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Current Research on Vitamin D Supplementation against Sarcopenia: A Review of Clinical Trials

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ABSTRACT

Vitamin D plays an important role in skeletal muscle function and metabolism. The aim of this review was A) to discuss the clinical evidence of vitamin D supplementation either alone or combined with other strategies in the prevention of sarcopenia in non-sarcopenic individuals and B) to critically discuss the clinical evidence on the effect of vitamin D combined with other strategies on muscle strength, mass and function in sarcopenic individuals without vitamin D deficiency. Sparse clinical data on non-sarcopenic individuals indicate that vitamin D alone has a subtle beneficial effect on knee extensor strength at doses 880–1600 IU/day without improving handgrip strength or muscle mass. When co-administered with other supplements such as protein, mixed effects appear to prevent the decline of muscle mass, possibly delaying the onset of sarcopenia in non-sarcopenic individuals, at doses of 800–1,000 IU/day over 6–12 weeks. In sarcopenic individuals, vitamin D 100–1,000 IU/day co-supplementation with protein results in increased handgrip strength between 9.8–40.5 %. However, there is no strong clinical evidence that vitamin D dosage correlates with changes in muscle strength or mass. Potential sources of discrepancy among studies are discussed. Future studies with appropriate experimental design are essential to dissect the net effect of vitamin D on sarcopenia.

Introduction

Sarcopenia is a skeletal muscle disorder characterized by the progressive loss of skeletal muscle mass and muscle strength or function as defined in 2010 by the European Working Group on Sarcopenia in Older People (EWGSOP) and updated in 2019 [1, 2]. Currently, there is no globally accepted threshold for sarcopenia, and various research groups have differing definitions [1–4]; the Asian Working Group for Sarcopenia (AWGS), for example, defined cutoffs and gave the definition for the Asian population [3], emphasizing that individual ethnic groups require different diagnostic criteria [3, 5, 6]. Secondary data analysis of general population studies suggests that the global prevalence of sarcopenia in those over 60 is around 10 % [7], while an estimated 50 % of those aged 80 or over are sarcopenic [8]. This phenomenon constitutes an ever-increasing health burden on our society as the consequences of sarcopenia include an increased risk of mortality, falls and fractures [9]. One third of patients over 65 experience falls in the community, while this figure rises to half of patients over 65 in long term care [10]. The risk factors for sarcopenia include older age, immobility or inactivity from a sedentary lifestyle, and following a poor diet resulting in malnutrition [11]. Diagnosis of sarcopenia is based on low muscle mass, strength and performance as evidenced by several non-invasive and invasive procedures such as anthropometric measurements, muscle strength and performance tests, diagnostic tools such as computed tomography, magnetic resonance imaging, dual x-ray absorptiometry, bio-electrical impedance analysis, ultrasound, muscle biopsies, biochemical markers, electromyography and longitudinal monitoring [12, 13].

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To promote healthy aging, multiple pharmacological approaches to treat sarcopenia have been developed and discussed in detail elsewhere. In brief, such experimental interventions include anabolic hormones, selective androgen receptor modulators, exercise mimetics, myostatin inhibitors, angiotensin converting enzyme inhibitors and several natural compounds [14, 15]. Besides, published guidelines [16] recommend physical exercise as the first approach to treating sarcopenia, as shown in ▶ **Fig. 1**. There is also compelling evidence on the benefits of resistance exercise training on muscle mass and strength [17], endurance training to improve muscle performance [18] and balance exercises [19] to improve postural instability, which is common in sarcopenic patients. Exercise is usually followed by a protein-rich diet or protein supplementation, including whey or leucine [16, 20, 21], as there is evidence to suggest that protein supplementation improves physical performance in older people [22], and ideally, this should be combined with exercise [3, 16]. Physical exercise combined with nutritional supplementation appears to be more effective in improving body composition and physical function than physical exercise per se, as Daly et al. [23] found that a protein-enriched diet, together with resistance training, increased lean muscle mass; however, there is also evidence to contradict this in that there is no significant improvement [24]. Although the recommended daily protein intake for adults is 0.8 g/kg of body mass, this target is met by only an estimated 40 % of adults [25, 26]. However, consumption of at least 20 g of protein per meal by older adults results in significant muscle growth [27].

