International Journal of Nursing Sciences 4 (2017) 389–401

HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

International Journal of Nursing Sciences

journal homepage: http://www.elsevier.com/journals/international-journal-of-nursing-sciences/2352-0132

Review

Effect of nutritional supplement combined with exercise intervention on sarcopenia in the elderly: A meta-analysis

Dan Luo [a], Zheng Lin [a, b, *], Sha Li [a], Shen-Jia Liu [c]

[a] School of Nursing, Nanjing Medical University, Nanjing, 210029, China
[b] Administrative Department of Nursing, The First Affiliated Hospital of Nanjing Medical University, Nanjing, 210029, China
[c] Information Technology Division, The Bank of Jiangsu, Nanjing, 210029, China

ARTICLE INFO

Article history:
Received 18 January 2017
Received in revised form
3 July 2017
Accepted 27 September 2017
Available online 16 October 2017

Keywords:
Sarcopenia
Exercise
Nutritional status
Meta-analysis

ABSTRACT

Objectives: This systematic review was conducted to explore whether nutritional supplement can improve the benefits of exercise intervention on sarcopenia in the elderly.
Methods: Databases, including PubMed, Embase, Cochrane Library, Web of Science, CINAHL, CBM, CNKI, WANFANG, and VIP, were searched. All related papers with randomized controlled trials (RCT) methodology that were included in the databases from inception to 19 July 2016 were selected for the study. The tool “assessing risk of bias” from Cochrane Handbook 5.10 was used to evaluate the quality of included papers. A meta-analysis of eligible studies was performed using Stata12.0. Data that we were unable to convene or merge were subjected to descriptive analysis.
Results: Six trials were included in our study, which included 429 elderly patients with sarcopenia. The overall methodological quality of the trials was moderate. Compared with the exercise group, patients who were given nutritional supplements gained a bigger boost in fat-free mass (standard mean difference (SMD) = 5.78, 95% CI: 5.17 to 6.40, $P = 0.000$) and muscle mass (SMD = 2.048, 95% CI: 0.907 to 3.189, $P = 0.000$), as well as showed enhancement of keen extension strength (SMD = 1.08, 95% CI: 0.71 to 1.45, $P = 0.000$) and usual walk speed (SMD = 0.570, 95% CI: 0.19 to 0.95, $P = 0.003$).
Conclusion: Nutritional supplementation may magnify the effect of exercise intervention on sarcopenia elderly in terms of muscle mass, muscle strength, and physical performance. Inconsistencies were present among research studies. More robust studies are needed to determine the most suitable type of nutrient and target population and to explore the actual role of combined intervention in managing sarcopenia in the elderly.

1. Introduction

With the increasing number of elderly people, many countries have entered into the graying society. Aging is accompanied with inevitable muscle reduction. The severity of reduction varies from person to person, and severe muscle loss may lead to sarcopenia [1,2], which is a disease prevailing in the elderly, with an incidence of 5%–13% in people who are 60–70 years of age, and 11%–50% in people older than 80 [3,4]. No standard definition of sarcopenia exists; however, according to the European Working Group on Sarcopenia in Older People (EWGSOP): ‘sarcopenia is an age-related syndrome characterized by progressive and generalized loss of skeletal muscle mass and function with a risk of adverse outcomes such as physical disability, poor quality of life, and death’. They proposed the diagnosis of sarcopenia using the criteria of low muscle mass and low muscle function (either low strength and/or low physical performance) (Page.748) [5]. Sarcopenia leads to huge medical expenses and wastes medical resources; the estimated direct health care cost caused by sarcopenia in the United States were $18.5 billion in 2000 [6]. Sarcopenia is a major cause of frailty

* Corresponding author. School of Nursing, Nanjing Medical University, Nanjing, 210029, China.
E-mail address: linzheng100@163.com (Z. Lin).
Peer review under responsibility of Chinese Nursing Association.

https://doi.org/10.1016/j.ijnss.2017.09.004

[7], and significantly predicts future mortality in older adults [8,9]. Effective measures are needed to slow down or even reverse the progress of sarcopenia in the elderly in order to reduce the incidence of undesirable clinical outcomes, lessen medical costs, and improve the quality of life of patients. Exercise interventions exert certain positive effects on elderly patients with sarcopenia [10]. The role of nutrition in sarcopenia has always attracted great attention. The balance between protein synthesis and decomposition definitely plays a pivotal role in the regulation of skeletal muscle mass [11]. Muscle protein metabolism is dependent on the adequate intake of dietary-derived nutrients [12]. The incidence of malnutrition ranges from 5% to 20% in community-dwelling elderly, and exceed 60% in institutionalized older adults [13]. Sarcopenia may be caused by nutritional deficiency [5]. Nutritional interventions which supply adequate energy and specific nutrients could be promising in preventing and/or reversing the progress of sarcopenia [14,15]; on the contrary, a meta-analysis study expressed disagreement [4]. Some researchers combined exercise interventions and nutritional supplements and analyzed interaction effects between them. Nutritional supplementation can improve the effect of exercise in healthy people [16] and can increase the effect of exercise intervention in sarcopenia. However, this conclusion was merely based on theoretical deduction, and an empirical study was lacking [17–19,37]. According to a review by Denison, dietary supplementation enhanced the benefits of exercise training in elderly patients with sarcopenia; however, the target population in his study was diversified, including not only elderly patients with sarcopenia, but also hospitalized elderly and other population [20]. Studies that focused on the combined effect of exercise and nutritional interventions on sarcopenia in the elderly are rare, and the conclusions were not unified. No systematic review has been conducted to evaluate the role of combined interventions exclusively in sarcopenia in the elderly. Our systematic review aims to gain a reliable conclusion and provide reference for clinical intervention by making a comparative analysis of related trials.

2. Methods

2.1. Eligibility criteria

Our systematic review included trials with the following characteristics:

2.1.1. Types of participants

Participants must show symptoms that are in accordance with the EWGSOP diagnostic criteria [21] for sarcopenia. They should be aged 65 years old or older.

2.1.2. Types of interventions

Trials that involved both nutritional supplementation and exercise training were selected. All types of exercise, such as aerobic, resistant, and mixed exercise were included. Nutritional supplementation involved offering participants nutrients, such as proteins, amino acids, leucine, whey proteins, and vitamin D during the exercise intervention. Nutritional supplementation was performed before, during, or after exercise training.

2.1.3. Type of control group

The control group only received exercise intervention.

2.1.4. Types of outcomes

Muscle mass (MM) was chosen as primary outcome, and muscle strength and physical performance as secondary outcomes. In reference to the consensus from EWGSOP [21], common measurements of MM included anthropometry (height, weight, and BMI), fat-free mass (FFM), fat mass (FM), and muscle mass (MM). Handgrip strength, knee flexion/extension, and peak expiratory flow were used as indicators for muscle strength. Short physical performance battery (SPPB), usual gait speed, get-up-and-go test, timed get-up-and-go test, and stair climb power test were performed to frequently measure the physical performance of patients.

2.1.5. Type of study design

Randomized controlled trials (RCTs) were included in this study.

2.2. Search strategy

From inception to 19 July 2016, we used MeSH terms, titles, and key words to search electronic databases, including PubMed, Embase, Cochrane Library, Web of Science, CINAHL, CNKI, CBM, WangFang, and VIP. Fig. 1 shows an example of strategies used to search the PubMed database.

2.3. Study selection

After removing duplicate articles, two researchers selected preliminary articles by reviewing the titles and abstracts independently. Subsequently, the full texts were reviewed to determine whether the trials met the eligibility criteria. Disagreements between researchers were resolved by a third researcher (Fig. 2).

2.4. Data extraction

Two independent researchers extracted data, which included the following categories: author, issuing time, participants, number of participants, sex distribution, age, details of exercise intervention and nutritional supplement, outcome measures, and main findings. We contacted the author(s) when the required data were not available in their published manuscripts.

