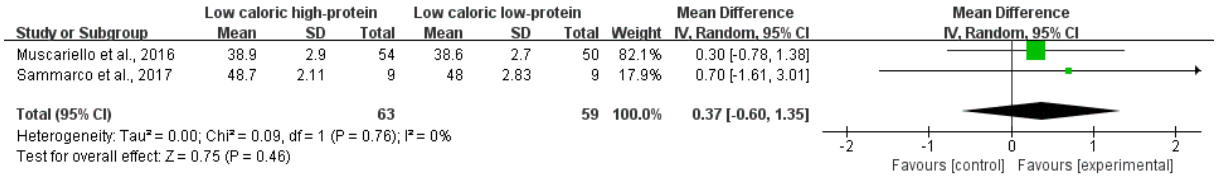


Fig. 7 Forest plot of the effectiveness of calorie control and protein intake on fat-free mass

3.6 Effects of non-pharmacological interventions on secondary outcomes

With regard to the parameters related to muscle strength, data were available for the meta-analyses of various interventions compared with the usual care from 6 studies (n=635) that measured grip strength. Exercise with and without nutritional interventions displayed significant effects on grip strength, with the evidence being of high and low-quality, respectively (Exercise: MD: 1.70 kg, 95% CI: 0.36, 3.04, P=0.01, I^2=59%; Exercise + Nutritional interventions: MD: 1.24 kg, 95% CI: 0.48, 1.99, P=0.001, I^2=0%; Fig. 8), while no significant influence was seen from nutritional interventions. In addition, the meta-analysis of the comparison between the effects of low-caloric high-protein diets and low-caloric low-protein diets on grip strength showed no significant differences (MD: 5.54 kg, 95% CI: -5.04, 16.13, P=0.30, I^2=97%; Fig. 8).

