

## Scoping Review

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**Abbreviations:**

1RM, one-repetition maximum; COPD, chronic obstructive pulmonary disease; CSA, cross-sectional area; RCT, randomised controlled trials; RT, resistance training; SPPB, short physical performance battery; TUG, timed up and go test; WBV, whole-body vibration training

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# Exercise combined with vitamin D supplementation has additive health effects on short physical performance battery and stair climbing in older adults: a scope review of randomised 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, which was conducted from the time of library construction to January 2024. Eligible studies were randomised controlled trials including men and women aged  $\geq 65$  years or mean age  $\geq 65$  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 thirteen 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<sub>3</sub>. A significant increase was identified in short physical performance battery and stair climbing but not in skeletal muscle mass, skeletal strength, the timed up and go 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 short physical performance battery and stair climbing. Furthermore, when vitamin D was deficient at baseline, the combined effect of exercise and vitamin D intervention significantly increased the timed up and go test and gait speed in older adults. In future randomised controlled trials on this topic, baseline vitamin D nutritional status, health condition and sex should be considered.

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

Exercise and nutrient intake are widely accepted interventional approaches in this population<sup>(2)</sup>. Exercise interventions, including resistance, aerobic, high-intensity interval and multimodal training, have been shown to reduce age-associated changes in the musculoskeletal system<sup>(5,6)</sup>. 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<sup>(7)</sup>.

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<sup>(8)</sup> but were not correlated with grip strength and balance tests among older patients<sup>(8)</sup>. 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<sup>(8)</sup>. 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<sup>(9)</sup>. Vitamin D supplementation also significantly increases limb strength in healthy adults<sup>(10)</sup> and athletes<sup>(11)</sup> and improves grip strength and physical performance in patients with osteoarthritis<sup>(12)</sup>. Nevertheless, the results of some studies do not support these notions<sup>(13)</sup>. In older participants, vitamin D<sub>3</sub> supplementation itself had no effect on upper- and lower-body muscular strength and performance, muscle fibre area or characteristics, and it showed no interaction with health status<sup>(14)</sup>. A meta-analysis of twelve randomised controlled trials (RCT), 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<sup>(15)</sup>. Moreover, RCT have reported that vitamin D supplementation at a relatively high dose had no beneficial effects on health outcomes in women with vitamin D insufficiency<sup>(16)</sup>. A systematic review and meta-analysis of fifty-four RCT 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 towards worsening the short physical performance battery (SPPB) total score<sup>(17)</sup>. 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 FOXO3 $\alpha$ -mediated E3 ubiquitin ligase pathway<sup>(18)</sup>. 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<sup>(19)</sup>. 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<sup>(20)</sup>. Therefore, multifactorial interventions (including nutrition and physical exercises) should be recommended for older adults. Consequently, the question of 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 a combination on skeletal muscle health. The results of a cross-section study in older adults<sup>(18)</sup> supported the viewpoint above. Yang *et al.* found vitamin D and physical activity had an interactive effect on 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<sup>(18)</sup>. In 2010, Daly *et al.* reported that regular exercise and adequate vitamin D supplementation were important for maintaining or optimising muscle morphology, strength, power and function in older adults<sup>(21)</sup>. Conversely, the findings from a limited number of factorial 2  $\times$  2 RCT showed that vitamin D supplementation does not enhance the effects of exercise on muscle morphology, function or fall risk<sup>(21)</sup>. 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<sup>(22)</sup>. 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 summarise emerging research findings<sup>(23)</sup>. Therefore, based on existing RCT, we aimed to re-examine 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 summarised the available evidence of RCT that aimed to evaluate the effectiveness of exercise combined with vitamin D supplementation on skeletal muscle health in older adults.

## Materials and methods

A scoping review is an appropriate methodology for reviewing a large body of literature to generate an overview of a research

topic<sup>(24)</sup>. This review was conducted using the five-stage methodological framework for scoping studies developed by Arksey and O'Malley<sup>(23)</sup>. 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, summarising and reporting the results. The methodologies used for each stage of the framework are outlined below.

### 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 a 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 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?

### 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 online 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 reference manager software (EndNote X9, Thomson Reuters).