2.5. Risk of bias

The quality of the trials was assessed by applying the 'risk of bias tool' from Cochrane Handbook 5.10 [22]. All steps were performed independently by two investigators, and a third researcher was consulted for suggestions whenever discrepancies existed and decisions were difficult to make. The evaluation included sequence generation, allocation concealment, blinding of participants, personnel or outcome assessors, completeness of outcome data, and selectivity of outcome reporting.

2.6. Data analysis and synthesis

The meta-analysis was performed using the Stata software (Version 12.0). For continuous outcomes, pooled effects were assessed by calculating their standardized mean differences (SMDs) with 95% confidence intervals (CIs). SMD was calculated based on the difference of changes in values from the baseline values. The standardized mean change was obtained by subtracting the final mean value from the mean value at baseline. Standard deviations for statistical results were referred from other studies of a similar meta-analysis [23]. Statistical heterogeneity among selected studies were quantified by determining values for I^2; where $I^2 <$ 30%, $I^2 > 50\%$, and $I^2 > 75\%$ were defined as moderate, substantial, and considerable heterogeneity, respectively. To eliminate clinical heterogeneity, we conducted subgroup analyses based on the type of nutrients. If no statistical difference was obtained among subgroups where $I^2<50\%$ and heterogeneity ($P \geq 0.1$), the fixed effect

#1 "sarcopenia"[MeSH Terms] OR "sarcopenia"[tiab]OR" decrease of muscle " [tiab]OR"muscle less" [tiab] OR"muscular atrophy" [tiab]

#2"dietary supplements" [MeSH Terms] or "(dietary supplement* or dietary intervention* or dietary support* or dietary therap* or dietary method* or dietary technique* or dietary treatment* or dietary modification or nutrition intervention* or nutrition supplement* or nutrition support* or nutrition therap* or nutrition method* or nutrition technique* or nutrition treatment* nutrition modification or multinutrient supplement* or multinutrient intervention* or multinutrient support* or multinutrient therap* or multinutrient method* or multinutrient technique* or multinutrient treatment* or multinutrient modification)"[tiab]

#3"proteins"[MeSH Terms] OR "proteins"[tiab] OR "protein"[tiab]

#4 "amino acids"[MeSH Terms] OR ("amino"[tiab] AND "acids"[tiab]) OR "amino acids"[tiab]

#5 "leucine"[MeSH Terms] OR "leucine"[tiab]

#6"whey proteins"[MeSH Terms] OR ("whey"[tiab] AND "proteins"[tiab]) OR "whey proteins"[tiab] OR ("whey"[tiab] AND "protein"[tiab]) OR "whey protein"[tiab]

#7"vitamin d"[MeSH Terms] OR "vitamin d"[tiab] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[tiab]

8 :#2 OR #3 OR # 4 OR # 5OR #6 OR #7

#9"exercise"[MeSH Terms] OR "exercise"[tiab] OR "resistance training "[tiab] or "(aerobic exercise* or aerobic intervention* or aerobic therap* or aerobic activity or aerobic technique* or aerobic treatment* or aerobic modification* or aerobic training)"[tiab]

#10 (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR double*

Fig. 1. PubMed database searching strategies.

model was used for meta-analysis; however, if statistical heterogeneity existed among subgroups ($P < 0.1$), a random effect model was used. $P < 0.05$ for the difference was considered statistically significant. Data that we were unable to convene or merge were subjected to descriptive analysis.

3. Results

3.1. Study selection

A total of 7406 articles were found in the preliminary examination. After excluding duplicates, 6643 articles satisfied our eligibility requirements. Full-text reports were obtained for 59 studies after reading the title and abstract. Among the 59 studies, 54 did not meet our inclusion criteria because of the following reasons: the target population was not only sarcopenia patients ($n = 39$), the interventions were not combined intervention ($n = 12$), and the articles were protocols ($n = 3$). Ultimately, five studies [24,25,27–29] were included in our systematic review. One [26] additional trial was later included through retrieving references cited in the original five studies. A flow chart describing our search strategy and article retrieval results is shown in Fig. 2.

3.2. Study characteristics

The six included studies [24–29] were published from 2012 to 2016 (Table 1), and conducted in Germany [24], Canada [25,26], Italy [27], Japan [28], and Malaysia [29]. The number of participants in the studies ranged from 26 to 155, and a total of 429 participants from the six studies were enrolled. All participants had been

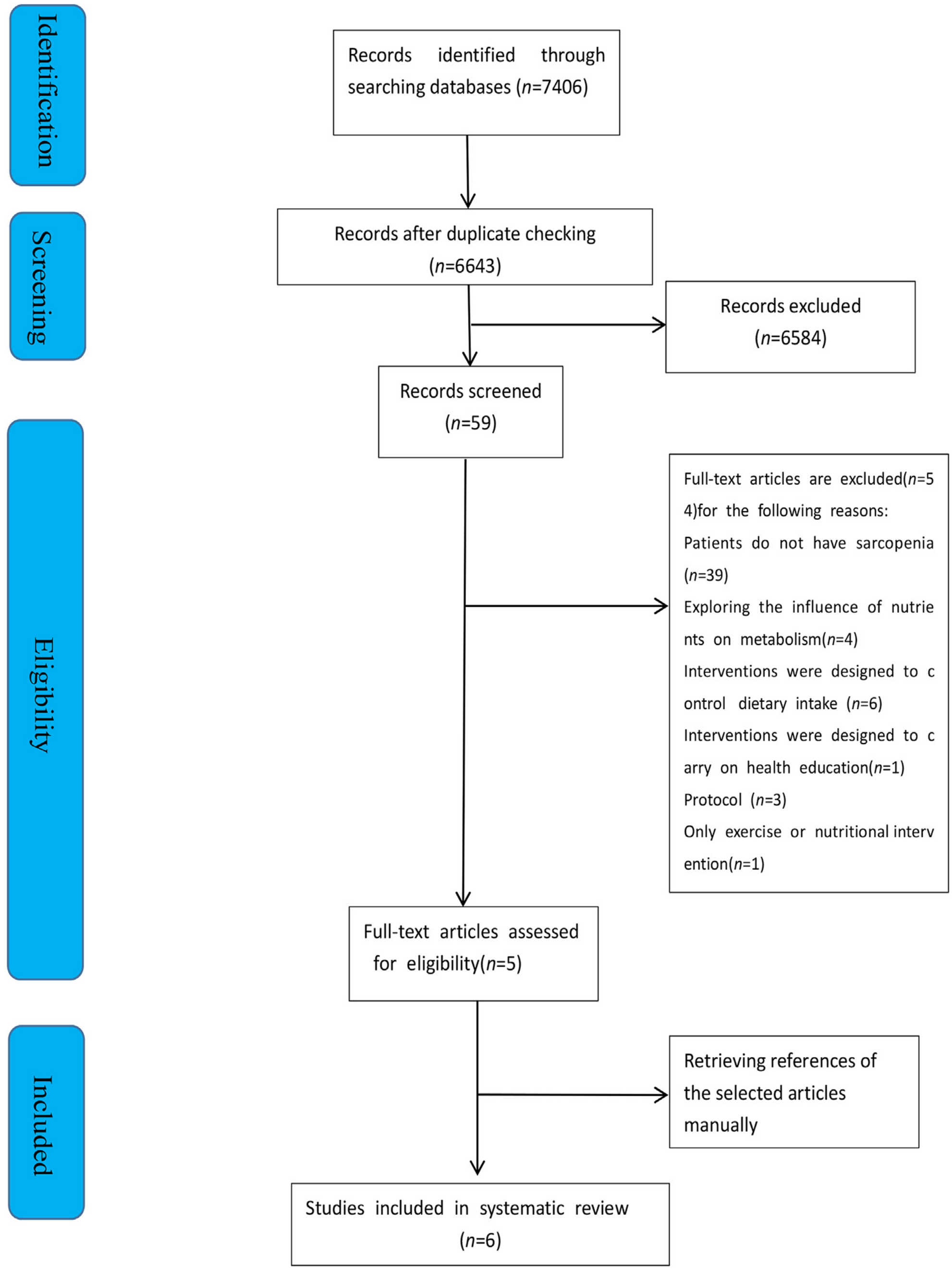

Fig. 2. Flowchart showing search results and article retrieval.

diagnosed with sarcopenia and were over 65 years old. The experimental group in each study received nutritional supplements during exercise intervention, while subjects in the control group were subjected to exercise training only.

