Exercise combined with vitamin D supplementation has additive health effects on SPPB and stair climbing in older adults: a scope review of randomized controlled trials

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Abstract

This scoping review aimed to evaluate the effect of exercise combined with vitamin D supplementation on skeletal muscle health in older individuals. We implemented a systematic search of electronic databases, including PubMed, the Cochrane Library, Web of Science, and Embase, was conducted from the time of library construction to January 2024. Eligible studies were randomized controlled trials (RCTs) including men and women aged ≥65 years or mean age ≥65 years; exercise training and vitamin D supplementation; outcomes of muscular strength, function, muscular power, body composition, and quality of life; and results compared with those of exercise intervention alone. The results showed 13 studies including 1483 participants were identified. The proportions of male and female sex were 22.05% and 77.95%, respectively. Exercise intervention methods included resistance exercises and multimodal exercise training. All vitamin D interventions involved supplementation with vitamin D_3. A significant increase was identified in short physical performance battery (SPPB) and stair climbing but not in skeletal muscle mass, skeletal strength, the timed up and go (TUG) test, and gait speed in older adults after exercise combined with vitamin D supplementation. In conclusion， exercise combined with vitamin D supplementation has additive health effects on SPPB and stair climbing. Furthermore, when vitamin D was deficient at baseline, the combined effect of exercise and vitamin D intervention significantly increased the TUG and gait speed in older adults. In future RCTs on this topic, baseline vitamin D nutritional status, health condition, and sex should be considered.

Keywords: exercise; vitamin D supplementation; skeletal muscle health; older adults

Abbreviations

RoB 2: The revised version of Cochrane risk-of-bias tool for randomized trials; PRISMA: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs: randomized controlled trials; TUG: Timed up and Go Test; 6MW: 6-Minute Walk Test; 12MW: 12-Minute Walk Test; HG: Hand grip strength; SPPB: the Short Physical Performance Battery. RT: resistance training; COPD: Chronic Obstructive Pulmonary Disease, 1RM: the one-repetition maximum, RPE: Borg's Rate of Perceived Exertion, Wmax: maximal workload

1. Introduction

Sarcopenia, accompanied by age, is a geriatric disease characterized by a progressive loss of skeletal muscle mass and muscle function (1). Loss of skeletal muscle mass and function lowers the quality of daily life in older adults (2) and increases the risk of sudden falls (3) and even death (4).

Exercise and nutrient intake are widely accepted interventional approaches in this population (2). Exercise interventions, including resistance, aerobic, high-intensity interval, and multimodal training, have been shown to reduce age-associated changes in the musculoskeletal system (5, 6). Research has shown that even passive forms of exercise intervention, such as whole-body vibration training (WBV), can significantly improve muscle mass and function, such as hand strength and sit-to-stand performance in older adults (7).

Serum 25(OH)D levels were significantly correlated with gait speed and the timed up and go test (TUG) in older patients with lumbar disc degeneration (8) but were not correlated with grip strength and balance tests among older patients (8). Moreover, older patients with lumbar disc degeneration and vitamin D insufficiency had prolonged physical performance times for gait speed, the chair stand test, and the TUG compared with those with vitamin D sufficiency (8). Furthermore, evidence has shown that vitamin D deficiency is associated with physical dysfunction, such as muscle weakness, low muscle mass, and a greater risk of falling (9). Vitamin D supplementation also significantly increases limb strength in healthy adults (10) and athletes (11) and improves grip strength and physical performance in patients with osteoarthritis (12). Nevertheless, the results of some studies do not support these notions (13). In older participants, vitamin D_3 supplementation itself had no effect on upper- and lower-body muscular strength and performance, muscle fiber area, or characteristics, and it showed no interaction with health status (14). A meta-analysis of 12 randomized controlled trials (RCTs), including 1739 potential reports, showed that vitamin D supplementation had no significant effect on hand grip strength, back muscle strength, or the TUG in postmenopausal women (15). Moreover, RCTs have reported that vitamin D supplementation at a relatively high dose had no beneficial effects on health outcomes in women with vitamin D insufficiency (16). A systematic review and meta-analysis of 54 RCTs also reported that vitamin D supplementation resulted in a significantly longer time spent performing the TUG and lower maximum knee flexion strength; it even had a tendency toward worsening the Short Physical Performance Battery (SPPB) total score (17). This evidence does not support the beneficial effects of vitamin D supplementation alone on muscle health, possibly owing to a decline in physical function, as older adults may show a sluggish or poor response to vitamin D supplementation alone.

