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Original Study

Interventions for Treating Sarcopenia: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

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A B S T R A C T

Background: Much interest has been focused on interventions for treating sarcopenia; however, the effects have gained little evidence.
Objective: To analyze the effectiveness of exercise, nutritional, drug, and combinational interventions for treating sarcopenia in older people.
Method: We systematically searched MEDLINE via PubMed, the Cochrane Library of Cochrane Reviews and Cochrane Central Register of Controlled Trials, and Ichushi-Web for randomized controlled trials (RCTs) from January 2000 to December 2016. We have assessed the type of intervention, the cohort used, the way sarcopenia was diagnosed, the outcomes, and the quality of evidence. We meta-analyzed the outcomes with the net difference between-group treatment from baseline to the end of the study.
Results: We screened a total of 2668 records and included seven RCTs that investigated the effects of exercise (4 RCTs), nutrition (5 RCTs), drug (1 RCT), and combination (4 RCTs) on muscle mass, strength, and function in older people with sarcopenia. Very low to low-quality evidence suggests that (1) exercise interventions may play a role in improving muscle mass, muscle strength, and walking speed in 3 months of intervention; (2) nutritional interventions may be effective in improving muscle strength in 3 months of intervention; (3) as drug intervention, selective androgen receptor modulator had no clear effect on muscle mass, strength, and physical function; and (4) a combined intervention of exercise and nutrition may have positive effects in improving the walking speed in 3 months of intervention.
Conclusion: Our systematic review and meta-analysis showed some positive effects of exercise and nutritional interventions for treating sarcopenia in older people, although the quality of the evidence was low. Future high-quality RCTs should be implemented to strengthen the results.

Sarcopenia—the age-related loss of skeletal muscle mass, strength, and function[1,2]—is a common clinical problem in older people and often leads to severe adverse outcomes. The growing interest of sarcopenia has highlighted the need to understand more about its management. The preservation or improvement of physical function and independent living are vital in frail older adults,[3] and sarcopenia is a major contributor to physical frailty.[4] Several definitions of sarcopenia have been globally proposed thus far,[5–12] although no consensus has been reached. Moreover, sarcopenia is now recognized as an independent condition by an ICD-10-CM code.[13]

Y.Y., H.K., and M.Y. declare no conflicts of interest. H.A. has accepted honoraria (eg, as lecture fees) of ≥500,000 yen in total annual income from each company (Abbott and Daiichisankyo), and has accepted clinical research funding of ≥1,000,000 yen in total annual research grants paid from a single company (Daiichisankyo). A.H. has accepted honoraria (eg, as lecture fees) of ≥500,000 yen in total annual income from a single company (Taisho Toyama Pharmaceutical). H.W. has accepted honoraria (eg, as lecture fees) of ≥500,000 yen in total annual income from each company (Clinico and Nestle). All authors are members of the Japanese Association on Sarcopenia and Frailty.

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Although the awareness of the clinical importance of sarcopenia has increased, the implementation of therapeutic interventions for sarcopenia remains challenging. Exercise and nutrition have been found to be effective for treating different conditions in various populations of adults and older people; however, the evidence of the effects of such treatment is scarce.[5,14] In the present study, we aimed to assess the effectiveness of exercise, nutritional, drug, and their combinational interventions for treating sarcopenia in older people, particularly reported in randomized controlled trials (RCTs).

Materials and Methods

We performed this systematic review in accordance with the PRISMA guidelines.[15] The protocol of this systematic review is registered at PROSPERO, as CRD42017054215.

Review Questions

(1) Does exercise intervention improve the muscle mass, strength, and physical function of older people with sarcopenia? (2) Does nutritional intervention improve the muscle mass, strength, and physical function of older people with sarcopenia? (3) Does drug intervention improve the muscle mass, strength, and physical function of older people with sarcopenia? and (4) Does a combined intervention improve the muscle mass, strength, and physical function of older people with sarcopenia?

Search Strategy

A systematic search was conducted on the MEDLINE via PubMed, Cochrane Library of Cochrane Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL), and Ichushi-Web (Igaku Chuo Zasshi; Japan Medical Abstracts Society)[16] databases to identify suitable articles from January 2000 to December 2016 (see Supplementary Material for details on the search strategies). Moreover, a manual search of the reference lists of relevant reviews and articles included in the systematic review was performed. We did not apply any language restrictions.

Types of Study to Be Included

We included RCTs to assess the effects of different treatments, including nutritional, exercise, and drug treatments, and their combination, in the treatment of sarcopenia. We also included trials that could not be analyzed on an intention-to-treat basis, and those that lacked blinding or placebo treatment use.

Types of Participants: Inclusion and Exclusion Criteria

We included all studies with older individuals diagnosed with sarcopenia. The studies included in this review provided the definition of sarcopenia based on the assessment of muscle mass, with or without muscle strength or physical performance. We expected that the participants would be diagnosed based on the definitions of the European Working Group on Sarcopenia in Older People (EWGSOP),[2] the Asian Working Group for Sarcopenia (AWGS),[12] or others.

We excluded the cases with the following conditions: not elderly, or those with decreased functional status due to other specific health conditions, such as cancer, diabetes, AIDS, chronic heart failure, chronic obstructive pulmonary disease, kidney failure, liver cirrhosis, rheumatoid arthritis, anorexia, recent surgery or transplant, or severe neurologic or cognitive disorders.

Types of Interventions

All types of exercise, nutritional, and drug interventions for the treatment of sarcopenia were included for assessment and were compared.

Types of Outcomes

The primary outcome was muscle mass (eg, appendicular skeletal muscle, skeletal muscle mass index, and lean body mass). The secondary outcomes included muscle strength (eg, handgrip strength, knee extension strength) and physical function (eg, walking speed).

Data Extraction

The full texts were read if the study was found to be eligible by at least 1 reviewer, and at least 2 reviewers (each from Y.Y., H.W., or M.Y.) then evaluated the eligibility of the retrieved full-text studies. Consensus on inclusion was reached via discussion among the reviewers. The excluded studies and the reasons for exclusion are listed. Any disagreements were resolved via a discussion. The following data were extracted from the included studies: (1) author,

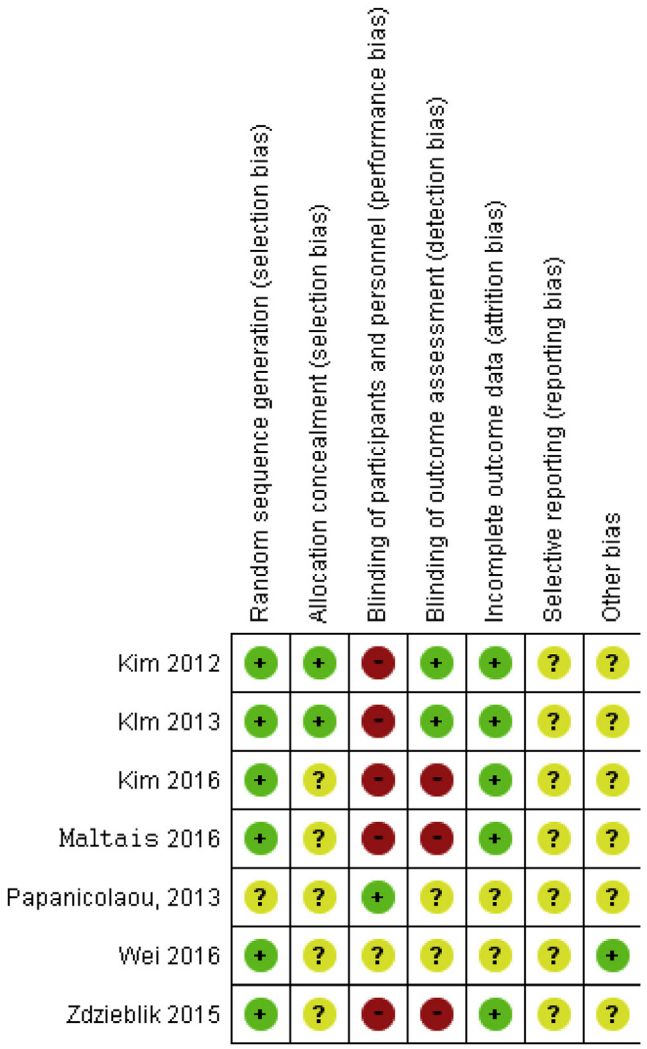


Fig. 1. Risk of bias summary of interventions: review authors' judgments about each risk of bias item for each included study.

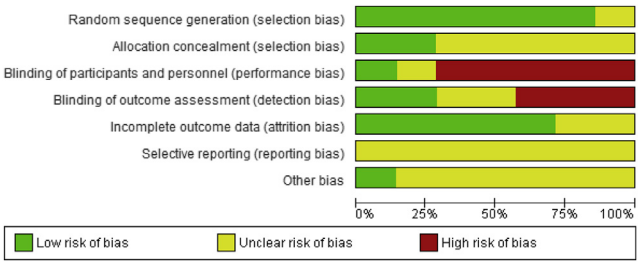


Fig. 2. Risk of bias graph of interventions: review authors' judgments about each risk of bias item presented as percentages across all included studies.

year, and intervention characteristics; (2) study design; (3) country of origin; (4) number of patients allocated to intervention and control; (5) participant characteristics [ie, age, sex, body mass index, activity level]; (6) criteria for the definition of sarcopenia; (7) mobility and functional level (assessed by, eg, gait speed); (8) upper and lower body muscle strength (eg, handgrip strength, knee extension strength); (9) muscle mass and body weight [assessed by bioelectrical impedance analysis (BIA), dual-energy x-ray absorptiometry (DXA), or anthropometric measurements such as limb circumference and body mass index]; and (10) disease-specific baseline characteristics of the participants.