3.3. Intervention characteristics

Protein supplements were used in four studies [25,26,28,29], whereas collagen peptide [24] and a mixture of whey protein, amino acids, and vitamin D [27] were chosen in the other two studies. The amount of proteins supplied were 6–40 g/day and 15 g for collagen peptide. The forms of exercise training included resistance exercise or combined exercise (e.g., resistance exercise combined with aerobic training). Both exercise interventions were performed for 1.5–3 h/week and lasted for 12 or 16 weeks. Variations among interventions used in six included studies existed.

3.4. Study quality (risk of bias)

The Cochrane risk of bias tool was used to assess the methodological quality of the six selected trials. Results are shown in Table 2. Three articles [24,25,27] used the sequence generation method correctly, whereas the other three [26,28,29] only referred to a random method without a detailed explanation. Two articles [25,26] employed an allocation concealment method, whereas the other four did not mention their concealment method. Five articles

Table 1
Characteristics of the included studies.

Authors	Population	Sample size (sex)	Age	Type of exercise Intervention	Intensity	Study length	Type of nutrient	Intervention time	Amount	Main outcomes	Findings
Kim HK, 2012[28]	community	155 (Man:0, woman:155)	79.1 y	Mixed-type	Moderate	60 min/d* 2d/wk*12wk	amino acids	2times*/d*12wk	6 g/d	1. Muscle mass: ①Body weight ②BMI ③Lean body mass ④Appendicular muscle mass ⑤Legs muscle mass 2. Muscle strength: ①keen extension strength 3. Physical activity: ①Usual walking speed ②Maximal walking speed	1 A significant group*time interaction between leg muscle mass, usual walking speed and knee extension strength ②knee extension improved only in the exercise + AAS group
Shahar S, 2013[29]	community	65 (Man:4, Woman:18)	67.1 y	Mixed-type	Moderate	60mins/d* 2d/wk*12wk	protein	No limits	Man:20 g/d; Woman:40 g/d	1. Muscle mass: ①Weight ②BMI ③Fat free mass (FFM) ④Appendicular muscle mass (AMM) 2. Muscle strength ①handgrip strength 3. physical performance: ①Chair stand Test ②Arm Curl Test ③six-minute Walk	①A remarkable reduction in body weight, BMI and body fat and increment in fat free mass with PrG. 2 The highest increment in lower and upper body strength were observed in the PrG (73.2%) and ExG (47.6%). 3 nutritional supplement cannot enhance the effect of exercise intervention
Zdzieblik D, 2015[24]	community	53 (Man:53, Woman:0)	72.2 y	Resistance exercise	Moderate	60 min/d* 3d/wk*12wk	Collagen peptide	60mins after exercise	15 g/d	1. Muscle mass: ①Weight ②Fat-free mass (FFM) ③Fat mass (FM) ④Bone mass (BM) 2. Muscle strength ①knee extension ②Isokinetic quadruceps strength (IQS)	①A remarkable reduction in FM and increment in FFM, BM with exercise group. ②collagen improved the effect of exercise intervention in FFM, FM and IQS.
Maltais ML, 2016[25]	community	26 (Man:26, Woman:0)	65 y	Resistance -exercise	Moderate	60 min/d* 3d/wk*16wk	①EAAsupple ② EAAmilk	Immediately after exercise	17 g/d	1. Muscle mass: ①Weight ②BMI ③Fat mass (FM) ④lean mass 2. physical	Resistance training significantly increased LM in all groups while only the EAAsupple group found FM

(continued on next page)

Table 1 (*continued*)

Authors	Population	Sample size (sex)	Age	Type of exercise Intervention	Intensity	Study length	Type of nutrient	Intervention time	Amount	Main outcomes	Findings
										performance: ①Physical Activity Scale for the Elderly (PASE)	decreased significantly after the intervention.
Maltais ML, 2016[26]	community	26 (Man:26, Woman:0)	66 y	Resistance -exercise	Moderate	60 min/d* 3d/wk*16wk	①EAAsupple ② EAAmilk	Immediately after exercise	17 g/d	3. Muscle mass: ①Weight ②BMI ③Muscle mass 2.Muscle strength: ①Bench press 4. physical performance: ①Walking speed (normal) ②timed up and go (TUG)	1 A significant improvement in lean body mass, MMI, total muscle mass with all groups 2 EAAsupp significantly improved in the 'timed up and go' (TUG) test.There is no different between the control and EAAmilk groups.
Rondanelli M, 2016[27]	Hospitalization	130 (Man:5, Woman:77)	80.3 y	Mixed-type	Moderate	20 min/d* 5d/wk*12wk	①Whey protein ② amino acids ③ vitamin D	With meal	①protein:32.9 g/d ②vitamin D:2.5 mg/d	1. Muscle mass ①Weight ②BMI ③Fat-free mass (FFM) ④Fat mass (FM) ⑤relative skeletal muscle mass (RSMM) 2. Muscle strength: ①Handgrip 3. physical performance: ①standardized summary scores for physical components②ADL	Compared with exercise group, combined group showed statistic difference in fat-free mass, relative skeletal muscle mass and handgrip strength.

Table 2
Risk of bias for included studies.

Study	①	②	③	④	⑤	⑥	⑦
Zdzieblik D, 2015[24]	Random number table	Not clear	Correctly	Not clear	Correctly	No	No
Maltais ML, 2016[25]	Not clear	Not clear	Correctly	Not clear	Correctly	No	No
Maltais ML, 2016[26]	Not clear	Correctly	Correctly	Not clear	Correctly	No	No
Rondanelli M, 2016[27]	Random number table	Correctly	Correctly	Not clear	Correctly	No	No
Kim HK, 2012[28]	Random by computer	Not clear	Correctly	Not clear	Correctly	No	No
Shahar S, 2013[29]	Not clear	Not clear	Not clear	Not clear	Correctly	No	No

①Random sequence generation ②Allocation concealment ③Binding of participants and personnel ④ Binding of outcome assessment ⑤ Incomplete outcome data ⑥ Selective reporting ⑦ Other bias.

used a double blind method, whereas the study [29] failed to mention the blinding procedure used. All included trials mentioned reasons for patients lost to follow up, with no selectivity of outcome reporting.

3.5. Outcomes

The six studies in our systematic review reported three types of outcomes, including muscle mass, muscle strength, and physical performance.

3.5.1. Muscle mass

Sarcopenia is characterized by significant reduction in muscle mass [9]. MM is the most important clinical outcome index to evaluate the intervention effect which include anthropometry (height, weight, BMI), fat free mass (FFM), fat mass (FM), MM, and so on.

3.5.1.1. Body mass index (BMI). A total of 275 participants from four trials received protein during exercise intervention [25,26,28,29], whereas 69 participants received a mixture of whey protein, amino acids, and vitamin D in one other trial [27]. These five trials used the BMI to examine whether nutritional supplement could amplify the effect of exercise on muscle mass (Fig. 3). Our systematic review revealed no significant difference between the combined group and exercise group concerning BMI (SMD = 0.621, 95%CI: −1.71 to 2.96, $P = 0.60$). The subgroup analysis across different types of nutrient exhibited the same outcome, which may be caused by differences in target population among trials. The study conducted by Shahar [29] illustrated that combined intervention could significantly reduce BMI (SMD = −1.202,95%CI: 1.94 to −0.46) in community sarcopenia in the elderly; on the contrary, Rondanelli [27] demonstrated that BMI was increased instead of reduced after combined intervention (SMD = 5.565, 95%CI: 4.8 to 6.3) in hospitalized people. In hospitalized people, the baseline nutritional status was poorer and malnutrition was more common than in the community population. Hospitalized elderly with sarcopenia tended to be more sensitive to nutritional supplements, which may have accounted for the phenomenon that BMI did not decline, but rather, increased after exercising.