The effects of vitamin D on skeletal muscle mass, strength and function are not well understood. Research reported that vitamin D deficiency accelerates muscle atrophy via the FOXO3α-mediated E3 ubiquitin ligase pathway (18). The evidence presented above, however, suggests that improving vitamin D nutritional status by supplementing with vitamin D alone does not confer benefits on muscle health. Physical exercise and/or nutritional supplementation are important strategies for improving muscle health and preventing sarcopenia (19). A systematic review and network meta-analysis showed that adding nutritional interventions to exercise had a larger effect on handgrip strength than exercise alone while showing a similar effect on other physical function measures (20). Therefore, multifactorial intervention (including nutrition and physical exercises) should be recommended for older adults. Consequently, the question on whether vitamin D supplementation combined with exercise can improve these differences arises. Theoretically, a combination of the two has better effects on promoting and maintaining skeletal muscle health, and several studies have explored the effects of such combination on skeletal muscle health. The results of cross-section study in older adults (18) supported the viewpoint aboved. Yang et al. found vitamin D and physical activity had an interactive effect in TUG and handgrip strength, meaning that the effects of vitamin D may be affected by the level of physical activity,and the effect of physical activity may also be affected by vitamin D levels (18). In 2010, Daly et al. reported that regular exercise and adequate vitamin D supplementation were important for maintaining or optimizing muscle morphology, strength, power, and function in older adults (21). Conversely, the findings from a limited number of factorial 2 × 2 RCTs showed that vitamin D supplementation does not enhance the effects of exercise on muscle morphology, function, or fall risk (21). In 2017, a systematic review and meta-analysis revealed that compared with resistance exercise alone, resistance exercise combined with vitamin D supplementation significantly improved muscle strength of the lower limbs in older adults, whereas it did not have the same effect on SPPB and the TUG (22). However, these two studies did not reach consistent conclusions. Recently, research on vitamin D has gained popularity, and many studies on vitamin D have emerged. Scoping reviews permit quick structured mapping of key concepts in a research area, identify gaps in the existing literature, and succinctly summarize emerging research findings (23). Therefore, based on existing RCTs, we aimed to reexamine whether exercise, not just resistance exercise combined with vitamin D supplementation, had additive effects on skeletal muscle health, relative to exercise alone. In this review, we systematically searched for relevant literature and summarized the available evidence of RCTs that aimed to evaluate the effectiveness of exercise combined with vitamin D supplementation on skeletal muscle health in the older adults.

2. Materials and Methods

Scoping review is an appropriate methodology for reviewing a large body of literature to generate an overview of a research topic (24). This review was conducted using the five-stage methodological framework for scoping studies developed by Arksey and O'Malley (23). Guided by this framework, the stages of this scoping review included (a) identifying the research question; (b) identifying relevant studies; (c) selecting studies; (d) charting the data; and (e) collating, summarizing, and reporting the results. The methodologies used for each stage of the framework are outlined below.

2.1 Identifying the research question

This scoping review primarily aimed to probe the effect of exercise combined with vitamin D supplementation on skeletal muscle health to determine the efficacy of such combination in older adults. Therefore, the following research question was purposefully refined to encompass the extensive range and nature of existing research activities in the literature: What is the effect of exercise combined with vitamin D supplementation on skeletal muscle health in older adults? The following research questions guided this review: (a) What is the design of an each RCT? (b) What are the characteristics of the participants? (c) What is the type, intensity, and duration of exercise? (d) What is the type and dosage of vitamin D supplementation? (e) What are the outcome measurements and results? All of these questions were condensed into a final key question: Is exercise combined with vitamin D supplementation more effective for skeletal muscle health in older adults?

2.2 Identifying research studies

We conducted a systematic search of PubMed, Cochrane Library, Web of Science, and Embase databases from the time of library construction to January 2024. The literature retrieval strategy is presented in Supplementary document 1. To avoid missing relevant studies, the reference lists of the relevant studies from these searches were cross-checked for additional citations. The studies were saved in a reference manager software (EndNote X9, Thomson Reuters, NY, USA).

2.3 Selecting studies

Published RCTs were identified for this scoping review. Literatures included the following: (1) male and/or female participants aged ≥65 years or mean age ≥65 years; (2) exercise intervention, including resistance exercise and endurance exercise, and vitamin D supplementation more than 400 IU/day which was recommended (25), including vitamin D_2 and vitamin D_3 (studies that adopted vitamin D and calcium supplementation were included); (3) measures of muscular strength, function, muscular power, body composition, and quality of life; and (4) results compared with those of exercise intervention alone. Articles were excluded if participants were supplemented with additional protein or any supplement/medication with known anabolic effects on skeletal muscle. RCTs were also excluded if they were written in any language other than English. The literature was independently screened by two researchers (Zhang and Zhu) based on the inclusion and exclusion criteria. When the two researchers disagreed, a third researcher (Cao) was consulted. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (26) were used to report the flow of articles included in this review.

2.4 Charting the data

Key information items from the included RCTs were charted onto a form developed based on the research question. The key information extracted from each article included the first author's name, year of publication, participant characteristics, vitamin D dosage, supplementation strategies, exercise intervention, methods utilized, intervention length, and main outcomes. Two independent authors (Zhang and Niu) extracted information from each RCT across each data extraction category. Any conflicts in data collection were resolved by discussion between the two independent authors; otherwise, only the third author (Cao) was consulted.