Analysis of Subgroups

All data were subgrouped according to the intervention type, and according to whether the patients received other interventions such as medication, other types of training, or combinations of these interventions.

Assessment of Quality and Risk of Bias of the Included Studies

The risk of bias was assessed according to the Cochrane Collaboration's tool for assessing quality and the risk of bias.[17] At least 2 reviewers independently assessed the risk of bias in the included studies by considering the following characteristics: (1) randomized sequence generation, (2) treatment allocation concealment, (3) blinding, (4) completeness of the outcome data, (5) selective outcome reporting, and (6) other sources of bias. Within each domain, an independent judgment by the 2 reviewers, in terms of high, low, or unclear risk of bias, was made.

Strategy for Data Synthesis

The outcome of the meta-analysis was the net difference in the outcome from the baseline to the end of the study between the intervention and control groups. A random effects model was used

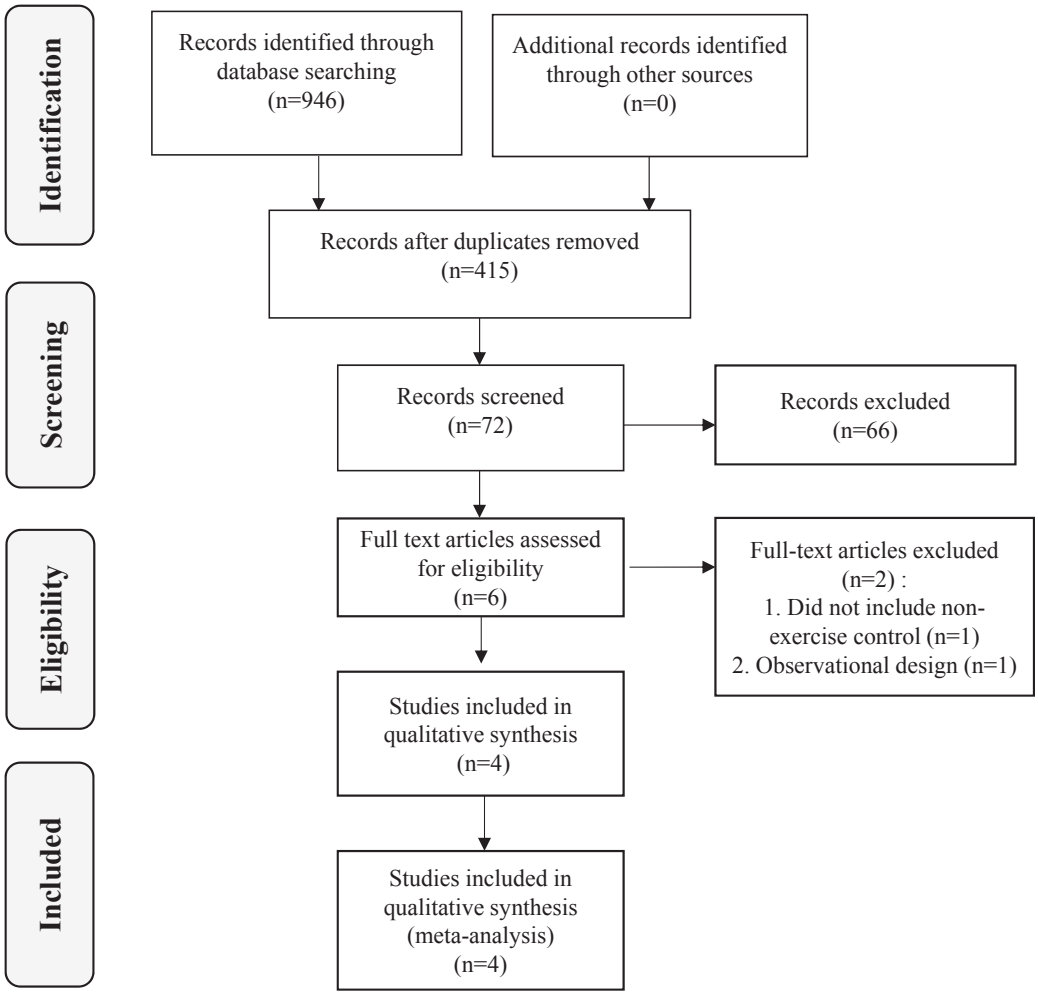


Fig. 3. PRISMA diagram of exercise intervention.

Table 1
Basic Characteristics of Randomized Controlled Trials Enrolled in the Meta-analyses

Study, Year	Participants	Diagnosis of Sarcopenia	Age, y	Sex	Sample Size, n	Design	Blinding	Randomization	Intervention(s)	Duration	Outcome
Kim et al, 2012[19]	Community dwelling with sarcopenia	Low ASM (with BIA) Low BMI Low knee extension strength Low walking speed	75 or older	Female	155	Parallel	Not stated	Computer-generated randomization	1. Exercise 2. Nutrition 3. Health education	3 mo	ASM Knee extension strength Usual walking speed Maximum walking speed
Kim et al, 2013[20]	Community dwelling with sarcopenia	Low ASM (with BIA) Low BMI Low knee extension strength Low walking speed	75 or older	Female	128	Parallel	Not stated	Computer-generated randomization	1. Exercise 2. Nutrition 3. Health education	3 mo	ASM Grip strength Knee extension strength Usual walking speed Maximum walking speed
Kim et al, 2016[21]	Community dwelling with sarcopenic obesity	Low ASM (with BIA) Low grip strength Low walking speed High body fat mass	70 or older	Female	139	Parallel	Not stated	Computer-generated randomization	1. Exercise 2. Nutrition 3. Health education	3 mo	ASM Grip strength Knee extension strength Usual walking speed Maximum walking speed
Maltais et al 2016[23]	Community dwelling with sarcopenia	Low ASMI (with DXA)	60-75	Male	26	Parallel	Double	Not stated	1. Exercise 2. Nutrition	4 mo	ASMI Usual walking speed Maximum walking speed Timed Up & Go test
Papanicolaou et al, 2013[24]	Community dwelling with sarcopenia	Low ASM (with DXA)	65 or older	Female	170	Parallel	Double	Not stated	Drug	6 mo	Appendicular LBM Total LBM Bilateral leg press Stair climbing power Walking speed SPPB, AM-PAC
Wei et al, 2016[22]	Community dwelling with muscle loss	Low SMI (with DXA)	65 or older	Male Female	80	Parallel	Not stated	Computer-generated randomization	Exercise	12 wk	Cross-sectional area of vastus medialis Knee extension strength
Zdzieblik et al, 2015[25]	Community dwelling with sarcopenia	Low muscle mass (with DXA) Low grip strength	65 or older	Male	53	Parallel	Double	Computer-generated randomization	Nutrition	3 mo	Fat-free mass Knee extension strength

AM-PAC, Activity Measure for Post Acute Care; ASM, appendicular skeletal muscle; BMI, body mass index; LBM, lean body mass; SMI, skeletal mass index; SPPB, Short Physical Performance Battery.

Table 2
Characteristics of Exercise Intervention Protocol

Study, Year	Case, n	Control, n	Exercise Intervention	Control	Others
Kim et al, 2012[19]	77	78	60-minute comprehensive training program twice a week	1. Nutrition: amino acid supplementation 2. Health education	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
Kim et al, 2013[20]	64	64	60-minute comprehensive training program twice a week	1. Nutrition: tea catechin supplementation 2. Health education	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
Kim et al, 2016[21]	71	68	60-minute comprehensive training program twice a week	1. Nutrition: amino acid and tea catechin supplementation 2. Health education	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
Wei et al, 2016[22]	20	60	WBV training	No training	There were 3 groups: WBV of (1) low frequency, of (2) medium frequency, and of (3) high frequency, and no WBV.

to account for the heterogeneity among studies. Forrest plots were generated for the graphical presentation of the outcomes. Statistical analysis was performed using RevMan 5 (Review Manager [computer program], version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) with the standard methods recommended by the Cochrane Collaboration. The effect size was represented by the weighted mean difference and 95% confidence interval.