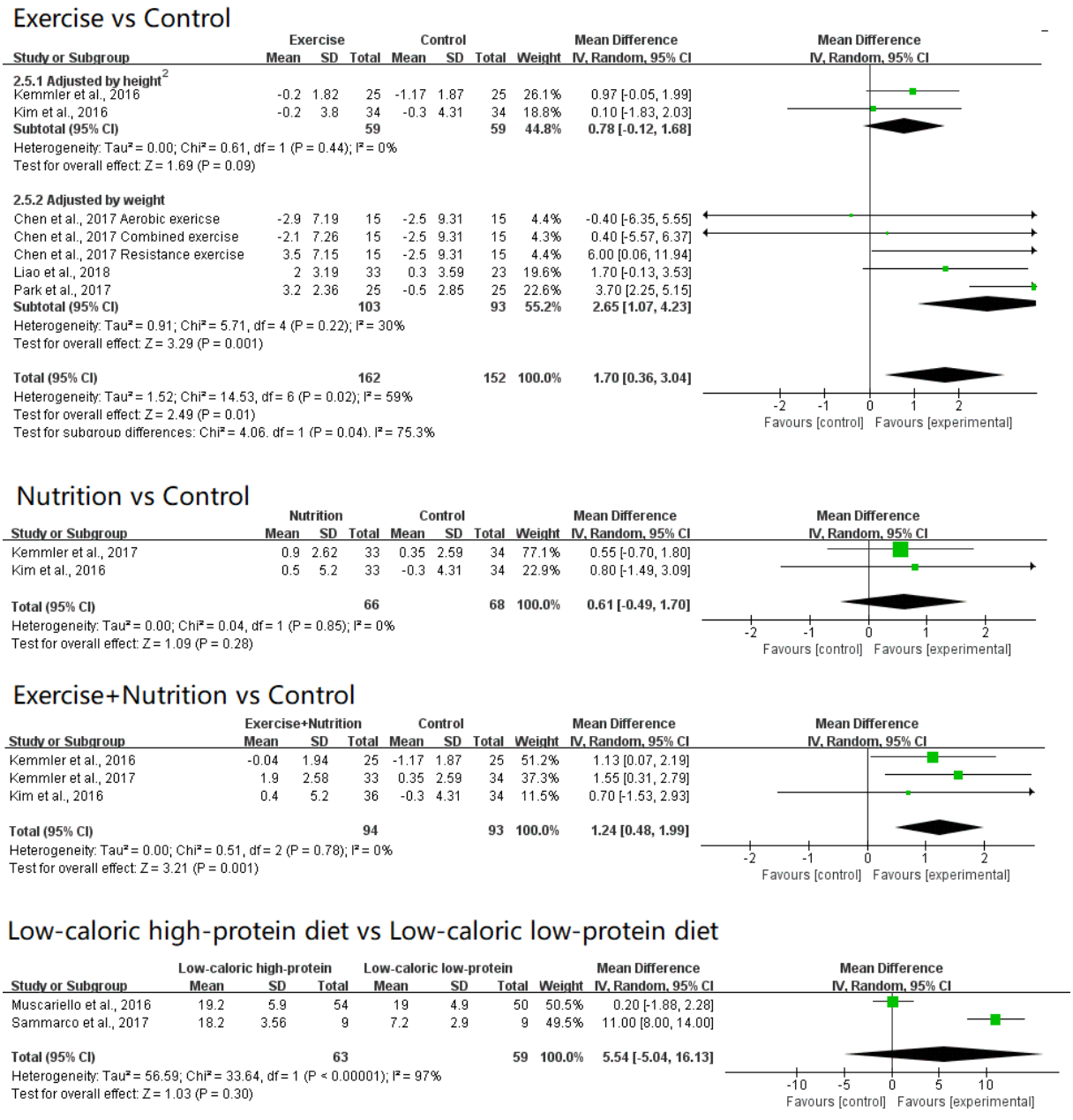


Fig 8. Forest plot of the effect of exercise and nutrition on grip strength

With regard to the parameters related to physical performance-related, data were available for the meta-analyses of various interventions compared with the usual care from 5 studies (n= 411) that measured gait speed. Exercise and exercise combined with nutritional interventions were shown to have significant effects on gait speed, with the evidence being of moderate and high-quality, respectively (Exercise: MD: 0.13 m/s, 95% CI: 0.08, 0.18, P<0.00001, I^2=0%; Exercise + Nutritional interventions: MD: 0.04 m/s, 95% CI: 0.02, 0.06, P=0.0002, I^2=0%; Fig. 9). In addition, the type of high-speed circuit exercise intervention was reported to have had a significant effect on the short physical performance battery (SPPB), but to have had no significant effect on the instrumental activities of daily living (IADL) (Balachandran et al., 2014). By contrast, no significant changes in SPPB were observed from the dietary intervention (Sammarco et al., 2017).