2.5 Quality assessment of the study methodologies

The revised version of Cochrane risk-of-bias tool for randomized trials (RoB 2) (27) was used to assess the included RCTs, assessing the following five bias domains: (a) randomization processes; (b) deviations from intended interventions; (c) missing outcome data; (d) measurement of the outcomes; and (e) selection of reported results. Several signaling questions were also included. Generally, signaling questions each had five answer options: Yes (Y), Probable Yes (PY), Probable No (PN), No (N), and No Information (NI). According to responses to the signaling questions, the risk of bias in each domain could be divided into three levels: “low risk of bias,” “some concerns,” and “high risk of bias.” If the bias risk assessment results in all domains were “low risk,” then the overall risk of bias was “low risk.” If the bias risk assessment results for some domains were “some concerns” and without “high risk,” then the overall bias risk was “some concerns.” As long as a domain bias risk evaluation result was "high risk," then the overall bias risk was considered "high risk." The Excel file of RoB 2 (Revised 2019) was downloaded from the Risk of Bias website (https://www.riskofbias.info/) to evaluate the risk of bias and draw a publication bias graph.

2.6 Collating, summarizing, and reporting the results

The "descriptive-analytical" method from the narrative tradition was utilized (23). For the included RCTs, we applied a common analytical framework and collected standard information for this scoping review. Any discrepancies between the two authors (Zhang and Zhu) during this period were clarified by consulting a third author (Cao) until a consensus on the final results was reached.

3. Results

3.1 Literature search

A total of 1608 studies were retrieved, and 5 relevant studies were obtained by tracking the references of the screened documents. Of these studies, 1411 were identified after removing duplicates, and 33 were considered potentially relevant after the initial screening of titles and abstracts. After applying the inclusion and exclusion criteria, 13 articles (28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40) were selected for the systematic review (Fig. 1). By carefully examining the included RCTs, we found that the studies by Aschauer et al. (30) and Draxler et al. (31) had the same study design and used different outcome indicators. For the purposes of the following narrative, we treated the two RCTs (30, 31) as two studies. In addition to the 3 articles (38, 39, 40) that were included the meta-analysis by Antoniak et al. (22), we included 10 articles (28, 29, 30, 31, 32, 33, 34, 35, 36, 37) in this review. Relevant information included in the literature is provided in Supplementary Table 1.

3.2 Study characteristics

Among the RCTs included in this review, the publication years ranged from 2003 to 2023. Of these, 2 articles each were published in 2012 (33, 35), 2015 (38, 40), 2018 (36, 37), 2021 (30, 34), respectively. The countries/regions where the research was conducted included the United States (28), Australia (29), Austria (30, 31), Belgium (32, 33), Brazil (34), Chile (39), Denmark (38), Finland (40), Germany (35), Japan (36), and Switzerland (37). Among the 13 RCTs (28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40) included in the review, 5 had two arms (28, 29, 33, 34, 38), 4 had three arms (30, 31, 35, 36), and 4 had four arms (32, 37, 39, 40).

The total number of participants included in this scoping review was 1483, ranging from 17 (38) to 409 (40) in each study. There were a total of 327 male participants, accounting for approximately 22.05%, with 1 RCT involving only male participants (38) and 4 RCTs involving only female participants (28, 32, 34, 40). Of the included RCTs, eight involved healthy participants (28, 30, 31, 32, 36, 38, 39, 40), and five involved non-healthy participants (29, 33, 34, 35, 37). The non-healthy participants in the included RCTs had COPD (33) with risk factors for falls and/or low bone mineral density (29), low bone mineral density (34), prefrailty (35), and acute hip fracture (37).

Of the included RCTs, seven adopted resistance exercise training (30, 31, 32, 35, 36, 38, 39), and six adopted multimodal exercise training (28, 29, 33, 34, 37, 40). Additionally, two RCTs adopted progressive-resistance training (PRT) (30, 38). The duration of the experimental intervention ranged from 10 weeks (30, 31) to 96 weeks (40). A total of four interventions had a duration of 12 weeks (33, 34, 35, 38), two interventions had a duration of 10 weeks (30, 31), two interventions had a duration of 24 weeks (32, 36), and two interventions had a duration of 48 weeks (29, 37); the frequencies of exercise intervention were two, three, and seven sessions per week, respectively. Among them, six articles had a frequency of two sessions/week (30, 31, 34, 35, 39, 40), five articles had a frequency of three sessions/week (28, 29, 32, 33, 38), and two articles had a frequency of seven sessions/week (36, 37). The one repetition maximum (1RM) is widely used as the intensity index for resistance exercise, with a range of 30% (40) to 121% 1RM (33). Among the RCTs that adopted multimodal exercise training, Brech et al. (34) and Jessup et al. (28) employed resistance and balance exercises. Uusi-Rasi et al. adopted balance challenges, weight-bearing, strengthening, agility, and functional exercises (40). Gianoudis et al. adopted a high-velocity PRT combined with diverse loading, moderate impact, weight-bearing exercises and high-challenge balance/functional exercises (29). Hornikx et al. adopted rehabilitation that included cycling, walking on a treadmill, stair climbing, strength exercises for the upper and lower extremities, and arm cranking (33). Stemmle et al. adopted a multimodal exercise, which included standing on both legs and then standing on one leg while holding onto a handrail, pulling a rubber band while sitting for arm and shoulder strength training, getting in and out of a chair, and up and down stairs (37).