"Summary of the Findings" Tables and Assessment of the Quality of the Evidence

We have presented the results for muscle mass, muscle strength, and physical function (our primary and secondary outcomes) in the Summary of the Findings tables (Supplementary Material) for easy comparison of each intervention versus the control. For the comparison of each outcome, we graded the evidence as "very low," "low,"

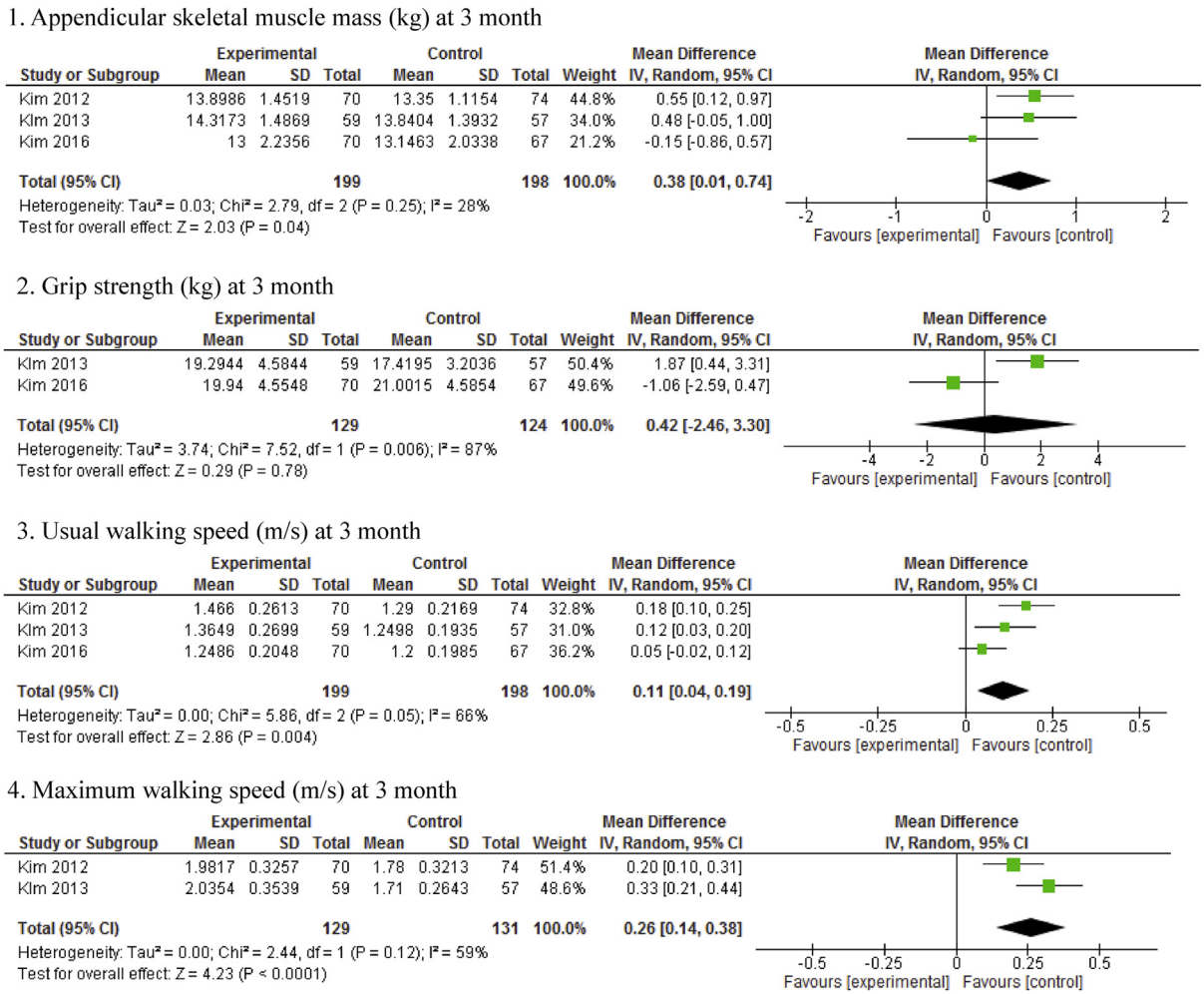


Fig. 4. Forest plot for exercise intervention.

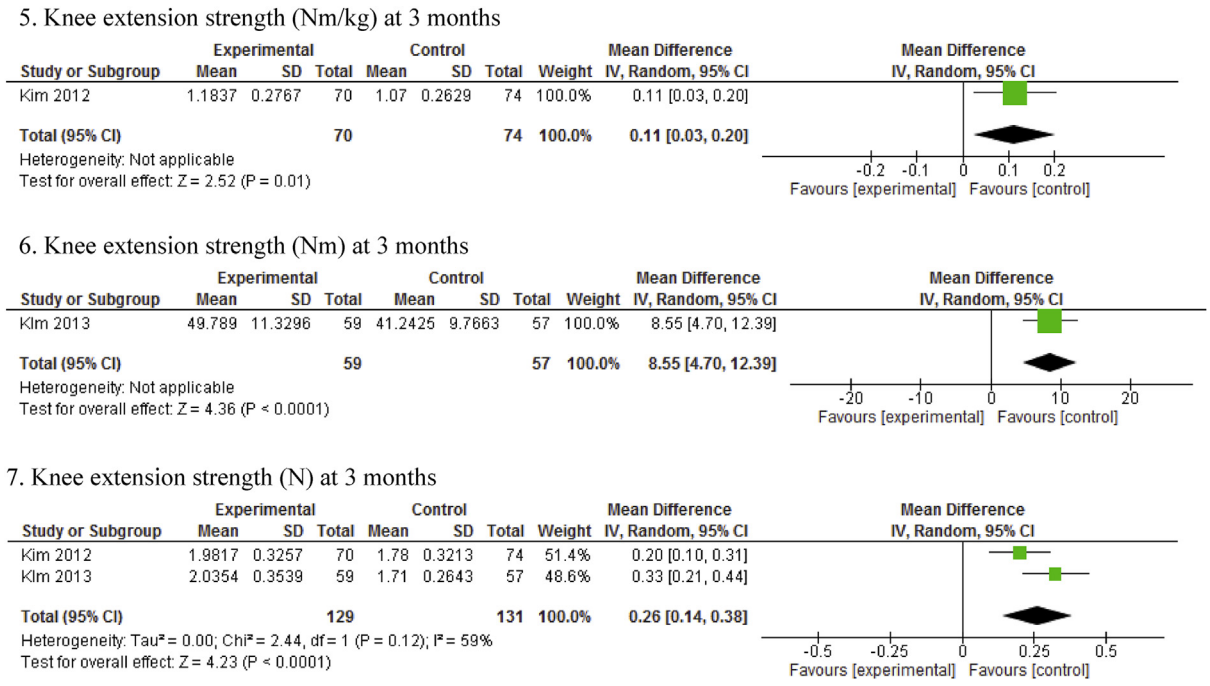


Fig. 4. (*continued*).

"moderate," or "high" in accordance with the GRADE working group criteria.[18]

Results

Search Results

We screened a total of 2668 records from MEDLINE (n = 1388), the Cochrane Library (n = 125), and Ichushi-Web (n = 1155) from January 2000 to December 2016. We did not identify any additional new trials from the PROSPERO database. Overall, with duplications, we screened a total of 946 records on exercise intervention, 1171 records on nutritional intervention, 1011 records on drug intervention, and 315 records on combined intervention. Figures 1 and 2 show the risk of bias summary and graph of the included studies, respectively.

Exercise Intervention

We screened a total of 946 records on exercise interventions. Figure 3 shows the PRISMA flow chart of the identified, discarded, and included articles. A total of 4 papers (sample size, 448) were finally included in the meta-analysis.

Details of the study population, methods, sarcopenia diagnosis, interventions, and outcomes of the individual trials are provided in Tables 1 and 2. All the trials included older participants living in the community with sarcopenia, and 1 included individuals with sarcopenic obesity. None of the trials employed established diagnostic criteria of sarcopenia, such as EWGSOP or AWGS; however, the loss of skeletal muscle mass was adopted for the diagnosis of sarcopenia in all the trials, including 1 trial wherein sarcopenia was diagnosed by combining the loss of muscle mass and strength and/or decline in physical function. Three of the trials used BIA and 1 used DXA to measure the muscle mass.

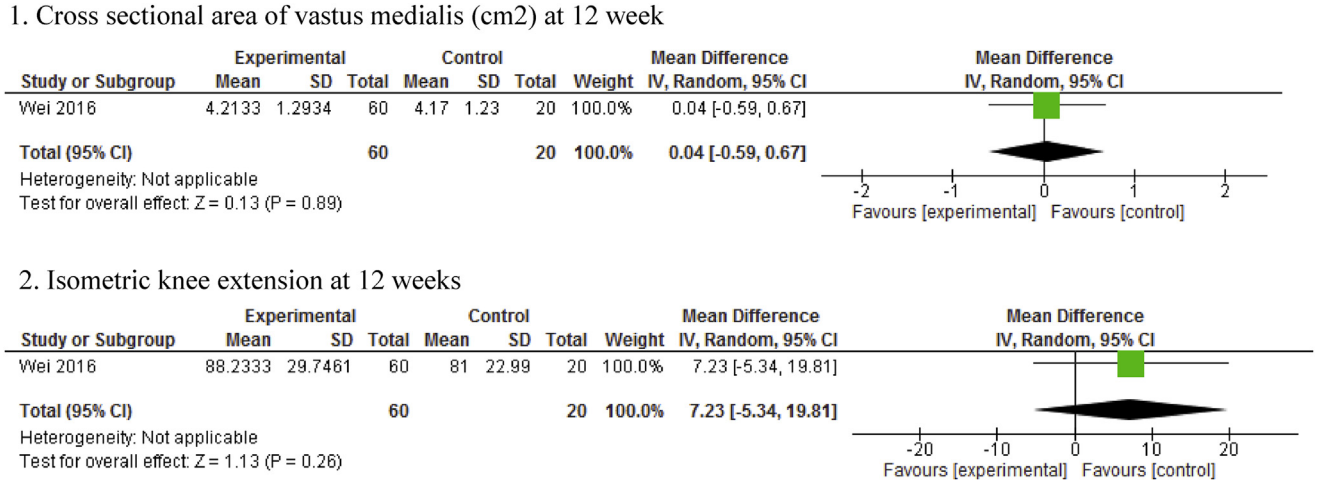


Fig. 5. Forest plot for WBV training intervention.