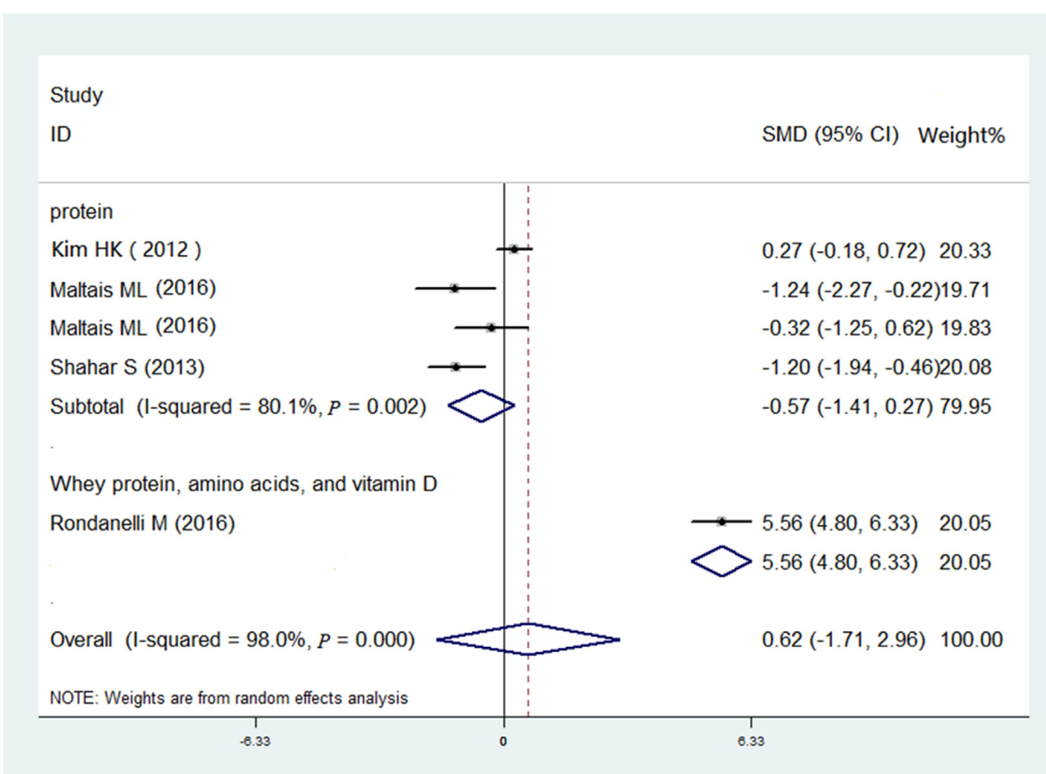

Fig. 3. Forest plot showing the effects of nutrient on BMI compared with exercise group.

3.5.1.2. Fat-free mass. Our meta-analysis of three RCTs (one took collagen peptide [24], one used protein [28], and the others employed a mixture of whey protein, amino acids, and vitamin D [27]) showed that nutritional supplement significantly boosted outcomes in FFM (SMD = 5.78, 95% CI: 5.17 to 6.40, P = 0.00) (Fig. 4). According to nutrient types, the subgroup analysis was conducted to show that all kinds of nutrients (collagen peptide, proteins, and mixed nutrients) could fortify the effect of exercise training by increasing the FFM of patients.

3.5.1.3. Fat mass. Three trials (collagen peptide [24], protein [25], and a mixture of whey protein, amino acids, and vitamin D [27] were used) reported a change of FM in their participants (Fig. 5). Although we failed to find a significant difference between the combined intervention and control groups, pooled SMD notably showed a reduced trend in FM (SMD = −2.51, 95% CI: −6.16 to 1.13). Zdzieblik [24] used collagen peptide as nutrient, and revealed a significant decrease in FM (SMD = −7.56,95%CI: −9.12 to −6.00) compared with exercise training alone. After using proteins as the nutritional supplement, Maltais [25] observed a great decline in FM which was close in reaching statistical significance (SMD = −0.786, 95% CI: 1.75 to 0.18), whereas Rondanelli [27] did not observe positive outcomes (Mean change: 114, 95% CI: −786 to 559, P = 0.689). Rondanelli showed that the average FM of patients before intervention was only 17.8 kg, which was significantly lower than the baseline FM in other trials.

3.5.1.4. Muscle mass. MM was measured in Five trials (four [25,26,28,29] used protein, whereas the others [27] used a mixture of whey protein, amino acids, and vitamin D). The meta-analysis (Fig. 6) revealed that the MM of patients notably increased when compared with exercise training group (SMD = 2.048, 95%CI: 0.907 to 3.189) regardless of the type of nutrient given.

3.5.2. Muscle strength

According to the European Consensus on Definition and Diagnosis of Sarcopenia, grip strength (GS), knee flexion/extension, and peak respiratory flow rate (Peak) were common outcome indexes for muscle strength [21], of which GS is the most popular.

3.5.2.1. Grip strength. Rondanelli [27] discovered a statistical difference (Fig. 7) between combined intervention group (using a mixture of whey protein, amino acids, and vitamin D as nutrients) and exercise group in GS (SMD = 8.773, 95%CI: 7.64 to 9.90). Shahar provided patients with proteins during exercise training, but unfortunately found no difference (SMD = −0.475, 95%CI: −1.16 to 0.21) [29], which is possibly because GS is a measure of upper body strength, and the focus of the exercise intervention used was the lower body. Thus, both the combined and exercise groups showed no improvement in GS.

3.5.2.2. Keen extension strength. Two trials (collagen peptide [24] and proteins [28] were selected) observed the change of muscle strength using the knee extension strength (Fig. 8). The upshot confirmed the observation that nutrition supplements may further strengthen knee extension (SMD = 1.08, 95% CI: 0.71 to 1.45) in the elderly during exercise training.