All vitamin D interventions involved supplementation with vitamin D_3. Vitamin D supplementation comes in various forms: daily, weekly, and monthly. The dose of daily supplementation varies from 400 IU (28, 39) to 2000 IU (35, 37), and the monthly form varies from 50000 IU (31) to 100000 IU (30, 33). The weekly dose was 50000 IU (34). Among the included RCTs, three RCTs involved receiving vitamin D supplementation before exercise intervention (30, 31, 38). Among the RCTs included in this scoping review, nine RCTs involved supplementation with calcium (28, 29, 30, 31, 32, 37, 38, 39, 40).

The risk of bias assessment results of the included studies are shown in Figure 2. Overall, the quality of RCTs based on the design and reporting was high. Among all studies, some concerns were observed in eight RCTs (28, 29, 32, 35, 36, 38, 39, 40). In the study by Agergaard et al. (38), although the participants were randomly divided, the strength/muscle cross-sectional area (CSA) was significantly different between the groups at baseline. This difference may have influenced the effect of exercise combined with vitamin D supplementation. In the same studies included in this review, some groups received exercise interventions, whereas others did not, which may have resulted in deviations from the intended interventions. Therefore, a number of RCTs were considered concerning (28, 29, 32, 35, 36, 38, 39, 40). Among all RCTs, there was no report on whether the tester of the outcome index was blinded, and we determined that blinding was possible. Therefore, the RCTs included in this review were all judged to be low-risk.

3.3 Main outcomes of RCTs

3.3.1 Vitamin D levels

At baseline, participants were vitamin D-deficient (25(OH)D levels <20 ng/mL or <50 nmol/L) in two studies (37, 39), insufficient (20–30 ng/mL or 50–75 nmol/L) in six studies (30, 32, 33, 35, 36, 40), and sufficient (>30 ng/mL or >75 nmol/L) in one study (38). After vitamin D supplementation, the participants achieved sufficient levels of serum 25(OH)D from deficient/insufficient levels in 6 RCTs (30, 32, 33, 35, 36, 40). Unfortunately, data on serum vitamin D levels were not reported by Brech et al. (34), Jessup et al. (28), Draxler et al. (31), and Gianoudis et al. (29).

3.3.2 The effects of exercise combined with vitamin D supplementation on muscle mass

Muscle mass was reported in six studies (29, 31, 32, 35, 36, 38). Draxler et al. (31) found that after 10 weeks of intervention, lean body mass was significantly increased in the group undergoing strength training combined with monthly vitamin D supplementation (VDM) but not in the groups undergoing strength training alone (CON) or strength training combined with daily vitamin D_3 supplementation (VDD). In a study by Aoki et al. (36), after 24 weeks of intervention, strength training alone, vitamin D supplementation alone, and strength training combined with vitamin D supplementation significantly increased lower limb muscle mass in community-dwelling older adults. However, the change in lower limb muscle mass was not significantly different among the three groups. Similarly, in a study by Agergaard et al. (38), resistance exercise combined with vitamin D supplementation and resistance exercise alone resulted in significant gains in the quadriceps muscle CSA after 12 weeks of resistance training. However, no significant differences were identified in the changes (4.9±2.0% *vs.* 8.5±2.8%) between groups. Drey et al. (35) found that after 12 weeks of intervention, no statistical differences were observed in changes in appendicular lean mass between participants undergoing strength training combined with vitamin D supplementation, power training combined with vitamin D supplementation, and vitamin D supplementation alone. However, in a study by Verschueren et al. (32), no significant change was identified in muscle mass after 6 months of WBV combined with high-dose vitamin D supplementation, WBV combined with low-dose vitamin D supplementation, high-dose vitamin D supplementation alone, or low-dose vitamin D supplementation alone. Additionally, Gianoudis et al. (29) found no significant effects of 12 month multimodal exercise combined with vitamin D supplementation or vitamin D supplementation alone on changes in lean mass (%).