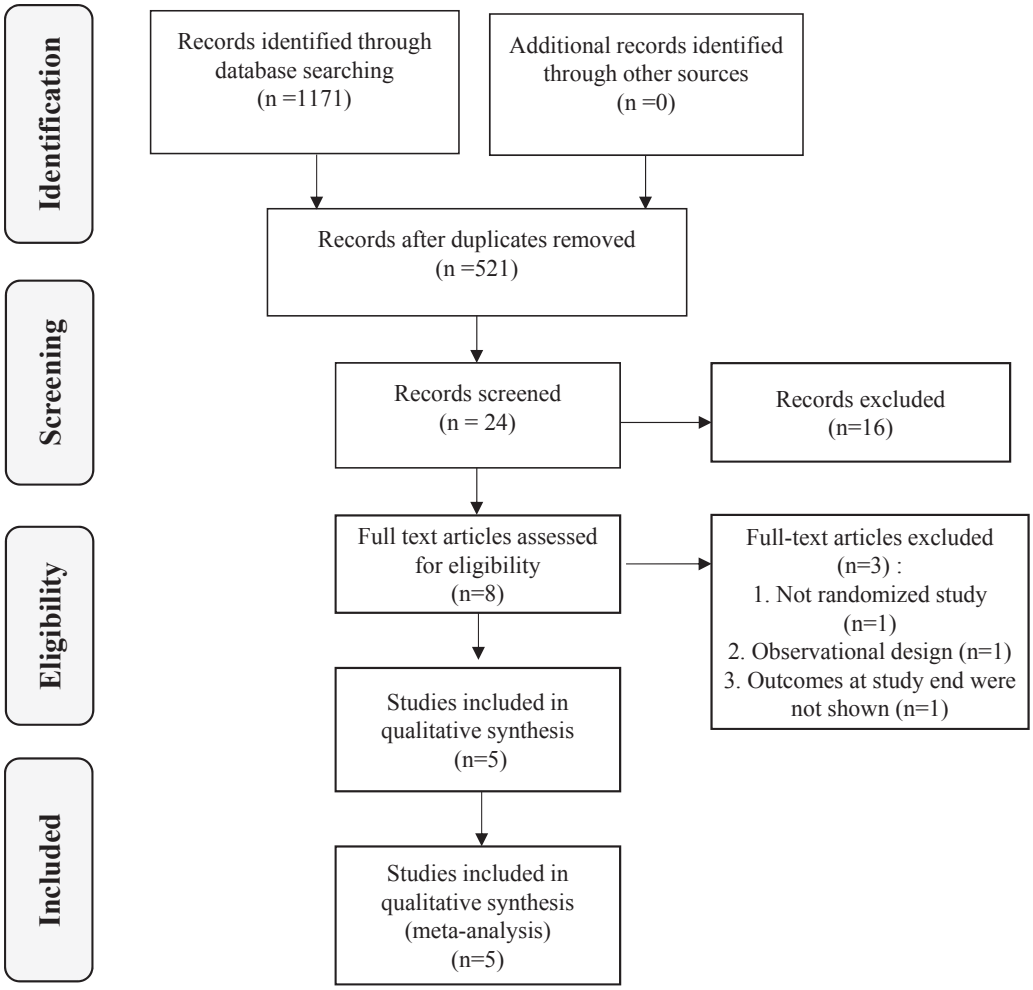


Fig. 6. PRISMA diagram of nutritional intervention.

In 3 trials,[19–21] the main objective was to verify the effects of the combined intervention of exercise and nutrition on sarcopenia improvement. To ascertain the effect of exercise intervention, we used subgroup analysis, including "exercise versus any types of nutrition" and "exercise versus education." These 3 trials used exercise interventions involving a 60-minute comprehensive training program that included resistance training twice a week for 3 months, with control groups of amino acid supplementation, tea catechin supplementation, amino acid and tea catechin supplementation, and health education.

Wei et al[22] used whole-body vibration (WBV) training for 12 weeks with a no-training control group. The authors included 4 groups of WBV training over 12 weeks: low-frequency/long duration (20 Hz, 720 seconds), medium-frequency/medium duration (40 Hz, 360 seconds), high-frequency/short duration (60 Hz, 240 seconds), and control (no training). We used subgroup analysis, including "all types of WBV training versus control," to ascertain the comprehensive effect of WBV training on sarcopenia.

Table 3
Characteristics of Nutritional Intervention Protocol

Study, Year	Case, n	Control, n	Nutritional Intervention	Control	Others
Kim et al, 2012[19]	77	78	EAA (3 g) supplementation (2 times a day: 6 g daily)	1. Exercise 2. Health education	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
Kim et al, 2013[20]	64	64	Tea catechin (540 mg) supplementation (daily)	1. Exercise 2. Health education	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
Kim et al, 2016[21]	70	69	EAA (3 g) and tea catechin (540 mg) supplementation (daily)	1. Exercise 2. Health education	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
Maltais et al, 2016[23]	16	10	Protein (12 g), with EAA (7 g), supplementation (daily)	1. Placebo (rice milk)	There were 3 groups: (1) EAA power, (2) EAA milk, and (3) placebo. All participants had resistance training program 3 times a week.
Zdzieblik et al, 2015[25]	26	27	Collagen peptide (15 g) supplementation (daily)	Placebo (silica)	There were 2 groups: (1) protein and (2) placebo. Both groups had resistance training program 3 times a week.

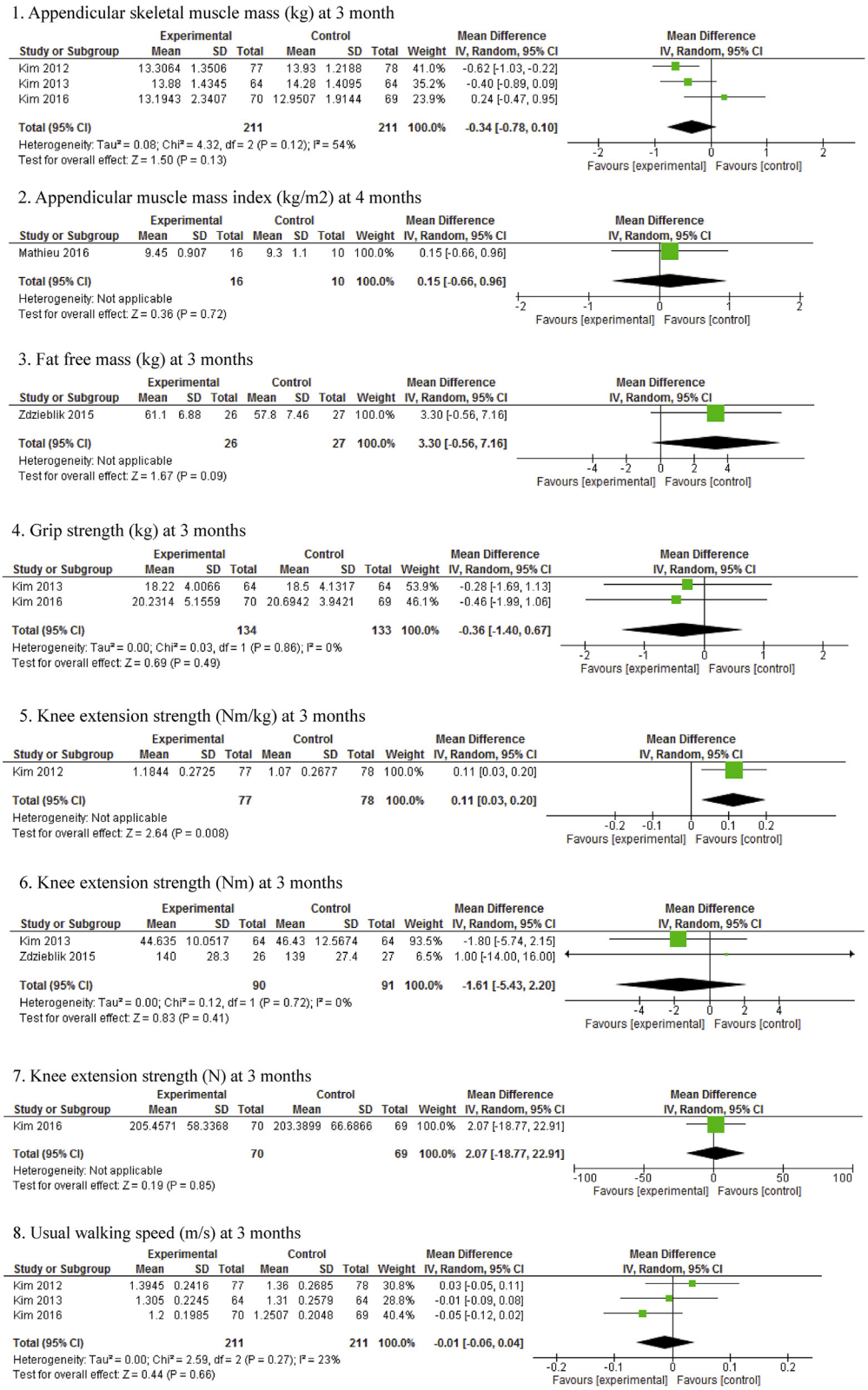


Fig. 7. Forest plot for nutritional intervention.