### Selecting studies

Published RCT were identified for this scoping review. Literatures included the following: (1) male and/or female participants aged  $\geq 65$  years or mean age  $\geq 65$  years; (2) exercise intervention, including resistance exercise and endurance exercise, and vitamin D supplementation of more than 10  $\mu\text{g}/\text{d}$ , which was recommended<sup>(25)</sup>, including vitamin D<sub>2</sub> and vitamin D<sub>3</sub> (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. RCT 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 guidelines<sup>(26)</sup> were used to report the flow of articles included in this review.

## Charting the data

Key information items from the included RCT 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 utilised, 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.

## Quality assessment of the study methodologies

The revised version of the Cochrane risk-of-bias tool for randomised trials<sup>(27)</sup> was used to assess the included RCT, assessing the following five bias domains: (a) randomisation processes; (b) deviations from intended interventions; (c) missing outcome data; (d) measurement of the outcomes; and (e) selection of reported results. Several signalling questions were also included. Generally, signalling 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 signalling 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 the revised version of the Cochrane risk-of-bias tool for randomised trials (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.

## Collating, summarising and reporting the results

The 'descriptive-analytical' method from the narrative tradition was utilised<sup>(23)</sup>. For the included RCT, 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.

## Results

### Literature search

A total of 1608 studies were retrieved, and five relevant studies were obtained by tracking the references of the screened documents. Of these studies, 1411 were identified after removing duplicates, and thirty-three were considered potentially relevant after the initial screening of titles and abstracts. After applying the inclusion and exclusion criteria, thirteen articles<sup>(28–40)</sup> were selected for the systematic review (Fig. 1). By carefully examining the included RCT, we found that the studies by Aschauer *et al.*<sup>(30)</sup> and Draxler *et al.*<sup>(31)</sup> had the same study design and used different outcome indicators. For the purposes of the following narrative, we treated the two RCT<sup>(30,31)</sup> as two studies. In addition to the three articles<sup>(38–40)</sup> that were included in the meta-analysis by Antoniak *et al.*<sup>(22)</sup>, we included ten articles<sup>(28–37)</sup> in this review. Relevant information

included in the literature is provided in online Supplementary Table 1.