3.3.3 The effects of exercise combined with vitamin D supplementation on muscular strength

Muscular strength was assessed in 10 studies (28, 29, 32, 33, 34, 36, 37, 38, 39, 40), with the exceptions of Aschauer et al. (30), Drey et al. (35), and Draxler et al. (31). In a study by Agergaard et al. (38), resistance exercise combined with vitamin D supplementation and resistance exercise alone significantly increased quadriceps muscle isometric strength. However, no significant differences were identified in the changes in isometric strength or the isometric strength/CSA ratio between the groups. In a study by Aoki et al. (36), muscular strength during knee extension and hip flexion significantly improved in the groups undergoing exercise alone, vitamin D supplementation alone, and exercise combined with vitamin D supplementation after 24 weeks of intervention ($P<0.001$). However, the changes in muscular strength during knee extension and hip flexion revealed no significant differences among the three groups. In the study by Brech et al. (34), after 12 weeks of intervention, muscular strength, including hand grip strength (dominant and non-dominant) and dynamometry isokinetic strength (evaluated by extension and flexion movements of the knee joint), significantly improved in the groups undergoing multimodal exercise combined with vitamin D supplementation and multimodal exercise alone. However, no significant difference was observed between the groups (34). In a study by Bunout et al. (39), trained participants (groups undergoing either exercise training combined with calcium supplementation or exercise training combined with calcium and vitamin D supplementation), instead of non-trained participants (groups undergoing either calcium supplementation alone or calcium and vitamin D supplementation alone), showed a significant increase in quadriceps strength after 9 months of intervention. However, handgrip strength (dominant and nondominant) did not differ between the groups (39). Uusi-Rasi et al. (40) found that after 2 years of intervention, maximal isometric leg extensor strength in the groups undergoing exercise alone and exercise combined with vitamin D supplementation significantly improved, compared with the group undergoing vitamin D supplementation alone. Verschueren et al. (32) showed that WBV intervention and vitamin D supplementation had significant effects on dynamic muscle strength, although neither had any interaction effects. Moreover, Verschueren et al. found that WBV alone, vitamin D supplementation alone, or a combination of both did not induce significant changes in isometric muscle strength (32). Jessup et al. (28) revealed that after 32 weeks of intervention, a significant improvement in grip strength was observed in the group undergoing exercise combined with vitamin D supplementation but not in the group undergoing exercise alone. Gianoudis et al. (29) found that after 12 months of intervention, the group undergoing exercise combined with vitamin D supplementation experienced greater gains in leg and back muscle strength than the group undergoing vitamin D supplementation alone. In patients with chronic obstructive pulmonary disease (COPD), after 12 weeks of intervention, rehabilitation alone, which includes cycling, walking on a treadmill, stair climbing, strength exercises for the upper and lower extremities, and arm cranking, and rehabilitation combined with vitamin D supplementation did not significantly improve quadriceps strength and expiratory muscular strength (33). However, rehabilitation combined with vitamin D supplementation can significantly increase inspiratory muscle strength, whereas rehabilitation alone does not have the same effect (33). Stemmle et al. found that, compared with 800 IU vitamin D supplementation alone, exercise combined with 800 IU vitamin D supplementation and exercise combined with 2000 IU vitamin D supplementation did not improve knee flexor strength and knee extensor strength (37).

3.3.4 The effects of exercise combined with vitamin D supplementation on physical function

Physical function was assessed in nine studies (29, 30, 33, 34, 35, 36, 37, 39, 40). Bunout et al. (39) showed that trained participants (those undergoing exercise training combined with calcium and exercise training combined with calcium and vitamin D) had significantly improved

SPPB scores and decreased TUG time after 9 months of intervention. Moreover, the TUG time decreased more in the participants undergoing training combined with calcium and vitamin D supplementation (39). Individuals supplemented with vitamin D (those undergoing calcium and vitamin D supplementation alone and exercise training combined with calcium and vitamin D supplementation) had a higher gait speed than those without vitamin D supplementation (those undergoing calcium supplementation alone and exercise training combined with calcium alone) (39). Uusi-Rasi et al. (40) found after 2 years of intervention, compared with that of the group that underwent neither, the speed of normal walking in the group undergoing exercise alone increased significantly (P=0.007), whereas such speed in the groups undergoing vitamin D supplementation alone and exercise combined with vitamin D supplementation was not significantly impacted. Moreover, the TUG time in the group receiving vitamin D supplementation alone increased significantly (P=0.01), whereas that in the groups undergoing exercise alone and exercise combined with vitamin D supplementation showed no significant effects (40). The time of the five-time chair stand test in the group undergoing exercise alone decreased significantly (P=0.03), whereas that in the group undergoing exercise combined with vitamin D supplementation showed a downward trend (P=0.05); however, the group receiving vitamin D supplementation alone experienced no significant impact (P=0.46) (40). Drey et al. found that after 12 weeks of intervention, strength training combined with vitamin D supplementation and power training combined with vitamin D supplementation significantly increased the SPPB score (35). However, no statistical difference was identified between the groups undergoing strength training combined with vitamin D supplementation and power training combined with vitamin D supplementation (35). Moreover, Drey et al. (35) reported no statistical differences in changes in muscular power of the lower limb, as assessed by sit-to-stand transfer, among groups undergoing strength training combined with vitamin D supplementation, power training combined with vitamin D supplementation, and vitamin D supplementation alone. Gianoudis et al. revealed that after 12 months of intervention, exercise combined with vitamin D supplementation led to modest yet significant net gains in the change of timed stair climbing