3.5.3. Physical performance

Commonly used outcome indexes for physical activity includes

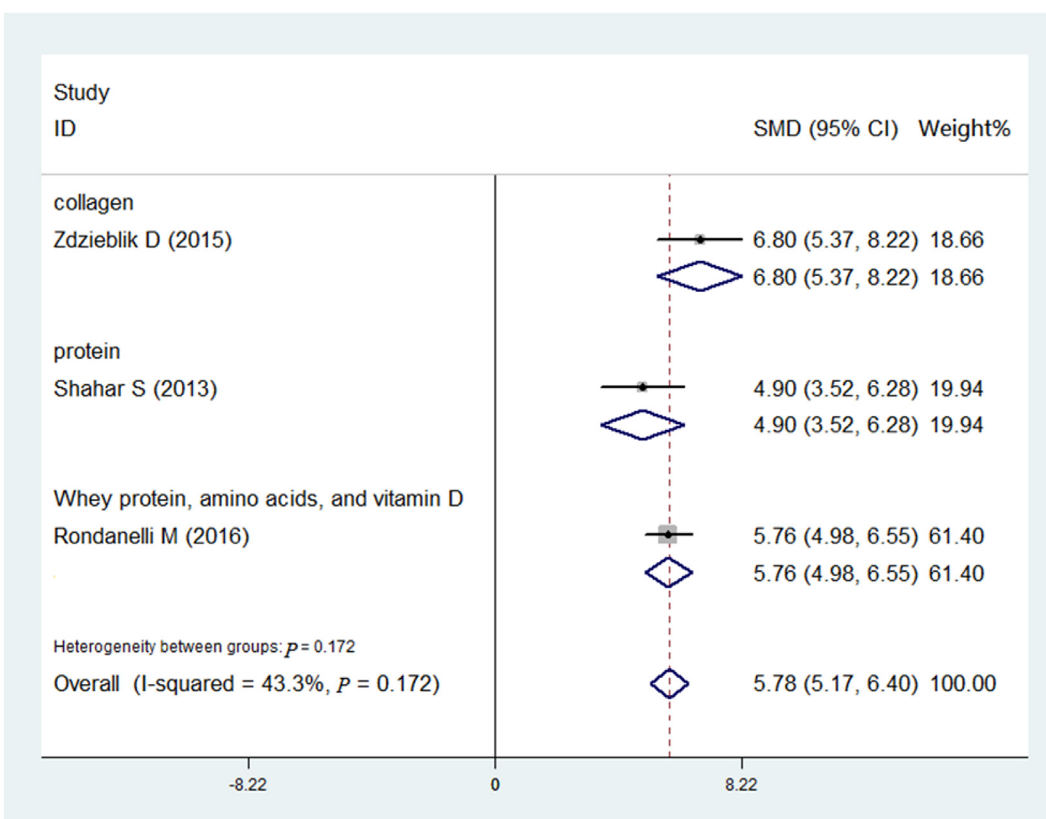

Fig. 4. Forest plot showing the effects of nutrient on FFM compared with exercise group.

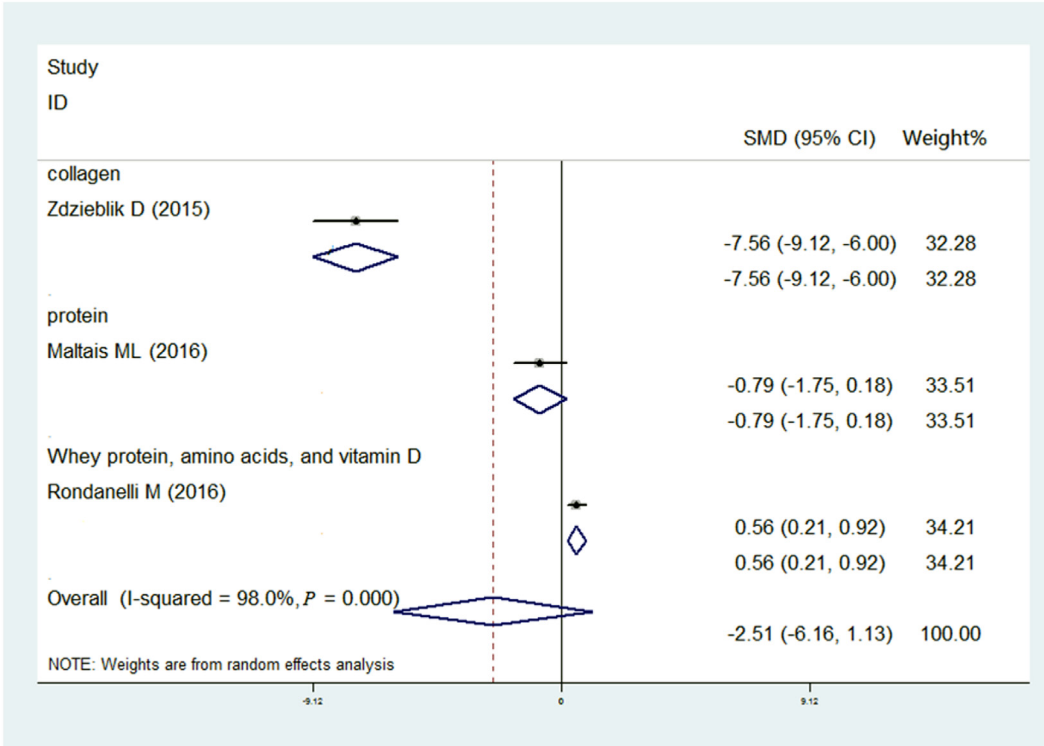

Fig. 5. Forest plot showing the effects of nutrient on FM compared with exercise group.

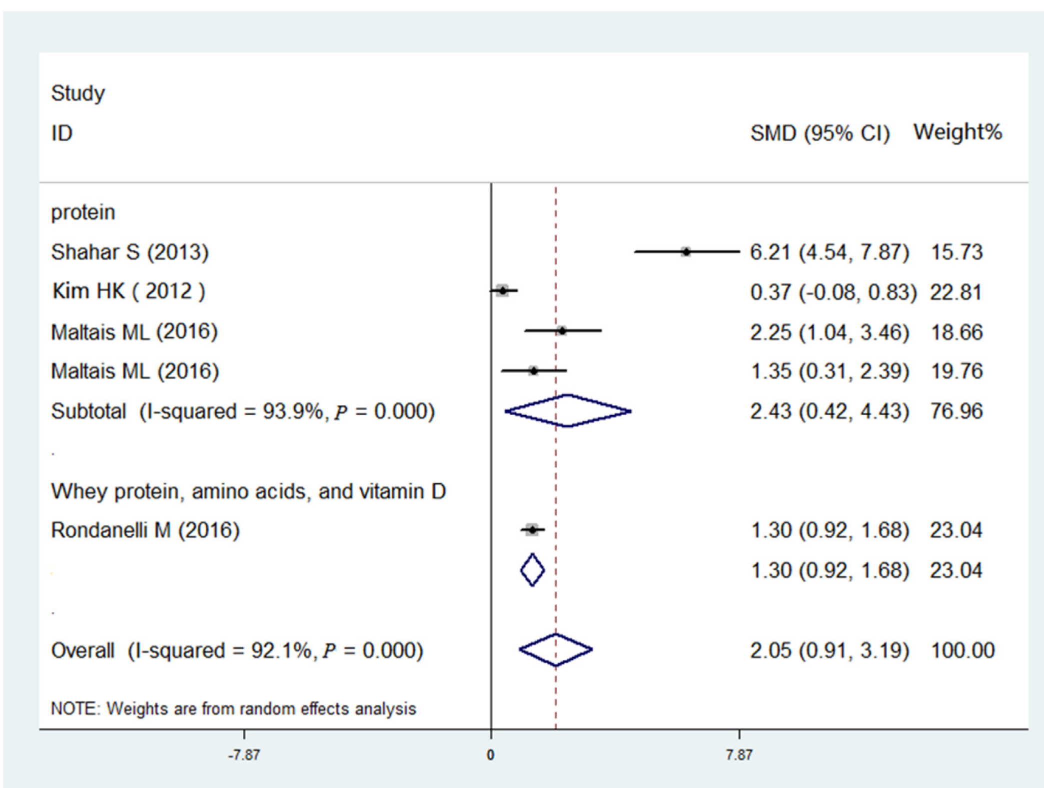

Fig. 6. Forest plot showing the effects of nutrient on MM compared with exercise group.