In general, there have been mixed findings around the benefits of dietary supplementation on muscle metabolism. High doses of the amino acids arginine and lysine are thought to slightly increase the levels of circulating growth hormone to act on muscle metabolism, while supplementing B-hydroxy-B-methylbutyrate (a metabolite of leucine) is thought to decrease muscle proteolysis and increase cholesterol synthesis [28]. However, beyond protein-rich diets, another nutritional supplement of increasing interest for sarcopenia is vitamin D [29–31]. Vitamin D is a fat-soluble vitamin either synthesized in the skin under sunlight exposure by converting 7-dehydrocholesterol into pre-vitamin D3 and in turn into cholecalciferol or naturally present in certain foods such as dairy products, fish and vegetables [32]. In addition to regulating Ca^{2+} concentration in the blood, vitamin D plays a regulatory role in skeletal muscle function and metabolism affecting protein synthesis [33], myogenesis [34], mitochondrial oxygen consumption [35] and myocyte differentiation and proliferation [36]. A systematic review [37] of 16 randomized control trials (mentioned as trials in the rest of the article) provided evidence of a beneficial effect of vitamin D supplementation in the older adults in terms of muscle strength and function. Conversely, an increasing number of studies show a lack of beneficial effects on muscle strength and function in the older adults [38–46]. Beyond this conflicting data, it has been reported that lean mass is improved in sarcopenic participants when leucine supplementation is co-administered with vitamin D [21]. However, vitamin D plus protein supplementation increased muscle strength in sarcopenic patients but found no strong evidence for an increase in muscle mass and performance [47].

While there appears to be abundant evidence linking vitamin D deficiency with sarcopenia in the older adults [48–52], there is conflicting evidence regarding the use of vitamin D as a nutritional supplement for the treatment and prevention of sarcopenia in non-vitamin D deficient individuals. It has been suggested that the discrepancies in results between studies showing positive effects from vitamin D supplementation on muscle strength, mass, and performance against studies showing no positive effects may be due to the duration of the interventions, the state of vitamin D insufficiency in the patients, or the amount and type of vitamin D used [31]. Therefore, the evidence for vitamin D supplementation as a nutritional therapy is rather inconsistent and requires further investigation towards a potential treatment for sarcopenia in patients without vitamin D deficiency [16, 31].

Previous trials of sarcopenic patients have investigated the effect of vitamin D when co-administered with other supplements, including proteins, vitamins, and fatty acids, and exercise, but no trials or papers have investigated the effect of vitamin D alone on non-vitamin D deficient sarcopenic patients, and thus examined how vitamin D might be used in the prevention of sarcopenia. Therefore, the aim of this review is A) to discuss the clinical evidence of vitamin D supplementation both i) alone and ii) combined with other strategies in the prevention of sarcopenia in non-sarcopenic individuals and B) critically discuss the clinical evidence on the effect of vitamin D combined with other strategies on muscle strength, mass and function in sarcopenic individuals without vitamin D deficiency.

Materials and Methods

Trial characteristics and interventions

An electronic literature search on the PubMed database was conducted and included trials published from 2011 onwards until December 2022 complying with the ethical standards of the Journal [53]. A combination of the following keywords 'sarcopenia', 'vitamin D', 'elderly', 'older adults' and 'trial' were used. Initially, 591 studies were identified (▶ **Fig. 2**). Upon screening the titles and abstracts, this was narrowed down to 69 randomized control trials. Non-clinical trial papers were not included in this review. After reading the full text, 18 trials were included in this review. Trials were excluded if there were no quantitative data; if the studies were open label (i. e. information was not blinded to participants); if both placebo and intervention groups were given vitamin D supplementation; if participants were not healthy or sarcopenia was secondary to another disease (such as COPD); if the sarcopenia criteria were not assessed; and if the patients were vitamin D deficient, since the link between vitamin D deficiency and sarcopenia is well established [48–52].