(P <0.05) in older adults with risk factors for falls and/or low bone mineral density relative to controls but not in the change of the time (29). Aoki et al. (36) reported that scores in the two-step test and the five-time sit-to-stand test (FTSTS) significantly improved in the groups undergoing exercise alone, vitamin D supplementation alone, and exercise combined with vitamin D supplementation after 24 weeks of intervention. However, no significant differences were identified in these indices among the three groups (36). Moreover, these interventions did not significantly affect the 25-question geriatric locomotive function scale (GLFS-25) (36). In the study by Aschauer et al. (30), no significant changes were observed in the times of the 30-s chair stand, 30-s arm curl test, TUG test, gait speed, and 6-min walk (6 MW) test distance in the groups undergoing resistance exercise alone, resistance exercise combined with daily vitamin D_3 supplementation, and resistance exercise combined with monthly vitamin D supplementation after 16 weeks of intervention. In patients with COPD, rehabilitation alone or that combined with vitamin D supplementation did not significantly improve the 6 MW test distance (33). In the study by Brech et al. (34), after 12 weeks of intervention, the 15-steps climbing test and 30-s chair stand test times significantly improved in the groups undergoing exercise combined with vitamin D supplementation and exercise alone. Moreover, compared with the group undergoing exercise alone, stair climbing ability was better in the group with exercise combined with vitamin D supplementation (34). Stemmle et al. found that, compared with group receiving 800 IU vitamin D supplementation alone, the group undergoing exercise combined with 800 IU vitamin D supplementation showed improved TUG scores, whereas the group undergoing exercise combined with 2000 IU vitamin D supplementation showed no improvement (37).

4. Discussion

To our knowledge, this is the first scoping review to comprehensively examine the extent, range, and methodological quality of reviews conducted to evaluate the effects of exercise combined with vitamin D supplementation on skeletal muscle health in older adults.

This scoping review identified 13 RCTs published between 2003 and 2023. Currently, relatively little research has addressed this topic, and research implementation has not focused on a specific year or country/region, indicating that this topic has great research prospects.

In the included studies, significant differences in the number of participants (range, 17–409) were noted, with <100 participants in 6 RCTs (approximately 46.15%) (28, 33, 34, 35, 38, 39). Regarding the sex of the participants, we found that the proportions of male and female patients were 22.05% and 77.95%, respectively. Additionally, four studies recruited female patients only, and one study recruited male patients only. These demographics suggest that research in this field focuses primarily on female patients, whereas research focusing on male patients is relatively rare. Goodpaster et al. found that with age, both men and women lose strength, with men losing almost twice as much strength as women (41). Moreover, as age increases, genes in the skeletal muscles undergo sex differences (42). In females, 239 genes are involved in glucose catabolism, NAD metabolic processes, and muscle fiber transition pathways (42). In males, 166 genes involved in replicative senescence, cytochrome C release, and muscle composition pathways were altered (42). Changes in skeletal muscle function caused by aging show sex differences and are caused by different pathways. Therefore, both males and females have equal research urgency and importance in preventing the decline in skeletal muscle function in the older population. Healthy older individuals were selected as participants in eight studies (approximately 61.54%), whereas only five RCTs recruited non-healthy participants (38.46%). Among studies including non-healthy participants, two involved participants with low bone mineral density (29, 34), and one involved patients with COPD (33), acute hip fracture (37), and prefrailty (35). Studies have suggested that bone mineral density is positively associated with the appendicular skeletal muscle mass index (43) and grip strength (44). COPD and acute hip fractures not only restrict exercise but may also directly lead to poor exercise performance (45). Therefore, the health statuses of participants may also affect intervention effectiveness.

Muscular function decreases with age. Regular exercise is an effective strategy to prevent frailty and improve sarcopenia and physical function in older adults (6). Resistance exercise training is more effective for increasing muscle mass and strength, whereas endurance exercise training is superior for maintaining and improving maximum aerobic power (6). Moreover, a systematic review revealed that resistance training significantly enhances muscular strength, muscular power, and functional outcomes in physically frail older individuals (46). Of the RCTs included in this review, seven adopted resistance exercises (53.85%), and six adopted multimodal exercise training (46.15%). Resistance training remains the primary method of promoting skeletal muscle health. The maximum duration of the exercise intervention was 12 weeks (4 RCTs, approximately 30.77%). The frequencies of exercise interventions were two, three, and seven times per week, with two times per week being the most commonly used (six RCTs, approximately 46.15%), followed by three times per week (five RCTs, approximately 38.46%). Notably, a systematic review and meta-analysis including 10 studies found that training frequencies of 2 sessions/week promoted superior hypertrophic outcomes to 1 session/week (47). Among the RCTs reporting intensity of exercise, the one-repetition maximum (1RM) (28, 29, 30, 31, 38, 48), Hz (32), Borg scale (35), maximal workload (33), and walking speed (33) indicators were used to evaluate intensity. In this review, 1RM was widely used as the intensity index for resistance exercise, with a range of 30%–121% 1RM. Holm et al. found that regardless of light (15.5% 1RM) or high load (70% 1RM), 12 weeks of resistance training 3 times per week could significantly cause muscle hypertrophy and increase muscular strength (49).