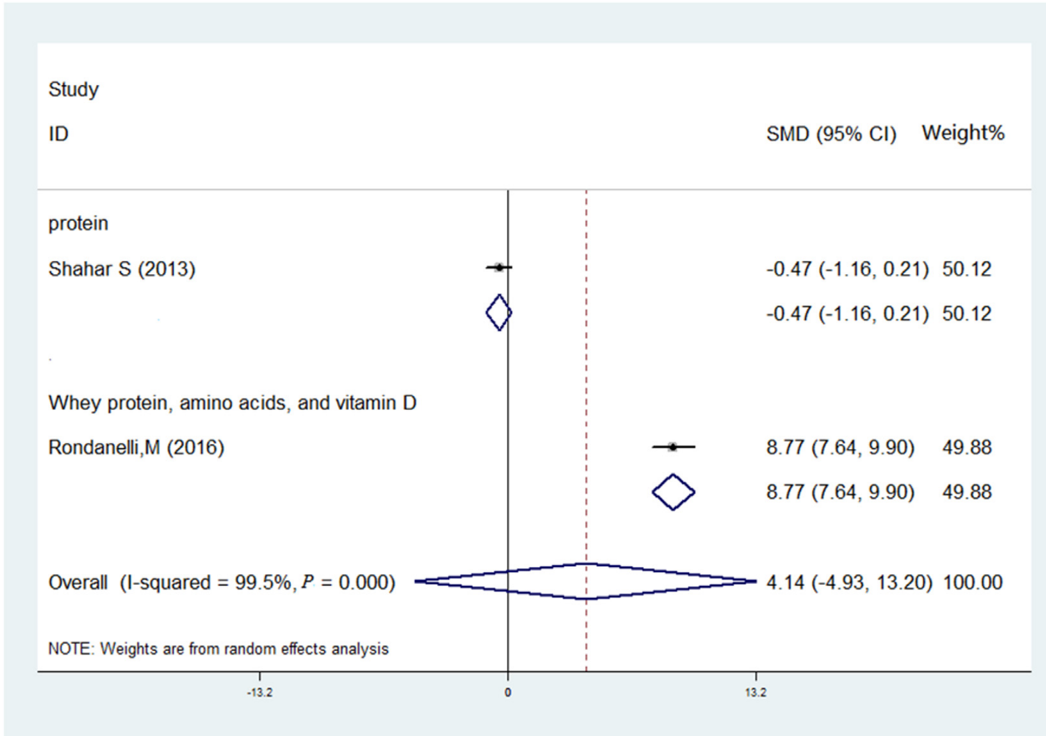

Fig. 7. Forest plot showing the effects of nutrient on GS compared with exercise group.

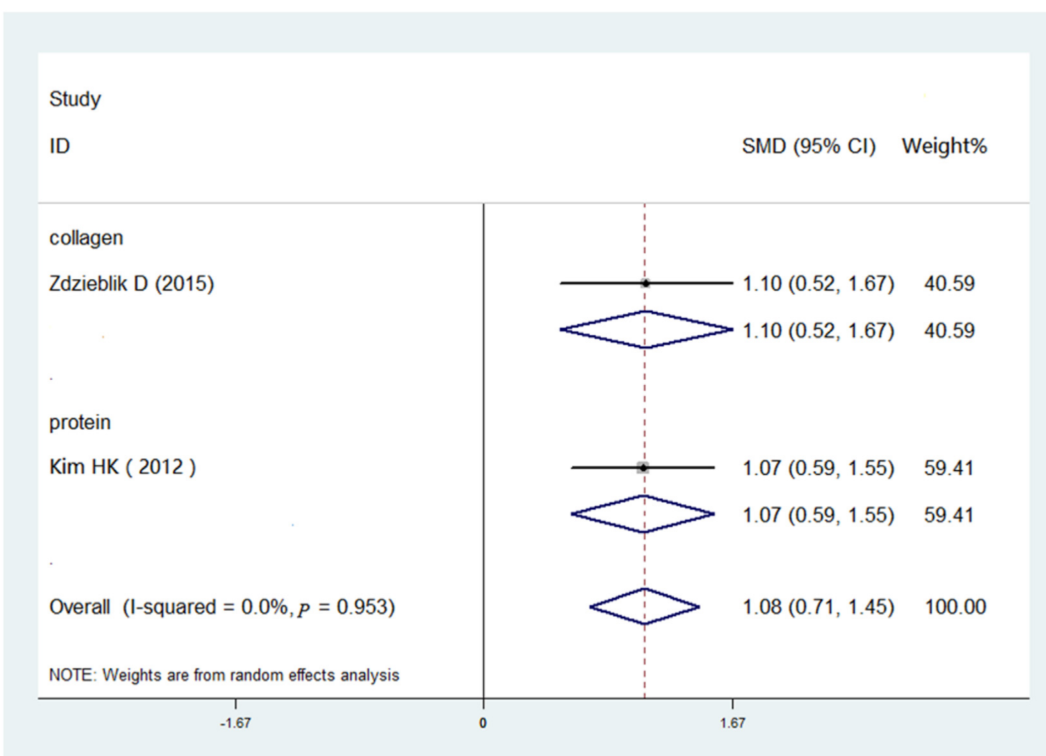

Fig. 8. Forest plot showing the effects of nutrient on Keen extension strength compared with exercise group.

short physical performance battery (SPPB), usual walk speed, timed get-up-and-go test, and stair climb power test [21], of which SPPB, usual walk speed, and get-up-and-go test were frequently used in the clinic.

3.5.3.1. Usual walk speed. The pooled results of two RCTs [26,28] demonstrated that usual walk speed has been enhanced in protein and exercise group (Fig. 9) (SMD = 0.570, 95%CI: 0.19 to 0.95). When taking only the RCT of Maltais into consideration [28], protein supplementation failed to improve the effect of exercise on usual walk speed of patients (SMD = 0.333, 95% CI: −0.60 to 1.27; SMD = 0.383, 95% CI: −0.56 to 1.32). The result may be due to the small sample size in the trial.

3.5.3.2. Other indexes. The score of the sitting-and-walking test [26] was higher in amino acid supplementation-combined intervention group than the control group ($P < 0.05$). Suzana [29] arrived at the same conclusion using the arm curl test; the score in the exercise group was even higher than that in the combined group.

4. Discussion

4.1. Summary of main results

To the best of our knowledge, this is the first systematic review that examines whether nutritional supplementation while conducting exercise training can bring more benefits to elderly patients with sarcopenia. Nutritional supplements may effectively magnify the effect of exercise intervention on muscle mass, muscle strength, and physical performance, although disagreements existed.

4.2. Applicability of evidence

The etiology, clinical manifestations, and prognosis of sarcopenia in young people and elderly are significantly different. Because the majority of sarcopenia patients are elderly, our systematic review only focused on patients older than 65. Considerable differences exist with regard to the diet structure and body composition between Western and Eastern people. The trials chosen by our study were conducted in both Western and Eastern countries to generalize conclusions. Furthermore, these trials enrolled both hospitals and community patients with sarcopenia, and considered the diversity of disease severity, which could support the idea that the results of our systematic review could be applied to the majority of the older people living with sarcopenia.

4.3. Quality of evidence

Our systematic review only included several trials, and the types of exercise intervention and nutritional supplement were not exactly the same. Thus, the specific type of nutritional supplement that is effective during exercise intervention in elderly patients with sarcopenia remains to be further explored. Additionally, the overall quality of evidence was medium, and our results may have been affected by bias.

4.4. Agreement and disagreement with other articles

We found that nutritional supplementation can amplify the effect of exercise intervention on FFM in elderly patients with sarcopenia, which is consistent with the review of Cermak [30]. Nutritional supplementation improves net muscle protein synthesis. However, other studies [31–36] reported that combined intervention exerts a small effect size on FFM among middle-aged and elderly population. This discrepancy may be due to the difficulty for elderly patients with sarcopenia to gain benefits from nutritional supplementation. Most of the elderly decreased their dietary intake proportionally after receiving nutritional supplements, thus the total daily energy intake remained substantially unchanged [37]. In addition, the amount and composition of nutrients provided to