Of note, the studies by Hajj et al. [54] and Takeuchi et al. [55] were included based on limited evidence on the effect of vitamin D alone, despite the authors studying both vitamin D deficient and non-deficient individuals. Similarly, the study by Verschueren et al. [56] was also included despite the intervention and placebo group both receiving vitamin D supplementation, because these studies [54, 56] were two out of the only three trials [54, 56, 57] conducted to assess vitamin D supplementation alone on non-sarcopenic individuals. In this review, we followed the EWGSOP criteria of sarcopenia: muscle strength (assessed in terms of handgrip and knee

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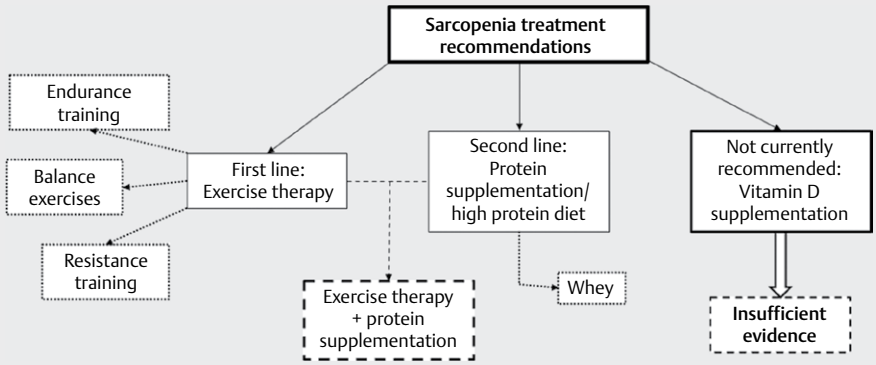
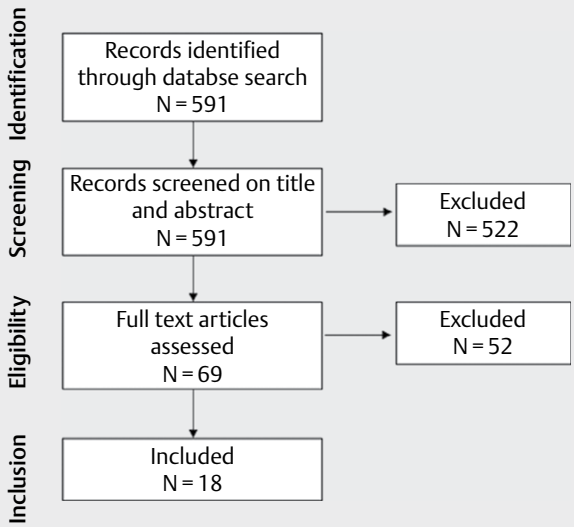


▶ **Fig. 1** Current treatment recommendations for sarcopenia. The first-line treatment option is exercise (which includes resistance and endurance training, and balance exercises). The second-line treatment is protein supplementation or for patients to follow a high-protein (which includes whey protein). Exercise therapy can be combined with protein supplementation to treat sarcopenia. Vitamin D is not currently recommended as a treatment option due to insufficient evidence on the effectiveness of supplementation of improving sarcopenia criteria in non-vitamin D deficient patients. This figure was created based on evidence from articles [16–23].



▶ **Fig. 2** Flow chart detailing the screening process for the trials included in this review. Records were excluded if they did not fit the inclusion criteria. N = 591 records were identified through PubMed search, by screening the title and abstract. N = 522 records were excluded at this stage. The full text was assessed in N = 69 articles, at which point N = 52 records were excluded. Eighteen studies have been included in this review that fit the inclusion criteria.

extensor strength), muscle mass (lean mass/appendicular/skeletal muscle mass index), and function (i. e. chair stand, gait speed, timed up-and-go (TUG), short physical performance battery test (SPPB) which consists of three tests: standing balance, gait speed, and 5-times sit-to-stand) [1, 2]. Other measures of physical function included 4-, 5-, or 6-minute walking tests. Although these tests are not standard measures of physical function according to the EGSWOP criteria, we included them in this review based on the limited data on physical function.