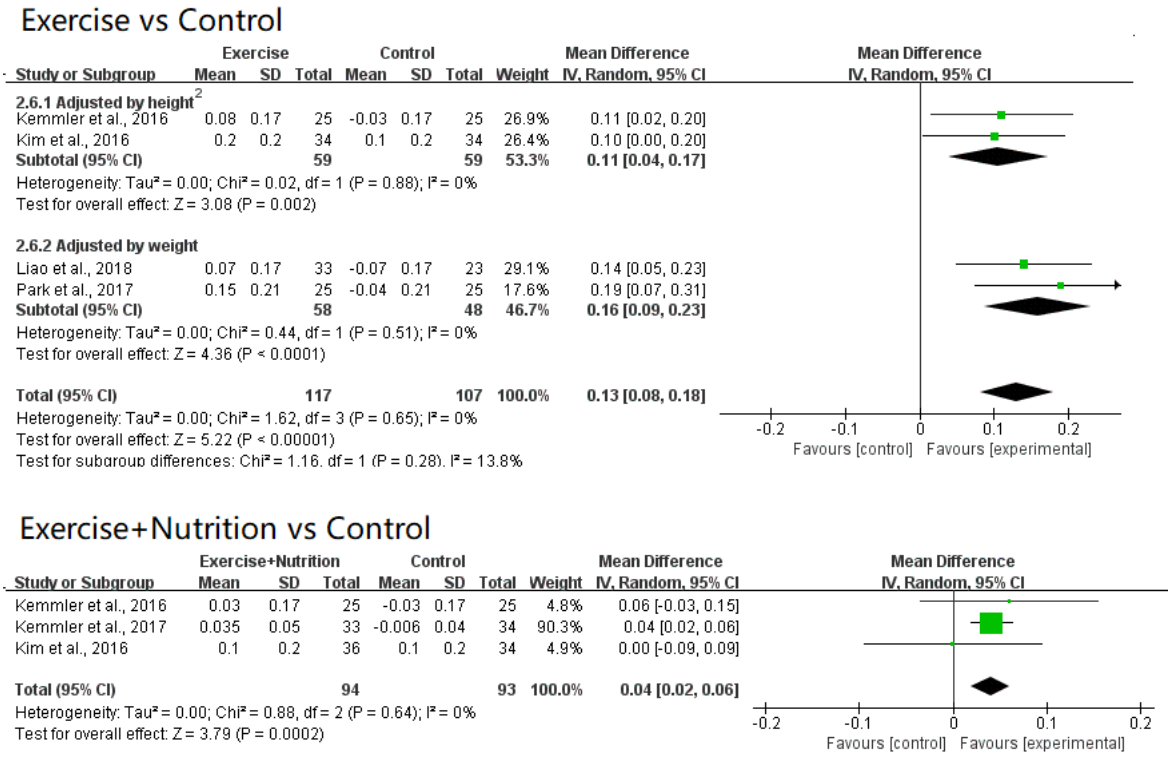


Fig. 9 Forest plot of the effectiveness of exercise and nutrition on gait speed

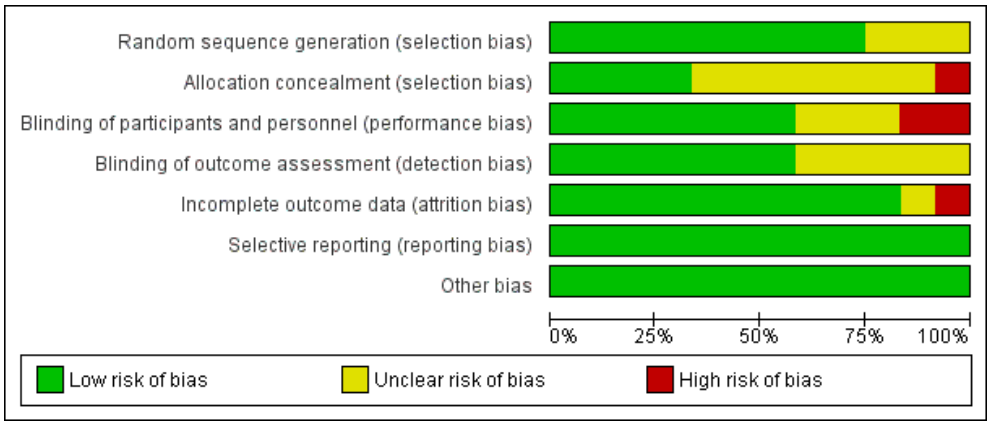
3.7 Subgroup analyses and sensitivity analyses

In the subgroup analyses depending on different diagnostic criteria for sarcopenia (i.e., skeletal muscle mass adjusted by height^2 versus adjusted by weight), the effects of exercise interventions were shown to be significantly different in terms of grip strength (Chi^2=4.06; P=0.04, Fig. 8), but not in SMI (Chi^2=0.19; P=0.66, Fig. 6) or gait speed (Chi^2=1.16; P=0.28, Fig. 9). A sensitivity analysis showed similar results among different correlation coefficients.

3.8 Risk of bias

The risk-of-bias assessment results were shown in Fig. 10 using the Cochrane tool. The random sequence generation was unclear in 3 studies (Chen et al., 2017; Park et al., 2017; Sammarco et al.,

2017), and the details of allocation concealment were not given in 8 studies (Balachandran et al., 2014; Chen et al., 2017; Gadelha et al., 2016; Kim et al., 2016; Park et al., 2017; Sammarco et al., 2017). Five studies did not describe the blinding of the outcome assessors (Kim et al., 2016; Nabuco et al., 2019; Park et al., 2017; Sammarco et al., 2017; Zhou et al., 2018). One study did not report the management of incomplete data (Balachandran et al., 2014). No studies had a reporting bias.