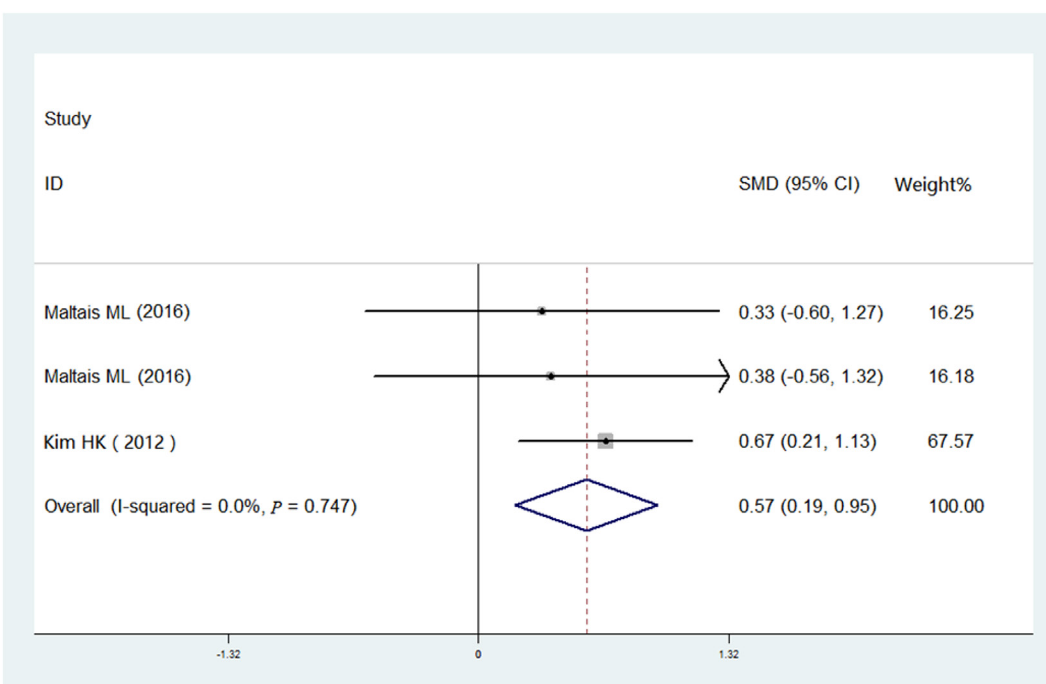

Fig. 9. Forest plot showing the effects of nutrient on usual walk speed compared with exercise group.

patients varied in studies, which may have caused the divergence. Therefore, it is vital to determine the appropriate amount when administering nutritional supplements. Although proteins promote the absorption of energy [38], the effect stops when intake exceeds a certain threshold [39]. Some experts recommend taking 25–30 g high-quality protein per meal, which may be a promising intervention for preventing and slowing down the progress of sarcopenia [40]. According to the latest guideline in China, "nutritional support of elderly patients—a common understanding of nutritional support" [41], high quality proteins at least up to more than half of the daily requirement of protein, such as leucine-rich oral amino acids, help to promote muscle protein synthesis. In our systematic review, the addition of nutrients failed to remarkably lessen FM compared with the exercise group, which was contradictory to a meta-analysis involving healthy people [42]. Possibly, the reason for the discrepancy is that Rondanelli [27] chose hospitalized elderly patients with sarcopenia as the target population, thus the baseline FM is extremely low that an apparent decline after intervention is difficult to achieve.

Nutrients also play a vital role in muscle strength. Prolonged disuse of muscle in many elderly, such as resting due to osteoporosis, leads to changes in protein synthesis and breakdown, which seriously decreases muscle strength [43]. Available data suggested that proteins could stimulate muscle protein anabolism, which can overcome 'anabolic resistance' developed with aging, and maintain muscle mass and function in combination with exercise training [44,45]. In our meta-analysis, proteins further strengthened knee extension strength compared with exercise training alone. Regrettably, we failed to find difference between protein supplement groups and exercise groups with regard to grip strength [29], which may be due to different selection of outcome indexes. Shahar chose GS as index, which measures the strength of upper body, whereas the exercise intervention focused on the lower body. Consistent with Paddon-Jones [40], we found that using a mixture of whey protein, amino acids, and vitamin D as nutrient demonstrated an obvious improvement in GS. The physical condition of patients and their preferences should also be taken into account when choosing nutrients [46]. The target population of trials were different in our meta-analysis. The baseline nutritional status may have a great impact on outcomes. The nutritional status of hospitalized elderly with sarcopenia is worse than those in community people; thus, they may benefit more from nutritional supplementation. This hypothesis is supported by De Jong [47]. Denison [48] proposed that nutritional supplements are only beneficial in malnourished people who live with sarcopenia.

Regarding physical performance, we found that some indexes were improved, whereas others were not. Only two studies measured usual walk speed, and found that the effect of exercise was improved when the patients were given nutrients. This result was similar to a previous report on community-dwelling, frail Japanese women [49]. Michelle [50] presented a contrary conclusion. More RCTs with large sample size are still required to resolve differences among studies.

5. Limitations

Our systematic review has some limitations that should be mentioned. The first limitation concerns the number of articles. Although we used a comprehensive search strategy to retrieve related trials, due to language barriers and other limitations, only six studies were included in our systematic review, of which two were the same experiment using different outcome indexes, and may have influenced the robustness of our evidence. Second, studies in our systematic review were only of moderate methodological quality because the criteria were unclear and the design permitted a high risk of bias, which inevitably affected the results of our analysis. Third, the studies included in our research were all conducted in foreign countries, and the reliability of the conclusions may have been affected by differences in living environment, dietary structure, and physical condition of the population. Therefore, clinical practitioners should consider racial and cultural differences when attempting to apply our results. Lastly, involving a large sample of randomized controlled trials in our country is necessary to verify the accuracy of the results.

6. Implications for further research

The main finding of our systematic review is that nutritional supplementation may enhance the benefits of exercise intervention in elderly patients with sarcopenia at some degree. Noting that only 6 studies were included, the conclusion is limited. Many outcome indexes for muscle mass or strength exist, and different studies adopted different indexes. Pooling the data and evaluating the effect of combined intervention is difficult to achieve. The small sample size in the present study is another problem. More rigorous, large-scale RCTs are needed, and more attention should be paid in setting the gold standard for evaluating the effects of an intervention. From the systematic review, we can find that the types, quantity, and timing of nutritional supplementation are different, highlighting the importance of choosing nutrients and finding the most appropriate time for administration in future studies. The baseline nutritional status of participants is another key factor. Possibly, the improved effects of exercise intervention by nutritional supplementation would only be expected in the malnutrition sub-group. Future studies can explore whether there is a need for nutrition status screening before the intervention in order to gain the maximum benefits.

7. Conclusion

Supplying nutrients during exercise intervention may magnify the effects for elderly patients with sarcopenia; however, existing evidence are inconsistent. Taking into account the small number of trials included in this systematic review, more robust studies are needed to establish the actual efficacy of combined intervention in sarcopenia elderly.

References

[1] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing 2010;39(4):412–23.
[2] Bosaeus I, Rothenberg E. Nutritional and physical activity for the prevention and treatment of agerelated sarcopenia. Proc Nutr Soc 2016;75(2):174–80.
[3] Chang SF. Sarcopenia in the elderly: diagnosis and treatment. Hu Li Za Zhi 2014;61(2):101–5.
[4] Hung WW, Ross JS, Boockvar KS, Siu AL. Recent trends in chronic disease, impairment and disability among older adults in the United States. BMC Geriatr 2011;11:47.
[5] Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014;43(6):748–59.
[6] Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. J Am Geriatr So 2004;52(1):80–5.
[7] Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. J Cachexia Sarcopenia Muscle 2014;5(4):253–9.
[8] Batsis JA, Mackenzie TA, Barre LK, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. Eur J Clin Nutr 2014;68(9):1001–7.
[9] Cooper R, Kuh D, Hardy R, Ahmad R, Sayer AA, Al Snih S, et al. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ 2010;341:c4467.