Effect of comprehensive training

Overall, comprehensive training was effective in improving appendicular skeletal muscle mass [0.38 kg; 95% confidence interval (CI), 0.01-0.74; $P = .04$], usual walking speed (0.11 m/s; 95% CI, 0.04-0.19; $P = .004$), maximum walking speed (0.26 m/s; 95% CI, 0.03-0.20; $P < .001$), and knee extension strength (0.11 Nm/kg; 95% CI, 0.03-0.20; $P = .01$; 8.55 Nm; 95% CI, 4.70-12.39; $P < .01$; 0.26 N; 95% CI, 0.14-0.38; $P < .001$) following 3 months of intervention (Figure 4). However, there was no significant effect of comprehensive training on grip strength (0.42 kg; 95% CI, −2.46 to 3.30; $P =$

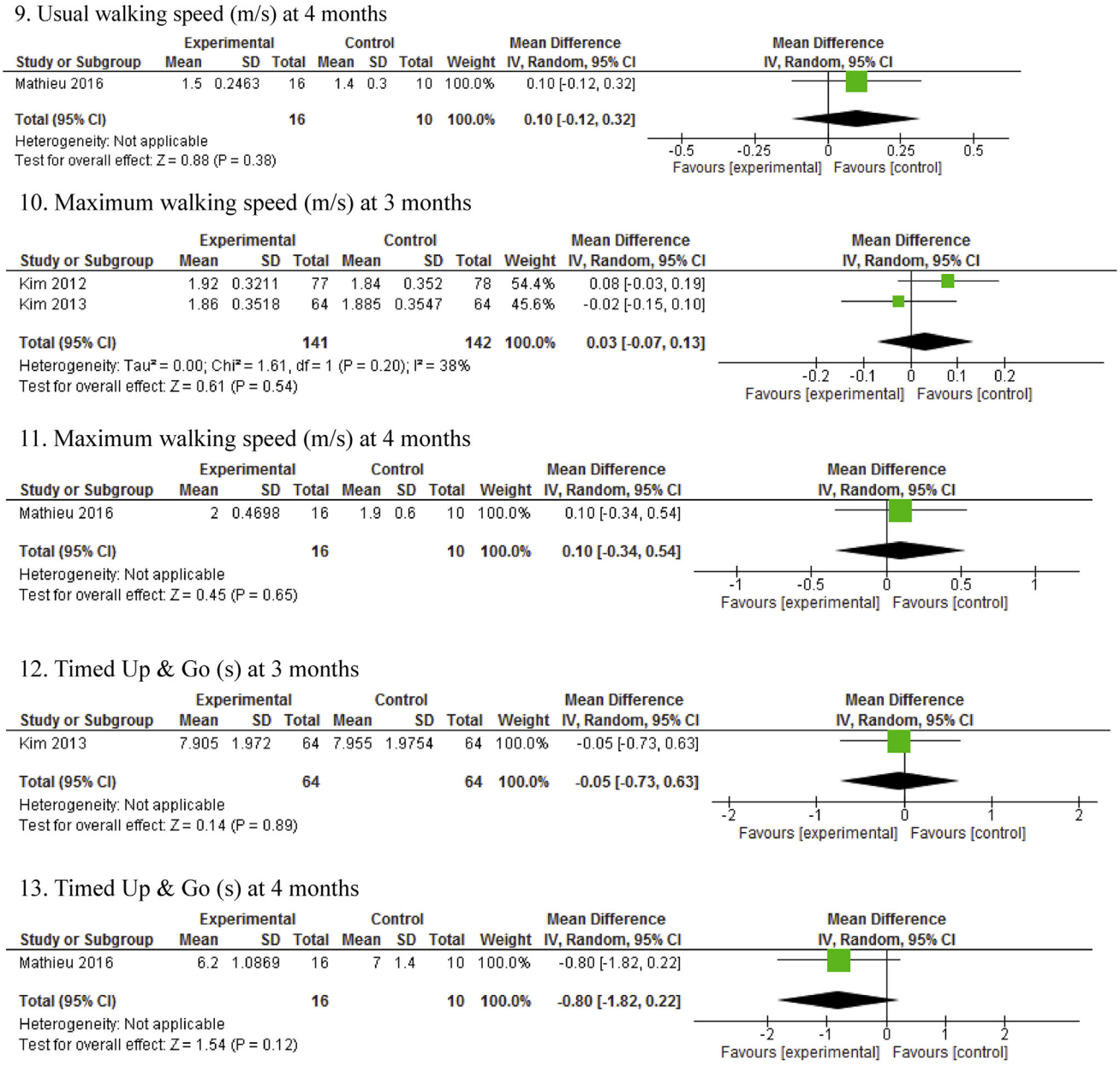


Fig. 7. (*continued*).

.78), and there was significant heterogeneity between studies (I^2 = 87; P = .006).

Effect of WBV training

In 1 RCT, WBV training was ineffective for improving the cross-sectional area of the vastus medialis (0.04 cm^2; 95% CI, −0.59 to 0.67; P = .89) and isometric knee extension (7.23 Nm; 95% CI, −5.34 to 19.81; P = .26) following 12 weeks of intervention (Figure 5).

Nutritional Intervention

A total of 1171 records on nutritional intervention were screened. Figure 6 shows the PRISMA flow chart of the articles included in the review. A total of 5 papers (sample size, 501) were finally included in the meta-analysis.

Details of the included trials are provided in Tables 1 and 3. All the trials included older adults with sarcopenia who were community-dwelling, and 1 included patients with sarcopenic obesity. None of the trials employed the established diagnostic criteria of sarcopenia, although the loss of skeletal muscle mass was adopted for the diagnosis of sarcopenia in all the trials. Three of the trials used BIA and 2 trials used DXA to measure muscle mass.

In 3 trials,[19–21] the main objective was to verify the effects of the combined intervention of exercise and nutrition on sarcopenia improvement. To ascertain the effect of nutritional intervention, we used subgroup analysis, including "any types of nutrition versus control (no nutrition)." These 3 trials used nutritional interventions over 3 months, which involved 3 g of essential amino acid (EAA) supplementation twice a day, 540 mg of tea catechin supplementation daily, and a combination of 3 g of EAA and 540 mg of tea catechin supplementation daily, each of which had a control group of exercise or health education.

Mathieu et al[23] used 12 g of protein and 7 g of EAA supplementation daily, with a placebo control group, over 4 months. In that

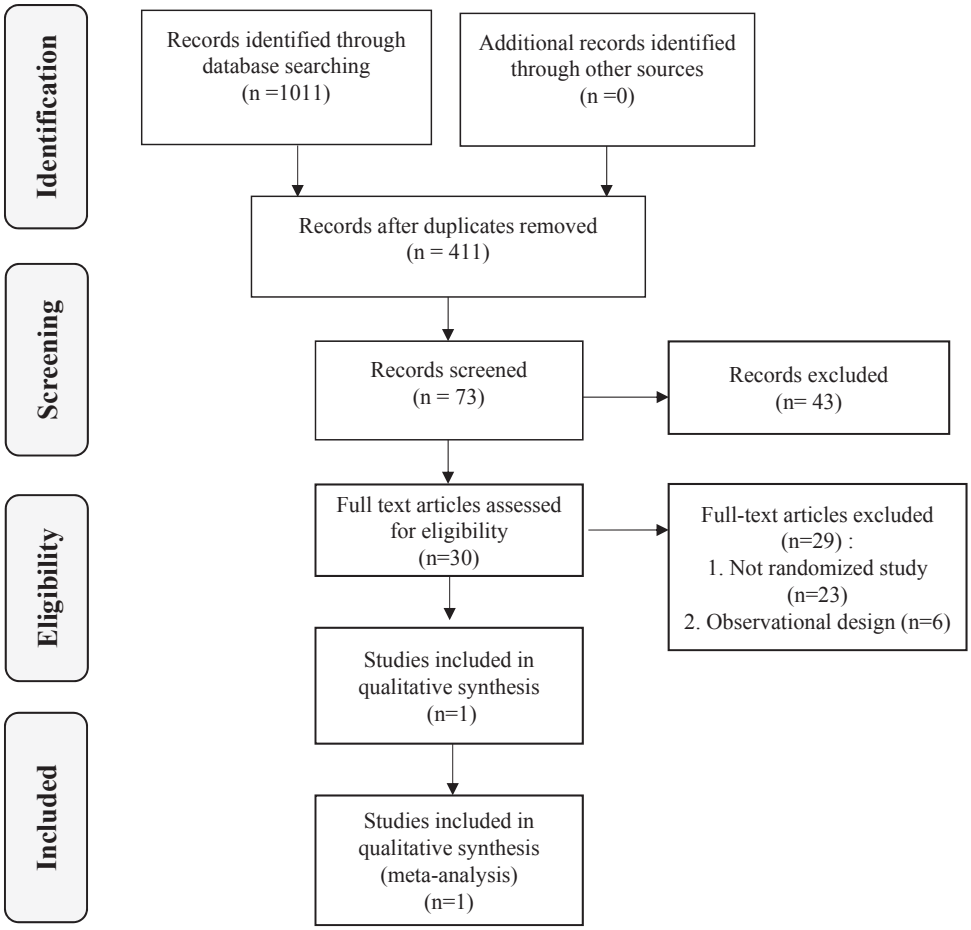


Fig. 8. PRISMA diagram of drug intervention.

study, both intervention and control groups participated in resistance training programs 3 times a week over the same period.

Overall, nutritional intervention was effective in improving knee extension strength (0.11 Nm/kg; 95% CI, 0.03-0.20; $P = .008$) following 3 months of intervention; however, there was no significant effect of nutritional intervention on appendicular skeletal muscle mass (index), fat-free mass, grip strength, knee extension strength (newton-meters and newtons), walking speed, and Timed Up & Go test results (Figure 7).