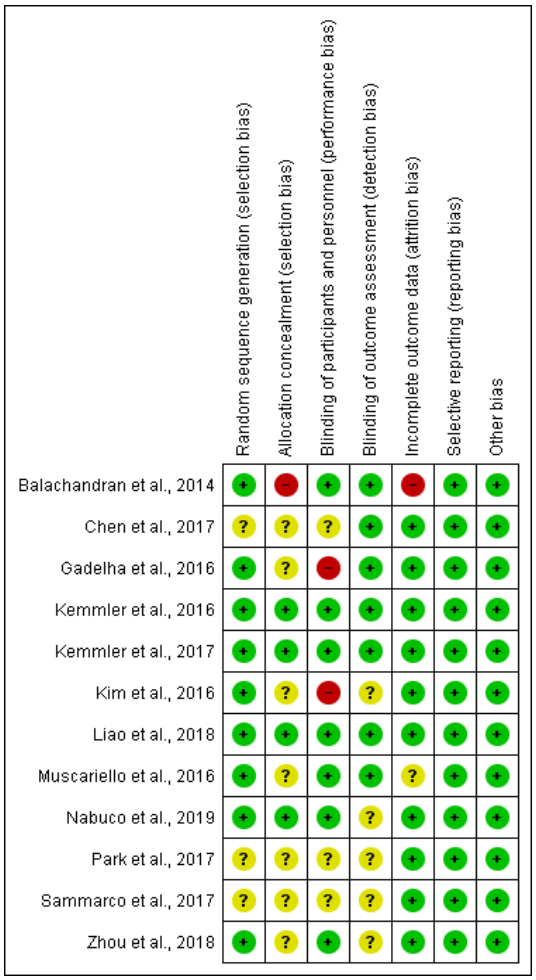


Fig 10. Risk of bias graph

4. Discussion

In this systematic review, we described the various diagnostic criteria for sarcopenic obesity and the components of the non-pharmacological interventions used in RCTs, and evaluated the effectiveness of the interventions through narrative synthesis and meta-analysis. We found that the studies were still lacking in the use of measurement of muscle strength as diagnostic criteria for sarcopenic obesity. Exercise (resistance, aerobic, combined exercise or machine-related exercise) and nutritional interventions (supplements intake, dietary intervention) were the most commonly used interventions in the studies. We found indications that exercise alone or combined with nutritional interventions were effective methods for improving body composition, grip strength, and gait speed, but the quality of the evidence ranged from very low to moderate. This was, mainly because the biases (unclear or high risk of selection bias/performance bias/detection bias) and the inconsistency (heterogeneity > 50%) domains assessed according to the GRADE were rated as serious in some studies (Table 4: summary of GRADE). The effects of nutritional interventions alone on body composition and grip strength were inconsistent. One individual study showed that electrical acupuncture was an effective option for managing body composition.

4.1 Diagnostic criteria for sarcopenic obesity

Given the wide variations in diagnostic criteria for sarcopenia, in 2018 the EWGSOP proposed an updated consensus on the definition of sarcopenia (Cruz-Jentoft et al., 2018). Differing diagnostic criteria used in studies may affect the recruitment of targeted participants and therefore influence the outcomes. If less stringent diagnostic criteria were adopted, the participants may not be representative of those with sarcopenic obesity, causing the effects of the intervention to be exaggerated or underestimated (Martínez-Mesa et al., 2016). According to our subgroup analyses, the effects of exercise on grip strength were significant when skeletal muscle mass was adjusted by weight instead of by height^2, while currently it is hard to say which measurement approach is better. In addition, only a few studies were included in the subgroup analyses with one study (Chen et al., 2017) having a high weight for the pooled effect, thus, it still needs further exploration for the effects of using different diagnostic criteria.

In addition, the lack of measurements of muscle strength and physical performance during the participant recruitment process in most of the studies may be due to the hope of recruiting more participants by reducing the constraints on selection.

Ethnicity also plays an important role in determining the cut-off points for the parameters of sarcopenic obesity. It is essential that there be a match between the reference cut-off values and the targeted study population. One study (Balachandran et al., 2014) did not give any explanation of how to identify the threshold of sarcopenia, while another study (Liao et al., 2018) referred to the cut-off points of different races instead of to those of the local population.

4.2 Effectiveness of non-pharmacological interventions

The findings of our review were similar to those of previous systematic reviews (Hita-Contreras et al., 2018; Hsu et al., 2019; Martínez-Amat et al., 2018). In all of the systematic reviews, exercise interventions were found to be effective at managing sarcopenic obesity, with the results relating to nutritional interventions still needing further exploration. However, the quality of the evidence, was not assessed in the previous systematic reviews. The assessment of the quality conducted in the current systematic review according to the GRADE showed that the evidence quality of the outcomes varied from very low to moderate. Thus, the findings need to be treated with caution.

We found that exercise interventions had more stable and better effects on reducing body fat and increasing muscle strength and gait speed than nutritional interventions, but the effect on increasing skeletal muscle mass was inconsistent. Exercise combined with nutritional interventions had a significant effect in increasing ASM, while exercise interventions solely was not, which may indicate that protein is essential for building muscle. This is supported by another review (Kob et al., 2015) which suggests that sufficient amounts of energy supply and myofibrillar protein are needed for myofibers to function normally. Interestingly, one previous systematic review (Weinheimer, Sands, & Campbell, 2010) affirmed the effect of exercise on increasing ASM, yet Hsu's review (Hsu et al., 2019) denied the additional benefits of nutrition on exercise for the management of sarcopenic obesity. The contrary results were probably due to relatively high heterogeneity across the studies.