The literature research identified 18 trials in total, and of these three trials investigated the effects on vitamin D supplementation alone on non-sarcopenic individuals [54, 56–58]. In these trials, the vitamin D intervention was generally administered at higher doses when given alone than when administered as a combined supplement, ranging from 1,000 IU/day for a period of 9 months to 10,000 IU three times per week for a period of 6 months [57, 58]. In the non-sarcopenic combined supplementation group, participants in two trials received the conventional dose of 800 IU/day for 6 weeks and 12 weeks [59, 60], while in one trial 1,000 IU/day was administered for 12 weeks [61]. In sarcopenic individuals, 12 trials [55, 62–72] were identified for vitamin D combined supplementation therapy. Here, vitamin D was administered as a combined supplement for 12 weeks (or 3 months) at doses of 100 IU [69], 130 IU [72], 250 IU [65], 800 IU [62, 63, 71] and 1,000 IU [67]; 500 IU over 8 weeks [55]; 702 IU for 6 months [64]; 800 IU for 4–8 weeks (until hospital discharge) [68]; and 800 IU over 13 weeks [70]. We denote when trials used additional supplements as part of their interventions. In non-sarcopenic participants, vitamin D was co-supplemented with: leucine [59, 60], whey, soy and casein [60], and amino acids [61]. In sarcopenic individuals, vitamin D was co-supplemented with: whey [63–65, 67–71]; leucine [62, 63, 68, 70]; branched-chain amino acids [55, 68]; omega-3 fatty acids [67, 72]; casein [67]; creatine [67]; medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) [62]; B-methylbutyrate [72]; and vitamin E [64]. Of the six non-sarcopenic trials analyzed, only one included exercise as an additional therapy, consisting of whole-body vibration training three times per week [56]. Six out of twelve trials for the sarcopenic participants included exercise therapy, which were resistance training [65, 67–69, 71], balance training [68, 69], aerobic exercise [65] and combined resistance/aerobic group training [72].

The non-sarcopenic group had a larger mean age range than the sarcopenic group of studies, as two trials focused on younger adults (mean age 58.4 years [60] and 58.8 years [57]. The other study population ages were 68 years [61], 71 years [59], 73.3 years [54], while the upper age limit was 79.6 in the study by Verschueren et al. [56].

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The sarcopenic study ages were 70.0 (in the subgroup that received only the nutritional supplement) [65], 71.0 [66], 73.2 [64], 74.8 [72], 77.4 [67], 77.7 [63, 70], 79.9 [55], 80.3 [69], 81.0 [68], 84.2 [71], and 86.6 [62]. Of note, in the study by Nilsson et al. [67], sarcopenia participants were randomized into groups along with non-sarcopenic participants, although this trial also included a sarcopenia-subgroup analysis of muscle strength, muscle mass, and physical function. However, the proportion of sarcopenic participants in the intervention and placebo groups compared to non-sarcopenic participants is unclear. Only a small number of sarcopenic participants were included in the trial, therefore increasing the risk of type 2 error so the results should be interpreted with caution. The trial characteristics are summarized in ▶ **Tables 1,2**. Changes in muscle strength, muscle mass and function have been calculated by the authors to the best of their ability as percentual changes against the baseline or placebo values as appropriate.

Effect of vitamin D supplementation alone on non-sarcopenic participants

Muscle strength: From the literature research, three trials [54, 56, 57] were identified for vitamin D supplementation alone on non-sarcopenic individuals, of which one had additional exercise therapy [56] (see ▶ **Table 1**). The participants were considered to be at risk of developing sarcopenia, namely post-menopausal women [56, 57]; and pre-sarcopenic participants [54]. No improvements were found in handgrip strength in any of the trials [54, 56, 57], but researchers noted increases in lower limb strength in two of the trials [56, 57]. Cangussu et al. [57], who supplemented vitamin D at a dose of 1,000 IU/day for 9 months, reported no significant alteration of grip strength compared to the baseline measurement or the placebo group, yet noted a 25.3 % increase from baseline of the chair rising test compared to the baseline measurement, which was indicative of improved strength and physical function. Hajj et al. [54] found an increase in handgrip strength of 3.2 % from baseline by supplementing vitamin D at a dose of 10,000 IU three times per week for 6 months, but this finding was not significant relative to the placebo group, while Verschueren et al. [56] (who supplemented vitamin D at a dose of 880 IU/day and 1600 IU/day for 6 months) reported a significant increase in dynamic knee extension strength of 6.4 % from baseline, for dynamic muscle strength only. An increase of 7.9 % from baseline was found overall in dynamic muscle strength in the study arm supplemented with 1600 IU/day vitamin D, while this increased by 6.3 % in the study arm with 880 IU/day. However, the evidence on the effect of vitamin D on knee extension strength in pre-sarcopenic individuals is limited to a single study [56]. The improvement in this measurement could perhaps be explained by the additional exercise therapy that participants in this study received (whole-body vibration training three times per week). Therefore, there is no robust clinical evidence to allow us to conclude that vitamin D alone improves leg strength in those at highest risk of developing sarcopenia, and there is also no conclusive evidence to suggest that vitamin supplementation significantly improves grip strength. Supplementation of vitamin D for 9 months [57] did not result in improved outcomes in grip strength compared to a 6-month supplementation period [54, 56]. Overall, these findings suggest that vitamin D supplementation alone (i. e. without additional protein) does not improve handgrip strength in non-sarcopenic participants [54, 56, 57]. However, vitamin D alone may have a small beneficial effect on leg extension strength at a dose between 880–1600 IU/day [56]. In line with this, it has been suggested that a dosage of ≥ 800 IU/day is adequate to achieve beneficial effects on muscle strength and balance [47].