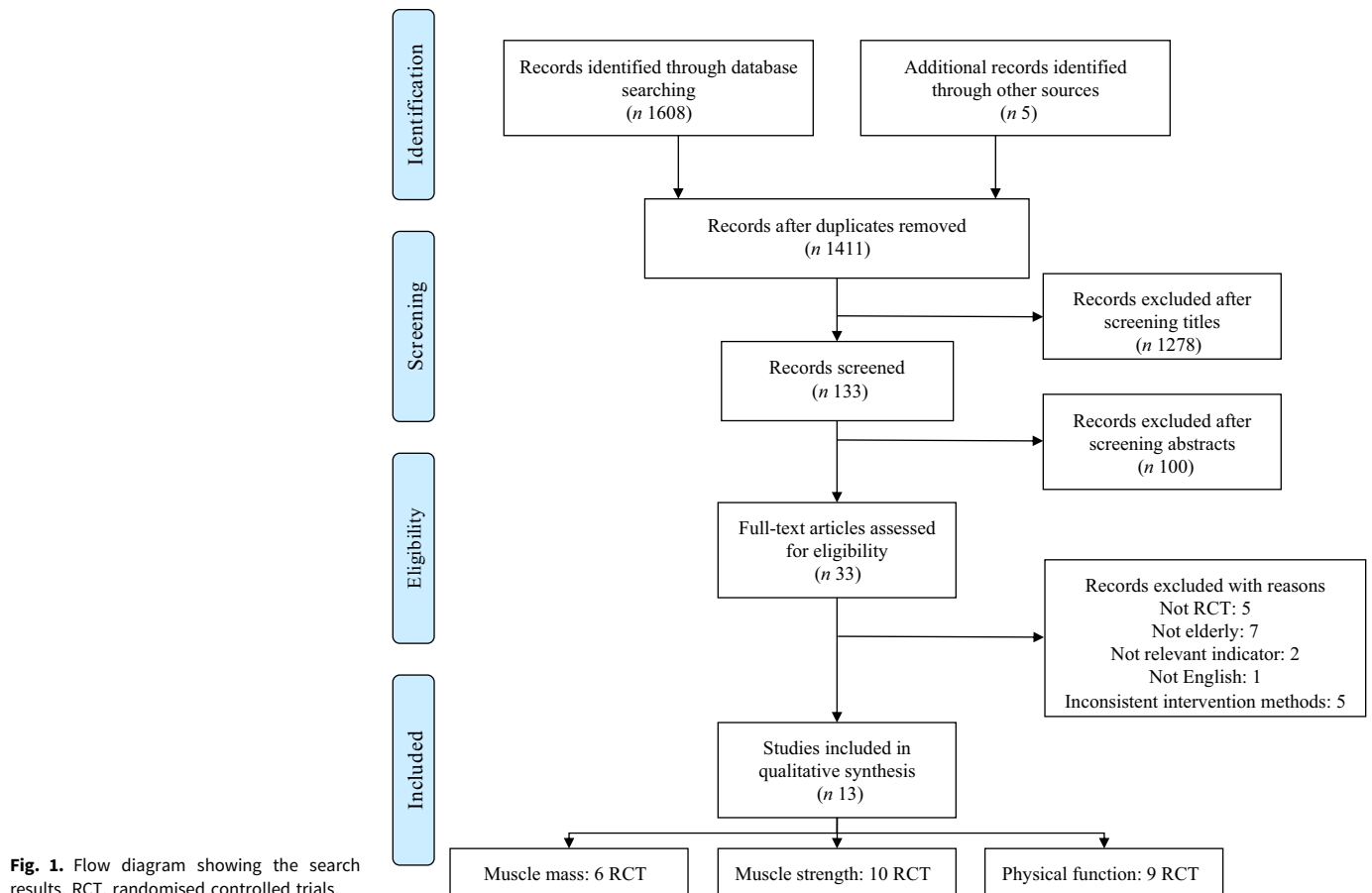
### Study characteristics

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

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

Of the included RCT, seven adopted resistance exercise training<sup>(30–32,35,36,38,39)</sup>, and six adopted multimodal exercise training<sup>(28,29,33,34,37,40)</sup>. Additionally, two RCT adopted progressive resistance training (RT)<sup>(30,38)</sup>. The duration of the experimental intervention ranged from 10 weeks<sup>(30,31)</sup> to 96 weeks<sup>(40)</sup>. A total of four interventions had a duration of 12 weeks<sup>(33–35,38)</sup>, two interventions had a duration of 10 weeks<sup>(30,31)</sup>, two interventions had a duration of 24 weeks<sup>(32,36)</sup> and two interventions had a duration of 48 weeks<sup>(29,37)</sup>; 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<sup>(30,31,34,35,39,40)</sup>, five articles had a frequency of three sessions/week<sup>(28,29,32,33,38)</sup> and two articles had a frequency of seven sessions/week<sup>(36,37)</sup>. The one-repetition maximum (1RM) is widely used as the intensity index for resistance exercise, with a range of 30<sup>(40)</sup> to 121 % 1RM<sup>(33)</sup>. Among the RCT that adopted multimodal exercise training, Brech *et al.*<sup>(34)</sup> and Jessup *et al.*<sup>(28)</sup> employed resistance and balance exercises. Uusi-Rasi *et al.* adopted balance challenges, weight-bearing, strengthening, agility and functional exercises<sup>(40)</sup>. Gianoudis *et al.* adopted a high-velocity progressive RT combined with diverse loading, moderate impact, weight-bearing exercises and high-challenge balance/functional exercises<sup>(29)</sup>. 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<sup>(33)</sup>. 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 and getting in and out of a chair and up and down stairs<sup>(37)</sup>.

All vitamin D interventions involved supplementation with vitamin D<sub>3</sub>. Vitamin D supplementation comes in various forms: daily, weekly and monthly. The dose of daily supplementation varies from 10 µg<sup>(28,39)</sup> to 50 µg<sup>(35,37)</sup>, and the monthly form varies from 1250 µg<sup>(31)</sup> to 2500 µg<sup>(30,33)</sup>. The weekly dose was 1250 µg<sup>(34)</sup>. Among the included RCT, three RCT involved receiving vitamin D supplementation before exercise intervention<sup>(30,31,38)</sup>. Among the



**Fig. 1.** Flow diagram showing the search results. RCT, randomised controlled trials.

RCT included in this scoping review, nine RCT involved supplementation with calcium<sup>(28–32,37–40)</sup>.