Even though the effects of nutritional interventions on managing body composition or muscle strength were inconsistent, the role of nutritional interventions cannot be ignored. According to individual studies (Muscariello et al., 2016; Sammarco et al., 2017), caloric control is an effective means of decreasing body fat. This is consistent with previous systematic reviews (Cheng, Hsu & Liu, 2018; Liao et al., 2017) that they found the most effective interventions for reducing body fat should contain the key features of low calorie, controlled fat and increased amounts of exercise. The function of protein on muscle building also cannot be ignored. Protein could help to prevent the loss of lean mass associated with weight reduction and help maintain physical performance (Anthony, 2016; Goisser et al., 2015). For example, one individual study (Sammarco et al., 2017) found a great reduction in lean body mass in a placebo group compared to a protein intake group.

Nutritional interventions may show weak effectiveness because of the short duration times of the interventions (Coulston et al., 2013). According to one individual study (Zhou et al., 2018) that was included in this systematic review, the ASM did not change significantly in the amino acids intake group in week 12 or 20, and only changed after week 28. This is also supported by Muscariello's study (Muscariello et al., 2016). Hence, 3 months nutritional interventions may be sufficient for losing body fat, while a longer time is needed to manage muscle-related parameters.

There were other limitations in the designs of the studies. First, none of the studies assessed the baseline nutritional status of the participants, even though malnutrition has a strong relationship with sarcopenia (Schaafsma, 2009). Differences in baseline measurements may have influenced the outcomes. Second, only two RCTs (Chen et al., 2017; Liao et al., 2018) conducted follow-up assessments 4 weeks or 6 months after the intervention. While lifestyle changes are a long-term process and the effects are directly influenced by the participant's level of adherence to the interventions (Middleton, Anton, & Perri, 2013), following up on and tracing the levels of adherence are extremely important, especially in nutritional studies. Third, due to insufficient data, subgroup analyses of levels of obesity, the sex of the participants, and the length of the interventions were not conducted. But the effects of these factors should also be considered when designing future studies.

The limitations of the study design were also evident in the GRADE assessment. The GRADE assessments showed that some of the evidence was of low or very low quality (e.g., the effects of exercise on SMI; the effects of dietary management on grip strength), indicating that the results need to be treated with caution, and that well-designed and rigorous studies are still needed to identify evidence-based interventions for managing sarcopenic obesity.

4.3 Limitations

Some limitations were identified in this systematic review. First, varying diagnostic criteria for sarcopenic obesity in the included studies made it hard to maintain homogeneity across the studies. Well-defined criteria for diagnosing participants should be considered (e.g., the European or Asian guidelines for sarcopenia). Second, the various interventions included in this review led to heterogeneity between studies, which may be because of clinical diversity or methodological diversity (e.g., different diagnostic criteria leading to variability in the participants; variabilities in the study design, and diversified biases). Thus, we performed the meta-analysis with a random effect model to incorporate heterogeneity. Third, some original data could not be obtained, so Change SDs had to be calculated by assuming the correlation coefficients (r) according to the recommended equations in the Cochrane Handbook (Higgins & Green, 2011). But we conducted sensitive analyses to test the rigour (Supplementary file: Appendix 4), and found similar results among different correlation coefficients (r). Fourth, some meta-analyses only contained two studies, which may have affected the generalizability of the results. More data is needed in the future to confirm the conclusions. Fifth, some articles that were published in other languages may have been missed due to language restrictions during the literature search.

Despite the limitations, the findings still could provide some insights on how to provide better lifestyle guidance to people with sarcopenic obesity. It could also shed some light on the management of osteosarcopenic obesity, which has a strong connection with sarcopenic obesity.

5. Conclusions

To the best of our knowledge, this review is the first systematic review of RCTs to include all kinds of non-pharmacological interventions for people with sarcopenic obesity. The majority of the studies only included muscle quantity as the diagnostic criteria for sarcopenia, but muscle strength and physical performance should be considered as well. Exercise with or without nutritional interventions was identified as the most commonly used approach to treat sarcopenic obesity. Electrical acupuncture also exhibited potential effects on body composition. The results of the meta-analysis indicated that interventions involving caloric control and appropriate exercise can reduce body fat. Combining exercise with nutritional interventions shows potential for improving grip strength and gait speed, while exercise is still the most effective method for managing sarcopenic obesity. But the above evidence should be treated with caution because some of the evidence was of low quality. Further studies with large samples, stringent diagnostic criteria for participants and long-term follow-ups are still needed to confirm the effects of nutritional interventions, whether combined with exercise or not, on muscle quantity for people with sarcopenic obesity.

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Author Contributions

Yue-Heng Yin conducted the literature search, selected the studies, extracted the data, assessed the quality of the included studies, conducted the meta-analysis, and wrote the first draft of the manuscript. Justina Yat Wa Liu selected the studies, extracted the data, assessed the quality of the studies, and commented on the manuscript. Maritta Välimäki checked and commented on the whole process and the manuscript.

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