Drug Intervention

A total of 1011 records on drug intervention were screened. Figure 8 shows the PRISMA flow chart of the articles included in the review. Finally, only 1 RCT (sample size, 170) was included in the analysis.

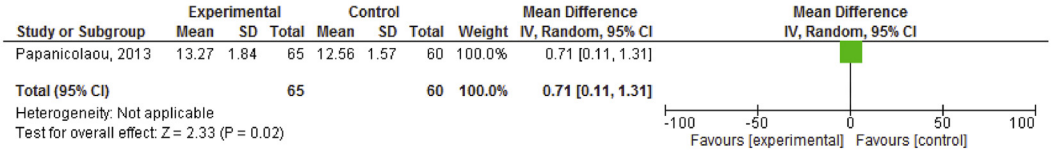
Details of the included trial by Papanicolaou et al[24] are provided in Tables 1 and 4. Papanicolaou et al conducted a double-blind, parallel-arm, placebo-controlled, multicenter, 6-month trial involving older adults with sarcopenia who were community-dwelling. Only the loss of appendicular skeletal muscle mass was adopted for the diagnosis of sarcopenia in this trial, and DXA was used to measure muscle mass. Papanicolaou et al used 50 mg of MK-0773—a selective androgen receptor modulator (SARM)—to improve muscle mass and function while minimizing the effects on other tissues, and all participants also received 2800 to 5600 IU of vitamin D and 25 to 35 g of protein supplementation daily.

In the RCT, SARM had no significant effect on total and appendicular lean body mass, bilateral leg press, stair climbing power, gait speed, Short Physical Performance Battery, or the Activity Measure for Post Acute Care physical movement following 6 months of intervention (Figure 9); however, in the original report, the authors concluded that SARM led to a significant increase in the total and appendicular lean body mass. They used a longitudinal data analysis method, wherein an effective advantage over the placebo was determined based on a significant difference in the between-group treatment from baseline to 6 months, which was different from the analytical method used in the current meta-analysis.

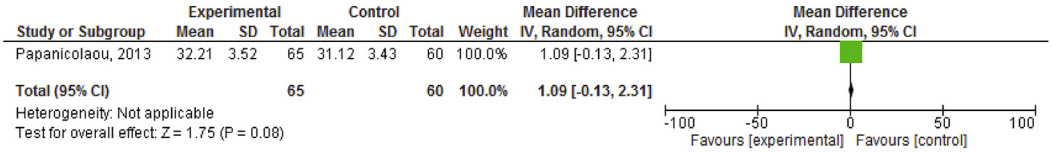
Table 4
Characteristics of Drug Intervention Protocol

Study, Year	Case, n	Control, n	Drug Intervention	Control	Others
Papanicolaou et al, 2013[24]	81	89	MK-0773 50 mg (daily)	Placebo	There were 2 groups: (1) MK-0773 and (2) placebo group. Both groups had protein (25-35 g) and vitamin D (2800-5600 IU) supplementation (daily) to reach the desired blood level.

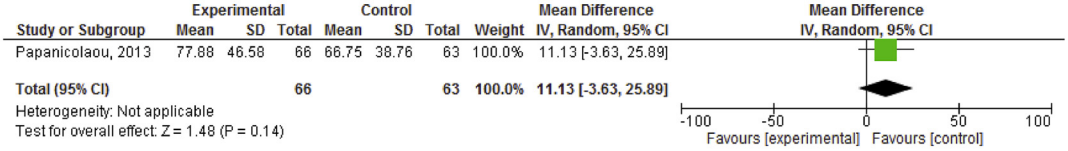
1. Appendicular LBM (kg) at 6 month



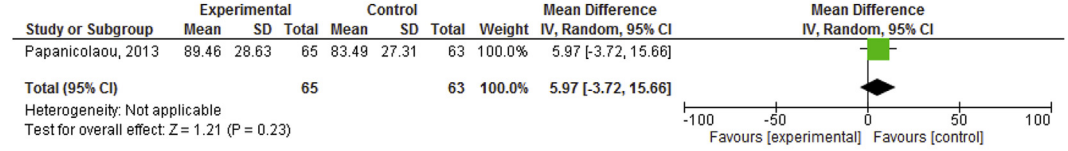
2. Total LBM (kg) at 6 month



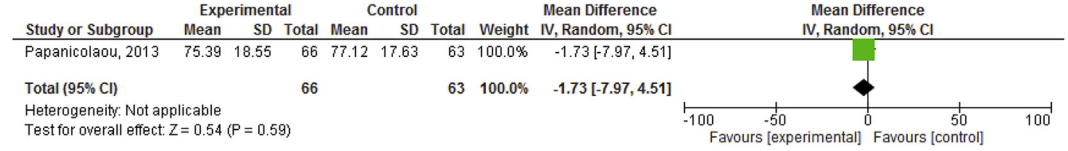
3. Bilateral leg press (lb) at 6 month



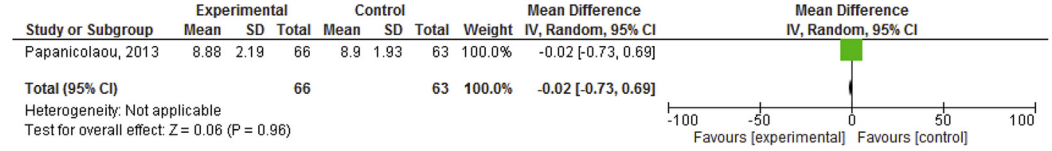
4. Stair climbing power (watts) at 6 month



5. Gait speed (cm/s) at 6 month



6. SPPB composite score at 6 month



7. AM-PAC physical movement at 6 month

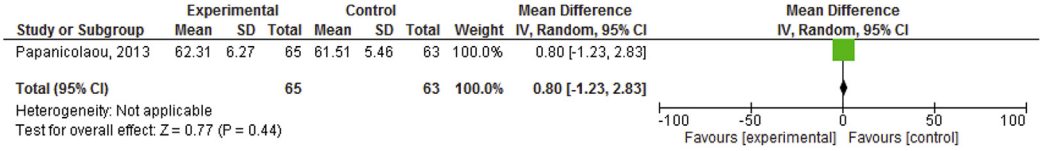


Fig. 9. Forest plot for drug intervention.

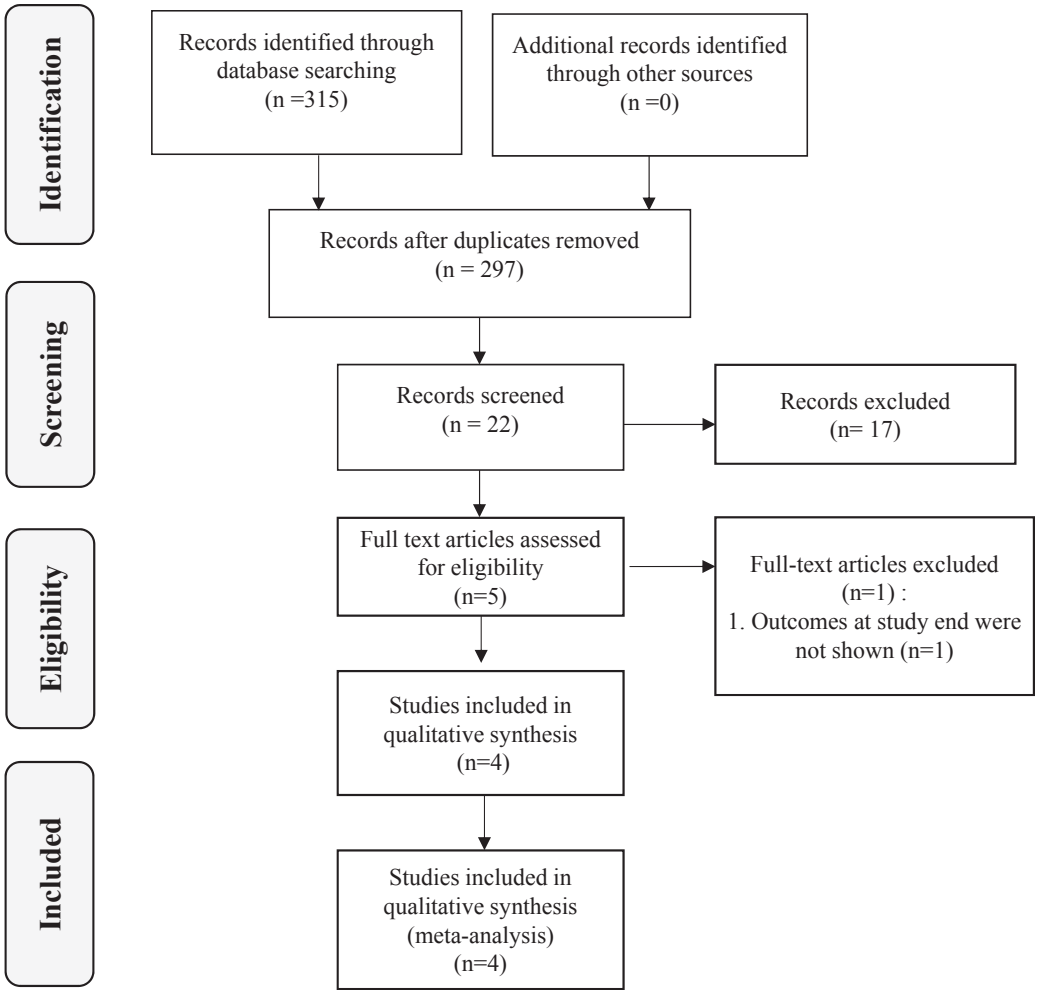


Fig. 10. PRISMA diagram of combined intervention.