The risk of bias assessment results of the included studies are shown in Fig. 2. Overall, the quality of RCT based on the design and reporting was high. Among all studies, some concerns were observed in eight RCT<sup>(28,29,32,35,36,38–40)</sup>. In the study by Agergaard *et al.*<sup>(38)</sup>, 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 RCT were considered concerning<sup>(28,29,32,35,36,38–40)</sup>. Among all RCT, there was no report on whether the tester of the outcome index was blinded, and we determined that blinding was possible. Therefore, the RCT included in this review were all judged to be low risk.

### Main outcomes of randomised controlled trials

#### Vitamin D levels

At baseline, participants were vitamin D-deficient (25(OH)D levels < 20 ng/ml or < 50 nmol/l) in two studies<sup>(37,39)</sup>, insufficient (20–30 ng/ml or 50–75 nmol/l) in six studies<sup>(30,32,33,35,36,40)</sup> and sufficient (> 30 ng/ml or > 75 nmol/l) in one study<sup>(38)</sup>. After vitamin D supplementation, the participants achieved sufficient levels of serum 25(OH)D from deficient/insufficient levels in six RCT<sup>(30,32,33,35,36,40)</sup>. Unfortunately, data on serum vitamin D levels

were not reported by Brech *et al.*<sup>(34)</sup>, Jessup *et al.*<sup>(28)</sup>, Draxler *et al.*<sup>(31)</sup> and Gianoudis *et al.*<sup>(29)</sup>.

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

Muscle mass was reported in six studies<sup>(29,31,32,35,36,38)</sup>. Draxler *et al.*<sup>(31)</sup> 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 but not in the groups undergoing strength training alone or strength training combined with daily vitamin D<sub>3</sub> supplementation. In a study by Aoki *et al.*<sup>(36)</sup>, 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.*<sup>(38)</sup>, resistance exercise combined with vitamin D supplementation and resistance exercise alone resulted in significant gains in the quadriceps muscle CSA after 12 weeks of RT. However, no significant differences were identified in the changes (4.9 ± 2.0% *v.* 8.5 ± 2.8%) between groups. Drey *et al.*<sup>(35)</sup> 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 Verschuere *et al.*<sup>(32)</sup>, no significant change was identified in muscle mass after 6 months of WBV combined with