Vitamins D_3 and D_2 are the most widely used compounds (50). Vitamin D_3 supplementation is a more effective method to elevate serum 25(OH)D levels than vitamin D_2 supplementation (51). Among the RCTs included in this review, the vitamin D interventions included supplementation with vitamin D_3. Vitamin D intervention methods included daily, weekly, and monthly interventions. A randomized clinical trial found that daily, weekly, and monthly administration of vitamin D supplementation, equivalent to 1000 IU/day, could elevate 25(OH)D levels > 20 ng/mL (52). The three supplementation methods showed equal efficacy and safety profiles (52). Similarly, vitamin D_3 supplementation, equivalent to 1500 IU/day, can be achieved equally well with daily, weekly, or monthly dosing frequencies in older patients with hip fractures (53). However, Chel et al. found that daily vitamin D supplementation, equivalent to 600 IU/day, was the most effective, followed by weekly and monthly supplementation, in older nursing home residents (54). The different effects of vitamin D_3 supplementation strategies in these three literatures (52, 53, 54) may be attributed to different doses. However, research has shown that vitamin D_3 supplementation did not improve muscle fiber CSA or muscle satellite cell activation in postmenopausal women with 25(OH)D levels of 55.1±22.8 nmol/L at baseline and 138.7 ± 22.2 nmol/L post-administration (55). Mori et al. (56) reported that the effects of vitamin D administration on muscle function depend on vitamin D sufficiency status at baseline. Therefore, baseline vitamin D nutrition may be an important factor impacting the effectiveness of combining exercise with vitamin D supplementation. Of the RCTs included in this review, three studies conducted vitamin D supplementation before the combined intervention of exercise and vitamin D (30, 31, 38). Improvement in the nutritional status of vitamin D to an adequate level may be based on the willingness of these three RCTs to supplement vitamin D before joint intervention. Unfortunately, in four studies (28, 29, 31, 34), vitamin D levels were not reported. This may have confounded the effects of combining exercise with vitamin D supplementation. Calcium is a prerequisite for the action of vitamin D in skeletal muscle. In this review, nine articles reported calcium supplementation (28, 29, 30, 31, 32, 37, 38, 39, 40), accounting for 64.29% of the articles. Therefore, improvements in skeletal muscle health may be ascribed to the combined effects of exercise, vitamin D, and calcium.

Regarding the mian outcome indicators, we found six RCTs evaluating skeletal muscle mass (29, 31, 32, 35, 36, 38), including three evaluating total body muscle mass (lean body mass (31), muscle mass (32), and % lean mass (29)), two evaluating lower limb muscle mass (ΔCSA of the quadriceps muscle (38) and lower-limb muscle mass (36)), and one evaluating appendicular lean mass (%) (35). Indicators for evaluating skeletal muscle quality are not uniform. However, regardless of the evaluation method, exercise combined with vitamin D supplementation had no additional effect on skeletal muscle mass in older individuals. Vitamin D supplementation decreased myostatin production (57). However, decreased myostatin mRNA expression due to vitamin D supplementation was only seen in the young men, instead of older adults (38). Therefore, in older adults undergoing exercise intervention, vitamin D supplementation lacks additional effects on skeletal muscle mass, which may also reflect the sluggish response of aging muscles (38).

Among the included studies, 10 articles evaluated muscular strength (28, 29, 32, 33, 34, 36, 37, 38, 39, 40), including 9 on lower-limb strength (29, 32, 33, 34, 36, 37, 38, 39, 40), 3 on upper-limb strength (28, 34, 39), and 1 on back strength (29) and respiratory muscle (33). Researchers are now paying more attention to lower limb muscle strength. Regarding the indicators for evaluating lower limb muscle strength, six RCTs evaluated muscle strength around the knee joint (32, 33, 34, 36, 37, 38, 40). Grip strength indicators were used to assess upper limb muscle strength in 3 RCTs (28, 34, 39). Hornikx et al. also evaluated respiratory muscle strength in patients with COPD (33). Unfortunately, none of these RCTs showed any additional effects of exercise combined with vitamin D supplementation on skeletal muscle strength. This results in this review were consistent with previous research findings (14, 58). One study performed on high-level, well-trained athletes indicated that 8 weeks of high-intensity interval training combined with vitamin D_3 supplementation did not induce better training responses (squat jumps, contermoverment jumps) than training alone (58). One RCT reported that there were no differences in change in leg or grip strength in vitamin D supplementation group (59). Vitamin D supplementation didn’t alter composition and cross-sectional area of muscle fiber in older adults (59). Moreover, vitamin D_3 supplementation did not enhance resistance training-associated increases in muscle fibre cross-sectional area or changes in muscle fibre proportions in older adults (14). It can be seen vitamin D supplementation does not provide additional health benefits on skeletal muscle strength.