Combined Intervention

A total of 315 records on the combined intervention were screened. Figure 10 shows the PRISMA flow chart of the articles included in the review. A total of 4 papers (sample size, 501) were finally included in the meta-analysis.

The details of the included trials are provided in Tables 1 and 5. All the trials included older adults with sarcopenia who were

Table 5
Characteristics of Combined Intervention Protocol

Study, Year	Case, n	Control, n	Intervention: Exercise Plus Nutrition	Control: Exercise or Nutrition Alone	Others
Kim et al, 2012[19]	38	39	60-minute comprehensive training program twice a week and EAA (3 g) supplementation (2 times a day: 6 g daily)	1. Exercise (same as left) alone	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
	38	39		2. Nutrition (same as left) alone	
Kim et al, 2013[20]	32	32	60-minute comprehensive training program twice a week and tea catechin (540 mg) supplementation (daily)	1. Exercise (same as left) alone	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
	32	32		2. Nutrition (same as left) alone	
Kim et al, 2016[21]	36	35	60-minute comprehensive training program twice a week and EAA (3 g) and tea catechin (540 mg) supplementation (daily)	1. Exercise (same as left) alone	There were 4 groups: (1) exercise + nutrition, (2) exercise, (3) nutrition, and (4) health education.
	36	34		2. Nutrition (same as left) alone	
Zdzieblik et al, 2015[25]	26	27	60-minute resistance training with fitness devices 3 times a week and collagen peptide (15 g) supplementation (daily)	1. Exercise (same as left) alone	There were 2 groups: (1) protein and (2) placebo group. Both groups had resistance training program 3 times a week.

community-dwelling, and 1 included patients with sarcopenic obesity. None of the trials employed the established diagnostic criteria of sarcopenia, although the loss of skeletal muscle mass was adopted for the diagnosis of sarcopenia in all the trials. Three trials used BIA and 2 used DXA to measure the muscle mass.

In 3 trials,[19–21] the main objective was to verify the effects of combined intervention of exercise and nutrition on sarcopenia improvement. To ascertain the effect of the combined intervention, we used subgroup analysis, including "combination of any type of exercise and nutrition versus exercise alone" and "combination of any type of exercise and nutrition versus nutrition alone."

Zdzieblik et al[25] divided patients into 2 groups: (1) those receiving 15 g of collagen peptide supplementation daily with 60-minute resistance training using fitness devices 3 times a week and (2) those receiving placebo (silica; control group) with exercise (same as the above) alone for 3 months.

By integrating the above-mentioned 4 RCTs, we used subgroup meta-analysis to assess the (1) combination of exercise plus nutrition versus exercise alone and (2) combination of exercise plus nutrition versus nutrition alone.

Exercise plus nutrition versus exercise

In the 4 RCTs, the combined intervention of exercise and nutrition was effective in improving the usual walking speed (−0.07 m/s; 95% CI, −0.13 to −0.00; $P = .04$) following 3 months of intervention; however, there was no significant effect on the appendicular muscle mass, fat free mass, grip strength, knee extension strength, or maximum walking speed (Figure 11).

Exercise plus nutrition versus nutrition

In 3 RCTs, the combined intervention of exercise and nutrition was effective for improving knee extension strength (10.43 Nm; 95% CI, 6.20-14.66; $P < .001$) following 3 months of intervention; however, there was no significant effect on the appendicular muscle mass, grip strength, knee extension strength (newton-meters per kilogram, newtons), or usual and maximum walking speed (Figure 12).

Adverse Effects

Papanicolaou et al[24] reported on the adverse effects following SARM intervention, which included increased transaminase levels in 8 (5 in the SARM group and 3 in the placebo group) of the 27 participants. None of the other trials reported any adverse effects.

Discussion

In the present systematic review of the limited number of trials currently available, we found 7 RCTs that investigated the effects of exercise (4 RCTs), nutrition (5 RCTs), drug (1 RCT), and their combination (4 RCTs) on muscle mass, strength, and function in older people with sarcopenia. The included studies were diverse in terms of the enrolled participants (different methods and cut-off points used to diagnose sarcopenia, without using the reported criteria), intervention strategies (difference in nutrients and doses, and exercise type and frequency), as well as design. Following the GRADE assessment of the primary and secondary outcomes in this review, the quality of the evidence was found to range from very low to low (see Supplementary Material).

Very low-quality evidence suggests that exercise interventions may play a role in improving muscle mass, muscle strength, and walking speed following 3 months of intervention. We found that exercise intervention should include resistance training,[5,26–30] and that WBV does not have positive effects on sarcopenia treatment,

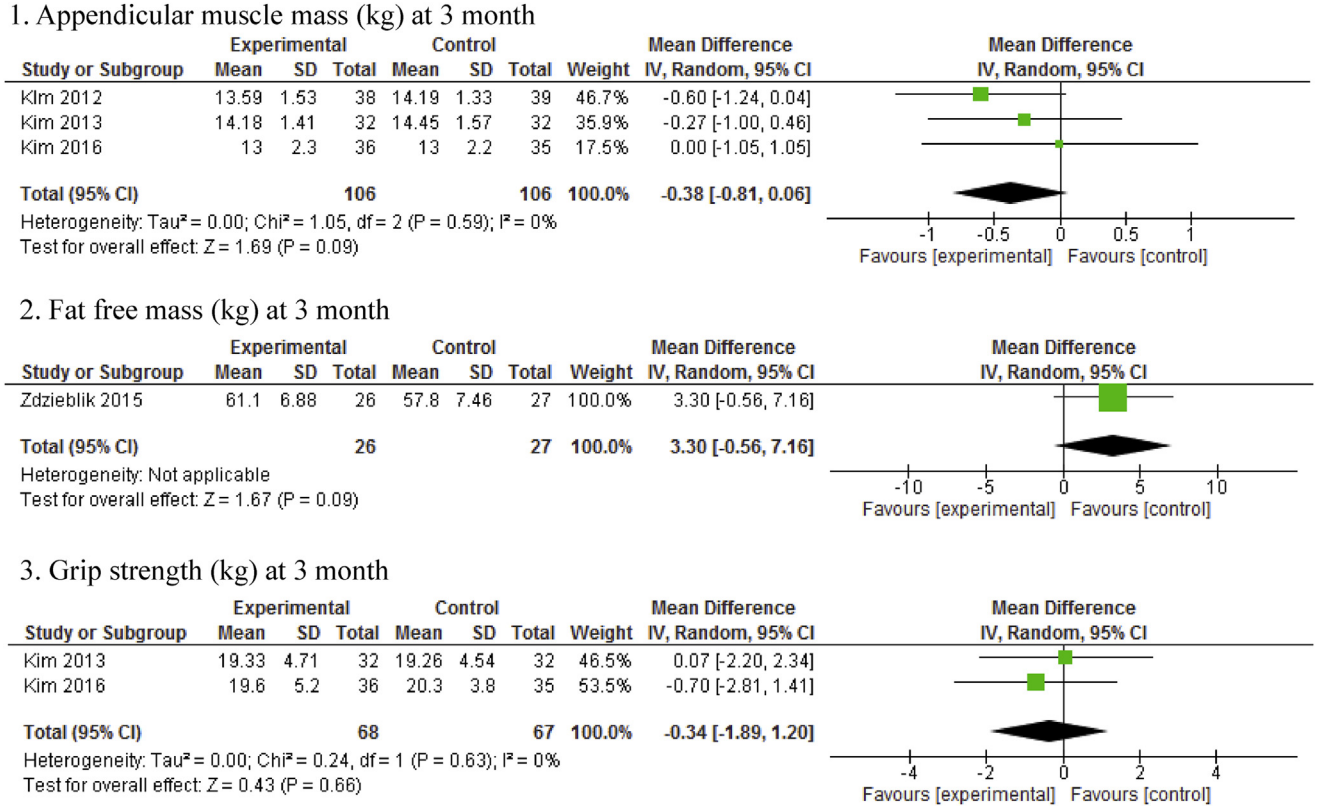


Fig. 11. Forest plot for combined intervention: exercise plus nutrition versus exercise.