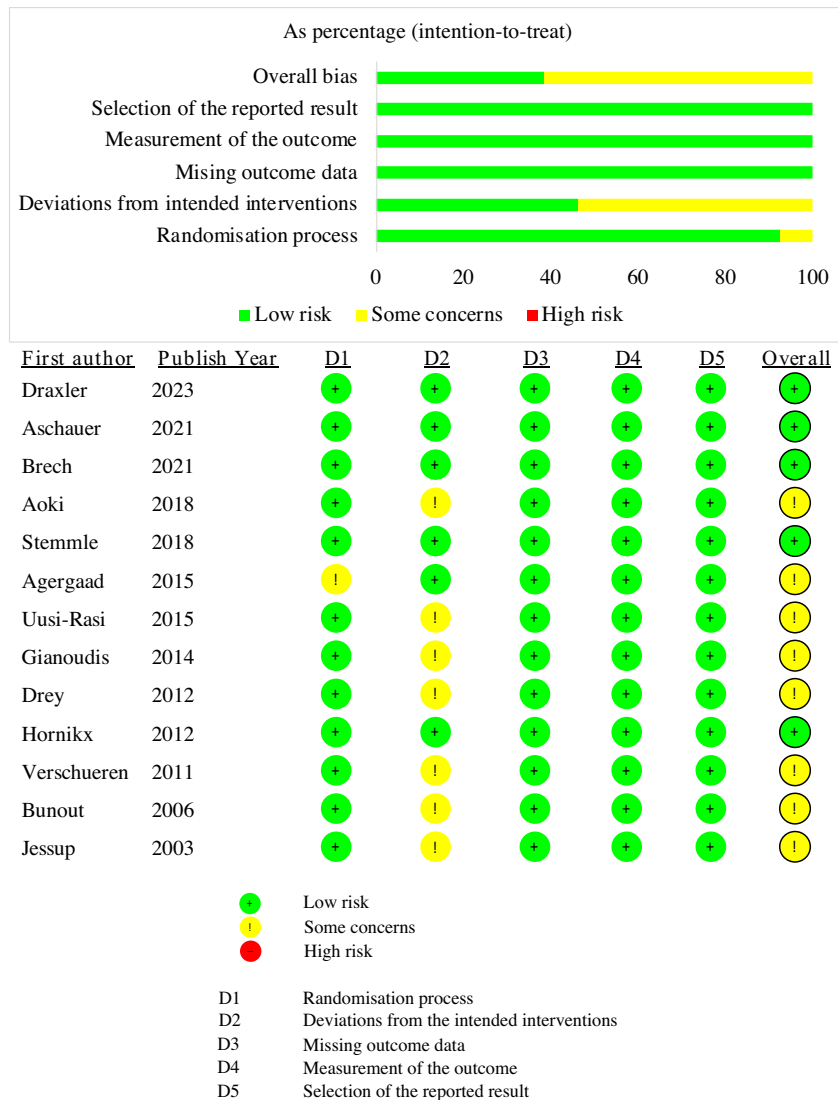


Fig. 2. Risk of bias of included studies.

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.*<sup>(29)</sup> found no significant effects of 12-month multimodal exercise combined with vitamin D supplementation or vitamin D supplementation alone on changes in lean mass (%).

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

Muscular strength was assessed in ten studies<sup>(28,29,32–34,36–40)</sup>, with the exceptions of Aschauer *et al.*<sup>(30)</sup>, Drey *et al.*<sup>(35)</sup> and Draxler *et al.*<sup>(31)</sup>. In a study by Agergaard *et al.*<sup>(38)</sup>, 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.*<sup>(36)</sup>, 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.*<sup>(34)</sup>, 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<sup>(34)</sup>. In a study by Bunout *et al.*<sup>(39)</sup>, 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 non-dominant) did not differ between the groups<sup>(39)</sup>. Uusi-Rasi *et al.*<sup>(40)</sup> 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.*<sup>(32)</sup> 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<sup>(32)</sup>. Jessup *et al.*<sup>(28)</sup> 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.*<sup>(29)</sup> 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 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<sup>(33)</sup>. However, rehabilitation combined with vitamin D supplementation can significantly increase inspiratory muscle strength, whereas rehabilitation alone does not have the same effect<sup>(33)</sup>. Stemmler *et al.* found that, compared with 20 µg vitamin D supplementation alone, exercise combined with 20 µg vitamin D supplementation and exercise combined with 50 µg vitamin D supplementation did not improve knee flexor strength and knee extensor strength<sup>(37)</sup>.

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

Physical function was assessed in nine studies<sup>(29,30,33–37,39,40)</sup>. Bunout *et al.*<sup>(39)</sup> 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<sup>(39)</sup>. 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)<sup>(39)</sup>. Uusi-Rasi *et al.*<sup>(40)</sup> 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<sup>(40)</sup>. 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 ( $P = 0.46$ )<sup>(40)</sup>. 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<sup>(35)</sup>. 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<sup>(35)</sup>. Moreover, Drey *et al.*<sup>(35)</sup> 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<sup>(29)</sup>. Aoki *et al.*<sup>(36)</sup> reported that scores in the two-step test and the five-time sit-to-stand test 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<sup>(36)</sup>. Moreover, these interventions did not significantly affect the twenty-five-question geriatric locomotive function scale<sup>(36)</sup>. In the study by Aschauer *et al.*<sup>(30)</sup>, 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 test distance in the groups undergoing resistance exercise alone, resistance exercise combined with daily vitamin D<sub>3</sub> 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-min walk test distance<sup>(33)</sup>. In the study by Brech *et al.*<sup>(34)</sup>, after 12 weeks of intervention, the fifteen-step 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<sup>(34)</sup>. Stemmler *et al.* found that, compared with the group receiving 20 µg vitamin D supplementation alone, the group undergoing exercise combined with 20 µg vitamin D supplementation showed improved TUG scores, whereas the group undergoing exercise combined with 50 µg vitamin D supplementation showed no improvement<sup>(37)</sup>.