[10] Montero-Fernandez N, Serra-Rexach JA. Role of exercise on sarcopenia in the elderly. Eur J Phys Rehabil Med 2013;49(1):131–43.
[11] Paddon-Jones D, Short KR, Campbell WW, Volpi E, Wolfe RR. Role of dietary protein in the sarcopenia of aging. Am J Clin Nutr 2008;87(5). 1562S–6S.
[12] Wolfe RR. Regulation of muscle protein by amino acids. J Nutr 2002;132(10). 3219S–24S.
[13] Sieber CC. Nutritional screening tools—how does the MNA compare? Proceedings of the session held in Chicago May 2–3, 2006 (15 years of mini nutritional assessment). J Nutr Health Aging 2006;10(6):488–92.
[14] Volkert D, Sieber CC. Protein requirements in the elderly. Int J Vitam Nutr Res 2011;81(2–3):109–19.
[15] Rolland Y, Dupuy C, Abellan van Kan G, Gillette S, Vellas B. Treatment strategies for sarcopenia and frailty. Med Clin North Am 2011;95(3):427–38.
[16] Naclerio F, Larumbe-Zabala E. Effects of whey protein alone or as part of a multi-ingredient formulation on strength, fat-free mass, or lean body mass in resistance-trained individuals: a meta-analysis. Sports Med 2016;46(1): 125–37.
[17] Abizanda P, López MD, García VP, Estrella Jde D, da Silva González Á, Vilardell NB, et al. Effects of an oral nutritional supplementation plus physical exercise intervention on the physical function, nutritional status, and quality of life in frail institutionalized older adults: the ACTIVNES study. J Am Med Dir Assoc 2015;16(5). 439.e9–439.e16.
[18] Nutrition and exercise intervention in sarcopenia elderly in China—an expert consensus. J Nutr 2015;37(4):320–4.
[19] Bosaeus I, Rothenberg E. Nutrition and physical activity for the prevention and treatment of agerelated sarcopenia. Proc Nutr Soc 2016;75(2):174–80.
[20] Denison HJ, Cooper C, Sayer AA, Robinson SM. Prevention and optimal management of sarcopenia: a review of combined exercise and nutritional interventions to improve muscle outcomes in older people. Clin Interv Aging 2015;10:859–69.
[21] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis. Age Ageing 2010;39(4):412–23.
[22] Higgins JP, Green S, editors. Cochrane Handbook for systematic reviews of interventions Version 5.1.0[update March2011][S/OL]. The Cochrane Collaboration; 2001. Available from: www.cochranehandbook.org.
[23] Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 2006;59(1):7–10.
[24] Zdzieblik D, Oesser S, Baumstark MW, Gollhofer A, König D. Collagen peptide supplementation in combination with resistance training improves body composition and increases muscle strength in elderly sarcopenic men: a randomised controlled trial. Br J Nutr 2015;114(8):1237–45.
[25] Maltais ML, Perreault K, Courchesne-Loyer A, Lagacé JC, Barsalani R, Dionne IJ. Effect of resistance training and various sources of protein supplementation on body fat mass and metabolic profile in sarcopenic overweight older adult men: a pilot study. Int J Sport Nutr Exerc Metab 2016;26(1):71–7.
[26] Maltais ML, Ladouceur JP, Dionne IJ. The effect of resistance training and different sources of postexercise protein supplementation on muscle mass and physical capacity in sarcopenic elderly men. J Strength Cond Res 2016;30(6):1680–7.
[27] Rondanelli M, Klersy C, Terracol G, Talluri J, Maugeri R, Guido D, et al. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly. Am J Clin Nutr 2016;103(3): 830–40.
[28] Kim HK, Suzuki T, Saito K, Yoshida H, Kobayashi H, Kato H, et al. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. J Am Geriatr Soc 2012;60(1):16–23.
[29] Shahar S, Kamaruddin NS, Badrasawi M, Sakian NI, Abd Manaf Z, Yassin Z, et al. Effectiveness of exercise and protein supplementation intervention on body composition, functional fitness, and oxidative stress among elderly Malays with sarcopenia. Clin Interv Aging 2013;8:1365–75.
[30] Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr 2012;96(6):1454–64.
[31] Bemben MG, Witten MS, Carter DL, Eliot KA, Knehans AW, Bemben DA. The effects of supplementation with creatine and protein on muscle strength following a traditional resistance training program in middle-aged and older men. J Nutr Health Aging 2010;14(2):155–9.
[32] Campbell WW, Crim MC, Young VR, Joseph LJ, Evans WJ. Effects of resistance training and dietary protein intake on protein metabolism in older adults. Am J Physiol 1995;268(6 Pt 1):E1143–53.
[33] Holm L, Olesen JL, Matsumoto K, Doi T, Mizuno M, Alsted TJ, et al. Protein-containing nutrient supplementation following strength training enhances the effect on muscle mass, strength, and bone formation in postmenopausal women. J Appl Physiol 2008;105(1):274–81.
[34] Iglay HB, Apolzan J, Gerrard D, Eash J, Anderson J, Campbell W. Moderately increased protein intake predominately from egg sources does not influence whole body, regional, or muscle composition responses to resistance training in older people. J Nutr Health Aging 2009;13(2):108–14.
[35] Kukuljan S, Nowson CA, Sanders K, Daly RM. Effects of resistance exercise and fortified milk on skeletal muscle mass, muscle size, and functional performance in middle-aged and older men: an 18-mo randomized controlled trial. J Appl Physiol 2009;107(6):1864–73.
[36] Verdijk LB, Jonkers R, Gleeson B, Beelen M, Meijer K, Savelberg H, et al. Protein supplementation before and after exercise does not further augment skeletal muscle hypertrophy after resistance training in elderly men. Am J Clin Nutr 2009;89(2):608–16.
[37] Milne AC, Avenell A, Potter J. Meta-analysis: protein and energy supplementation in older people. Ann Intern Med 2006;144(1):37–48.
[38] Millward DJ, Fereday A, Gibson N, Pacy PJ. Aging, protein requirements, and protein turnover. Am J Clin Nutr 1997;66(4):774–86.
[39] Waters DL, Baumgartner RN, Garry PJ, Vellas B. Advantages of dietary, exercise-related, and therapeutic interventions to prevent and treat sarcopenia in adult patients: an update. Clin Interv Aging 2010;5:259–70.
[40] Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care 2009;12(1):86–90.
[41] Bai Huijing, Sun Jianqing, Chen Min, Xie Hua, Xu Danfeng. Effects of branched-chain amino acids on senile myasthenia and its synergistic effect with resistance. Chin J Geriatric Dent 2015;34(5):476–7.
[42] Miller PE, Alexander DD, Perez V. Effects of whey protein and resistance exercise on body composition: a meta-analysis of randomized controlled trials. J Am Coll Nutr 2014;33(2):163–75.
[43] Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr 2014;33(6):929–36.
[44] Boirie Y, Morio B, Caumon E, Cano NJ. Nutrition and protein energy homeostasis in elderly. Mech Ageing Dev 2014;136–137(3–4):76–84.
[45] Rennie MJ, Selby A, Atherton P, Smith K, Kumar V, Glover EL, et al. Facts, noise and wishful thinking: muscle protein turnover in aging and human disuse atrophy. Scand J Med Sci Sports 2010;20(1):5–9.
[46] Calvani R, Miccheli A, Landi F, Bossola M, Cesari M, Leeuwenburgh C, et al. Current nutritionalal recommendations and novel dietary strategies to manage sarcopenia. J Frailty Aging 2013;2(1):38–53.
[47] De Jong N, Chin A, Paw MJ, de Groot LC, Hiddink GJ, van Staveren WA. Dietary supplements and physical exercise affecting bone and body composition in frail elderly persons. Am J Public Health 2000;90(6):947–54.
[48] Denison HJ, Cooper C, Sayer AA, Robinson SM. Prevention and optimal management of sarcopenia: a review of combined exercise and nutritional interventions to improve muscle outcomes in older people. Clin Interv Aging 2015;10:859–69.
[49] Kim H, Suzuki T, Kim M, Kojima N, Ota N, Shimotoyodome A, et al. Membrane (MFGM) supplementation on body composition, physical function, and hematological parameters in community dwelling frail Japanese women: a randomized double blind, placebo controlled, follow-up trial. PLoS One 2015;10(2):e0116256.
[50] Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritionalal supplementation and resistance training in nutritionally at risk older adults following lower limb fracture: a randomized controlled trial. Clin Rehabil 2006;20(4):311–23.