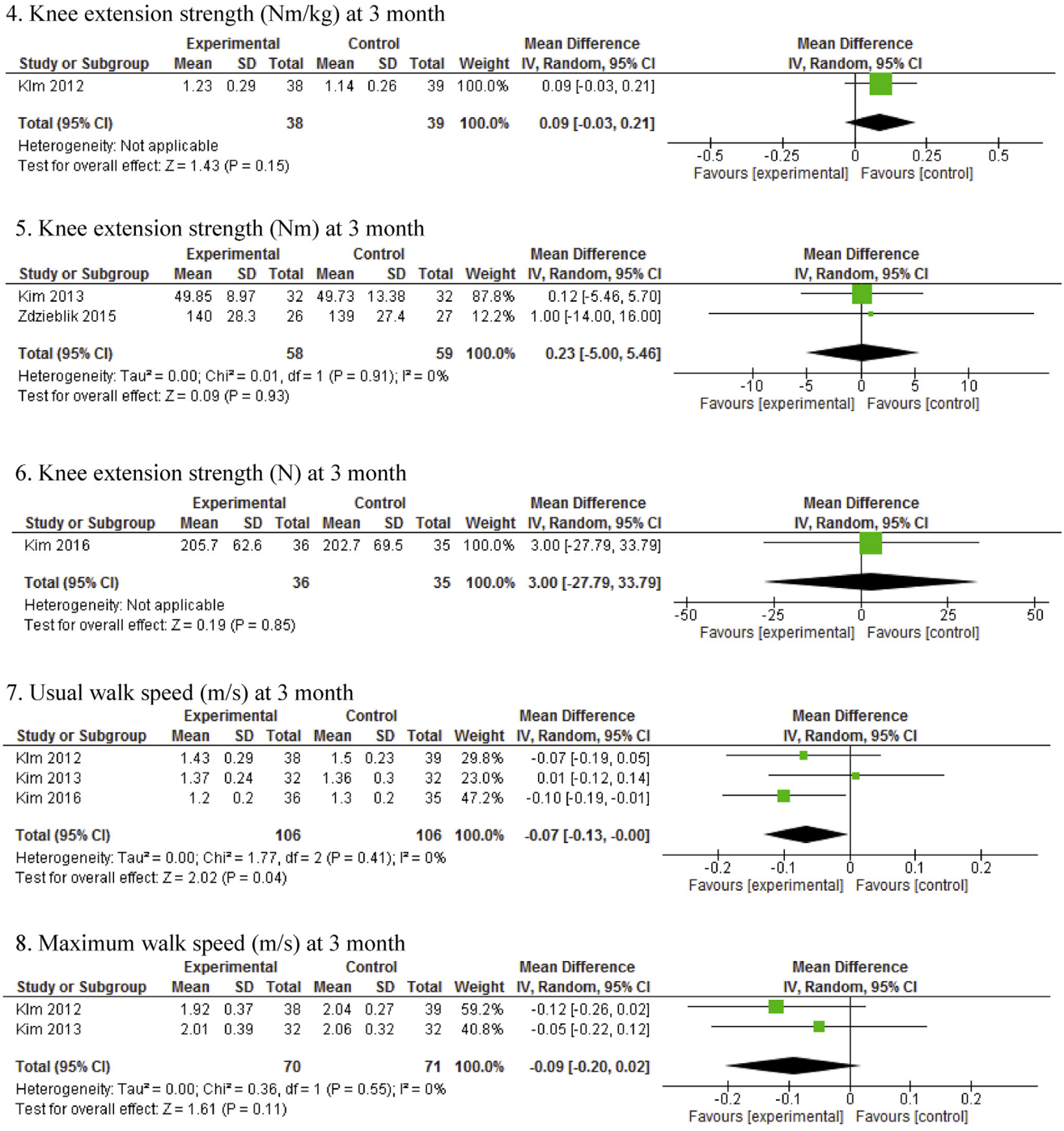


Fig. 11. (*continued*).

although WBV may serve as an alternative exercise method for preventing or treating sarcopenia.[30–32]

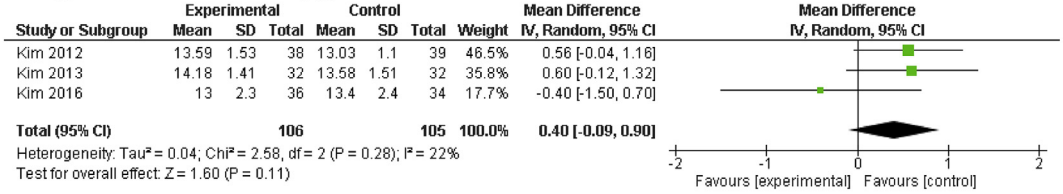
Moreover, very low-quality evidence suggests that nutritional interventions may be effective in improving muscle strength following 3 months of intervention. The included RCTs used EAA, collagen peptide, protein, and tea catechin as nutritional supplements. Other potentially effective nutritional supplements include beta-hydroxy-beta-methylbutyrate,[5,14,30,33–36] leucine[5,14,30,36–38] branched-chain amino acid,[5,14,30,36,39–41] vitamin D,[5,14,30,36,37,41] and creatine.[5,14,30,36,41]

With regard to drug intervention, very low quality evidence suggests that SARM had no clear effect on muscle mass, strength, or physical function. Other possible candidate drugs for sarcopenia treatment include angiotensin-converting enzyme inhibitors,[30,42,43] insulin-like growth factor 1,[30,44] myostatin inhibitor,[45,46] and ghrelin agonist.[30,47]

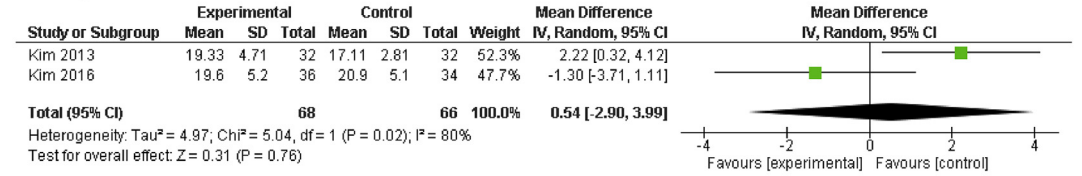
Low-quality evidence suggests that combined intervention of exercise and nutrition may have positive effects in improving the walking speed following 3 months of intervention.

The variety of interventions used to treat sarcopenia limits the data synthesis. The failure to confirm strong effects does not imply that there is no effect, but may simply reflect the low number of trials included and the low compliance rate of the reported criteria for sarcopenia diagnosis. After careful consideration of the methodological limitations and scope of these studies, we propose certain recommendations for future interventional trials of

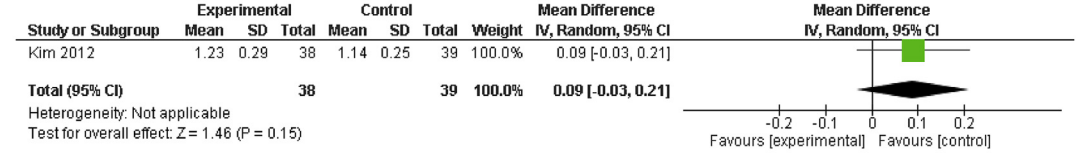
1. Appendicular muscle mass (kg) at 3 month



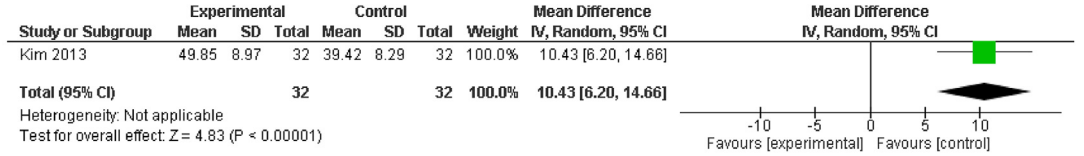
2. Grip strength (kg) at 3 month



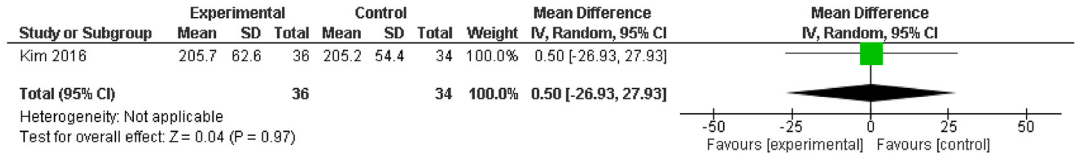
3. Knee extension strength (Nm/kg) at 3 month



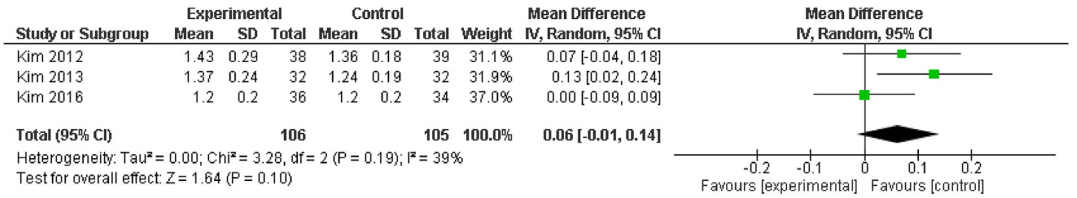
4. Knee extension strength (Nm) at 3 month



5. Knee extension strength (N) at 3 month



6. Usual walk speed (m/s) at 3 month



7. Maximum walk speed (m/s) at 3 month

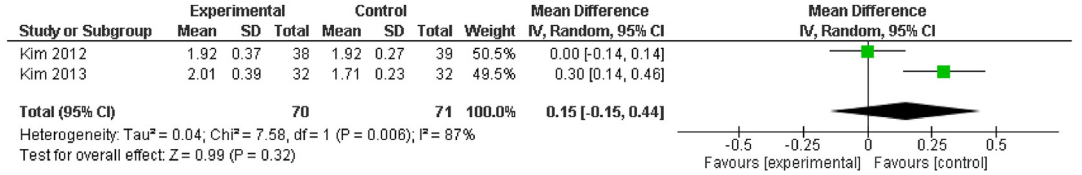


Fig. 12. Forest plot for combined intervention: exercise plus nutrition versus nutrition.

sarcopenia: (1) large, well-designed, adequately powered, preferably multicenter trials and the (2) development of internationally unified diagnostic criteria of sarcopenia for promoting high-quality interventional trials.

In conclusion, our systematic review and meta-analysis showed some positive effects of exercise and nutritional interventions for treating sarcopenia in older people, although the quality of the evidence was very low. Future high-quality RCTs should be implemented to strengthen the results.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jamda.2017.03.019.

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