#### **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 thirteen RCT 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 six RCT (approximately 46.15%)<sup>(28,33–35,38,39)</sup>. 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<sup>(41)</sup>. Moreover, as age increases, genes in the skeletal muscles undergo sex differences<sup>(42)</sup>. In females, 239 genes are involved in glucose catabolism, NAD metabolic processes and muscle fibre transition pathways<sup>(42)</sup>. In males, 166 genes involved in replicative senescence, cytochrome C release and muscle composition pathways were altered<sup>(42)</sup>. 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 RCT recruited non-healthy participants (38.46%). Among studies including non-healthy participants, two involved participants with low bone mineral density<sup>(29,34)</sup>, and one involved patients with COPD<sup>(33)</sup>, acute hip fracture<sup>(37)</sup> and prefrailty<sup>(35)</sup>. Studies have suggested that bone mineral density is positively associated with the appendicular skeletal muscle mass index<sup>(43)</sup> and grip strength<sup>(44)</sup>. COPD and acute hip fractures not only restrict exercise but may also directly lead to poor exercise performance<sup>(45)</sup>. 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<sup>(6)</sup>. 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<sup>(6)</sup>. Moreover, a systematic review revealed that RT significantly enhances muscular strength, muscular power and functional outcomes in physically frail older individuals<sup>(46)</sup>. Of the RCT 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 (four RCT, 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 RCT, approximately 46.15%), followed by three times per week (five RCT, approximately 38.46%). Notably, a systematic review and meta-analysis including ten studies found that training frequencies of two sessions/week promoted superior hypertrophic outcomes to one session/week<sup>(47)</sup>. Among the RCT reporting intensity of exercise, the 1RM<sup>(28–31,38,48)</sup>, Hz<sup>(32)</sup>, Borg scale<sup>(35)</sup>, maximal workload<sup>(33)</sup> and walking speed<sup>(33)</sup> 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 RT three times per week could significantly cause muscle hypertrophy and increase muscular strength<sup>(49)</sup>.

Vitamins D<sub>3</sub> and D<sub>2</sub> are the most widely used compounds<sup>(50)</sup>. Vitamin D<sub>3</sub> supplementation is a more effective method to elevate serum 25(OH)D levels than vitamin D<sub>2</sub> supplementation<sup>(51)</sup>. Among the RCT included in this review, the vitamin D interventions included supplementation with vitamin D<sub>3</sub>. Vitamin D intervention methods included daily, weekly and monthly interventions. A randomised clinical trial found that daily, weekly and monthly administration of vitamin D supplementation, equivalent to 25 µg/d, could elevate 25(OH)D

levels > 20 ng/ml<sup>(52)</sup>. The three supplementation methods showed equal efficacy and safety profiles<sup>(52)</sup>. Similarly, vitamin D<sub>3</sub> supplementation, equivalent to 37.5 µg/d, can be achieved equally well with daily, weekly or monthly dosing frequencies in older patients with hip fractures<sup>(53)</sup>. However, Chel *et al.* found that daily vitamin D supplementation, equivalent to 15 µg/d, was the most effective, followed by weekly and monthly supplementation, in older nursing home residents<sup>(54)</sup>. The different effects of vitamin D<sub>3</sub> supplementation strategies in these three literatures<sup>(52–54)</sup> may be attributed to different doses. However, research has shown that vitamin D<sub>3</sub> supplementation did not improve muscle fibre 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<sup>(55)</sup>. Mori *et al.*<sup>(56)</sup> 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 RCT included in this review, three studies conducted vitamin D supplementation before the combined intervention of exercise and vitamin D<sup>(30,31,38)</sup>. Improvement in the nutritional status of vitamin D to an adequate level may be based on the willingness of these three RCT to supplement vitamin D before joint intervention. Unfortunately, in four studies<sup>(28,29,31,34)</sup>, 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<sup>(28–32,37–40)</sup>, 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 main outcome indicators, we found six RCT evaluating skeletal muscle mass<sup>(29,31,32,35,36,38)</sup>, including three evaluating total body muscle mass (lean body mass<sup>(31)</sup>, muscle mass<sup>(32)</sup> and % lean mass<sup>(29)</sup>), two evaluating lower-limb muscle mass ( $\Delta$ CSA of the quadriceps muscle<sup>(38)</sup> and lower-limb muscle mass<sup>(36)</sup>) and one evaluating appendicular lean mass (%)<sup>(35)</sup>. 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<sup>(57)</sup>. However, decreased myostatin mRNA expression due to vitamin D supplementation was only seen in young men, instead of older adults<sup>(38)</sup>. 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<sup>(38)</sup>.