The chair stand test was used to evaluate lower limb muscle endurance; however, the testing protocol different among the studies (29, 30, 34, 35, 40). Only one RCT evaluated upper limb muscle endurance function using the 30-s arm curl test (30). Walking is a dynamic activity that requires appropriate muscle function (60), and the evaluation indicators of walking endurance included the two-step test (36), 15-step test (34), gait speed (30), 6 MW (30, 33), 12 MW (39), and normal walking speed (40). The comprehensive evaluation indicators included the SPPB and TUG. The SPPB was used to assess gait speed, chair stand ability, and balance. However, among the included literatures, only two articles used SPPB (35, 39). Although the TUG is a mobility test that requires both static and dynamic balance, only five of the included RCTs used this test (29, 30, 37, 39, 40). Furthermore, only two RCTs used the stair climbing test (29, 34), which evaluates the ability to ascend and descend stairs to assess the strength, power, and balance of the lower limbs (61). Physical exercise has a beneficial effect on muscle mass, muscle strength, or physical performance in healthy subjects aged 60 years and older (62). However, the additional effect of dietary supplementation has only been reported in a limited number of studies (17.8%) (62). In this review, we found that, compared with the individual effects of exercise and vitamin D, the combined effects of exercise and vitamin D significantly increased walking endurance in the study by Bunout et al. (39) but not in the studies by Uusi-Rasi et al. (40), Aschauer et al. (30), and Hornikx et al. (33). Furthermore, the combined effects of exercise and vitamin D significantly increased TUG ability in the studies by Bunout et al. (39), and Stemmle et al. (37), but not in the studies by Uusi-Rasi et al. (40), Gianoudis et al. (29), and Aschauer et al. (30). In the studies by Bunout et al. (39) and Stemmle et al. (37), after vitamin D supplementation, the nutritional status of vitamin D increased from deficient to insufficient, whereas in other studies, it increased from insufficient to sufficient. Mesinovic et al. found that vitamin D supplementation at 4000 IU/day had no effect on gait speed in overweight or obese older adults (aged 60±6 years) whose statuses of vitamin D were sufficient, with or without multimodal exercise (63). Thus, the nutritional status of vitamin D impacts the effect of exercise combined with vitamin D supplementation on walking ability and the TUG. Additionally, in this review, we found that, compared with the individual effects of exercise, the combined effect of exercise and vitamin D significantly increased stair climbing ability (29) and SPPB (35, 38) in older individuals. After 13 weeks of resistance training, the vitamin D_3 arm showed increased expression of gene sets involved in endothelial proliferation and blood vessel morphogenesis, compared with the placebo arm (14), which promotes blood vessel formation and supplies tissues with nutrients and oxygen. This may explain the combined effect of exercise and vitamin D supplementation on stair climbing and the SPPB.

This review had several strengths. First, a scoping review method was selected to draw literature related to the combined effect of exercise and vitamin D supplementation on skeletal muscle health in older individuals, which can provide a reference for exercise and vitamin D interventions in older populations. Second, a comprehensive and rigorous search strategy across four databases (PubMed, Cochrane Library, Web of Science, and Embase) was used to identify relevant RCTs that met the study criteria. Third, a systematic, in-depth data extraction process was implemented in duplicate to ensure reliability. Despite these strengths, this scoping review had some limitations. The results of this review may have been influenced by the search terms, number of databases searched, and selection of databases used in the search. Additionally, owing to a lack of resources, the search did not consider research in languages other than English. Therefore, the conclusions of this scoping review may have been influenced by publication bias.

5. Conclusions

This scoping review identified 13 RCTs that provided information on the effects of exercise combined with vitamin D supplementation on the skeletal muscle health of older adults. Resistance training and vitamin D_3 supplementation were the main interventions, and older female adults were the most common research participants. The results showed that the combined intervention of exercise and vitamin D supplementation had additive health effects on SPPB and stair climbing but not on skeletal muscle mass, muscular strength, and other physical functions. Furthermore, when vitamin D was deficient at baseline, the combined effect of exercise and vitamin D intervention significantly increased the TUG and gait speed in older adults. In future RCTs on this topic, baseline vitamin D nutritional status, health condition, and sex should be considered.

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Conflict of Interest

No potential conflicts of interest relevant to this article were reported.

Authorship

Jinghua Zhang: Investigation, Methodology, Data curation, Formal analysis, Writing–original draft, Writing–review & editing, Visualization. Zheng Zhu: Investigation, Methodology, Data curation. YanJun Niu: Data curation. Zhen-Bo Cao: Conceptualization, Writing – review & editing, Supervision, Project administration.

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