Among the included studies, ten articles evaluated muscular strength<sup>(28,29,32–34,36–40)</sup>, including nine on lower-limb strength<sup>(29,32–34,36–40)</sup>, three on upper-limb strength<sup>(28,34,39)</sup> and one on back strength<sup>(29)</sup> and respiratory muscle<sup>(33)</sup>. Researchers are now paying more attention to lower-limb muscle strength. Regarding the indicators for evaluating lower-limb muscle strength, six RCT evaluated muscle strength around the knee joint<sup>(32–34,36–38,40)</sup>. Grip strength indicators were used to assess upper-limb muscle strength in three RCT<sup>(28,34,39)</sup>. Hornikx *et al.* also evaluated respiratory muscle strength in patients with COPD<sup>(33)</sup>. Unfortunately, none of these RCT 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<sup>(14,58)</sup>. One study performed on high-level, well-trained athletes indicated that 8

weeks of high-intensity interval training combined with vitamin D<sub>3</sub> supplementation did not induce better training responses (squat jumps, countermovement jumps) than training alone<sup>(58)</sup>. One RCT reported that there were no differences in change in leg or grip strength in the vitamin D supplementation group<sup>(59)</sup>. Vitamin D supplementation didn't alter the composition and CSA of muscle fibre in older adults<sup>(59)</sup>. Moreover, vitamin D<sub>3</sub> supplementation did not enhance RT-associated increases in muscle fibre CSA or changes in muscle fibre proportions in older adults<sup>(14)</sup>. It can be seen that 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 was different among the studies<sup>(29,30,34,35,40)</sup>. Only one RCT evaluated upper-limb muscle endurance function using the 30-s arm curl test<sup>(30)</sup>. Walking is a dynamic activity that requires appropriate muscle function<sup>(60)</sup>, and the evaluation indicators of walking endurance included the two-step test<sup>(36)</sup>, 15-step test<sup>(34)</sup>, gait speed<sup>(30)</sup>, 6-min walk test<sup>(30,33)</sup>, 12-min walk test<sup>(39)</sup> and normal walking speed<sup>(40)</sup>. 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<sup>(35,39)</sup>. Although the TUG is a mobility test that requires both static and dynamic balance, only five of the included RCT used this test<sup>(29,30,37,39,40)</sup>. Furthermore, only two RCT used the stair climbing test<sup>(29,34)</sup>, which evaluates the ability to ascend and descend stairs to assess the strength, power and balance of the lower limbs<sup>(61)</sup>. Physical exercise has a beneficial effect on muscle mass, muscle stand ability strength or physical performance in healthy subjects aged 60 years and older<sup>(62)</sup>. However, the additional effect of dietary supplementation has only been reported in a limited number of studies (17.8%)<sup>(62)</sup>. 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.*<sup>(39)</sup>, but not in the studies by Uusi-Rasi *et al.*<sup>(40)</sup>, Aschauer *et al.*<sup>(30)</sup> and Hornikx *et al.*<sup>(33)</sup>. Furthermore, the combined effects of exercise and vitamin D significantly increased TUG ability in the studies by Bunout *et al.*<sup>(39)</sup> and Stemmler *et al.*<sup>(37)</sup>, but not in the studies by Uusi-Rasi *et al.*<sup>(40)</sup>, Gianoudis *et al.*<sup>(29)</sup> and Aschauer *et al.*<sup>(30)</sup>. In the studies by Bunout *et al.*<sup>(39)</sup> and Stemmler *et al.*<sup>(37)</sup>, 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 100 µg/d 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<sup>(63)</sup>. 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<sup>(29)</sup> and SPPB<sup>(35,38)</sup> in older individuals. After 13 weeks of RT, the vitamin D<sub>3</sub> arm showed increased expression of gene sets involved in endothelial proliferation and blood vessel morphogenesis, compared with the placebo arm<sup>(14)</sup>, 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 RCT 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.

### Conclusions

This scoping review identified thirteen RCT 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<sub>3</sub> 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 RCT on this topic, baseline vitamin D nutritional status, health condition and sex should be considered.

**Supplementary material.** For supplementary material/s referred to in this article, please visit <https://doi.org/10.1017/S0007114524002320>.

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