Muscle mass: In terms of muscle mass, Hajj et al. [54] showed an improvement of 3.0 % from baseline in appendicular skeletal muscle mass, while the other two trials showed no significant improvements [56, 57]. The improvements seen by Hajj et al. [54] could perhaps be explained by that fact that participants included in the study were vitamin D deficient, and vitamin D supplementation has been shown to be beneficial in these individuals [48–52]. Secondly, the study by Hajj et al. [54] administered vitamin D doses of 10,000 IU of vitamin D three times per week, which is a several-fold higher dose of supplement and could perhaps explain the improvement compared to the other trials by Verschueren et al. [56] and Cangussu et al. [57]. However, Cangussu et al. [57] reported that there was a 6.8 % loss of muscle mass in the placebo group, concluding that the vitamin D supplementation helped to prevent further loss of muscle mass. Therefore, although there were no significant improvements in muscle mass, it cannot be ruled out whether vitamin D is beneficial against muscle mass loss in those at the highest risk of sarcopenia, especially when given at a higher dose.

Physical function: Physical function was not determined at all in any of the trials except Cangussu et al. [57]. Although this trial found a significant increase in the chair-rising test, the lack of robust evidence does not allow us to determine whether vitamin D supplementation is effective in improving other measures of physical function.

Effect of combined vitamin D supplementation on non-sarcopenic participants

Muscle strength: Three studies were identified for vitamin D plus other nutritional supplements on non-sarcopenic older adults [59–61], none of which included additional exercise therapy. Vitamin D in combination with other supplements (i. e. 21 g leucine-enriched whey protein, 9 g carbohydrates, 3 g fat [59]; and 10 g casein, 8 g whey, 2 g soy protein [60] in non-sarcopenic participants showed no significant differences in grip strength in any of the trials, aside from the trial by Negro et al. [61], who co-supplemented 1,000 IU vitamin D twice daily with Essential Amino Acids (EAA)-based multi-ingredient nutritional supplement (5,000 mg EAA, 1,500 mg creatinine, and muscle restore complex). Maximal voluntary contraction was measured in place of grip or knee extensor strength and showed a 5.7 % improvement from baseline. However, it is important to consider that even in studies on non-sarcopenic people, where vitamin was supplemented alone, higher doses did not consistently produce greater improvements in strength, mass, or function. Therefore, there are no conclusive data that vitamin D causes a significant improvement in grip strength when in combination with other supplements, given that: no other trials in this category showed improvement; the measure of handgrip strength was not used (making it more difficult to compare); and the co-supplemented ingredients may have had a significant impact on the findings. Additionally, the 1,000 IU vitamin D supplemented twice per day is a several fold-higher dose of vitamin D than

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▶ **Table 1** The effects of vitamin D supplementation on the sarcopenia criteria in non-sarcopenic patients.

Author, year	Population	Mean Age (Years)	Sample Size	Intervention	Exercise	Duration	Sarcopenia Indices			Hand grip strength	Lean mass	Physical function
							HS/MS	LM	PF			
Cangussu et al., 2015[57]	Postmeno-pausal women	58.8 ± 6.6/ 59.3 ± 6.7	160, 20 discont.	1000 IU/day vit D	No exercise	9 months	HS	ALM, TLM	CRT	Not altered significantly	Not altered significantly	Improved CRT: + 25.3 %
Chanet et al., 2017[59]	Elderly men	71 ± 4	24	800 IU/day vit D + 21 g leucine-enriched whey + 9 g carbs + 3 g fat	No exercise	6 weeks	HS	SMMI	SPPB	Not altered significantly	Improved ALM: + 2.4 %	Not altered significantly
Hajj et al., 2018[54]	Pre-sarco-penic elderly	73.3 ± 2.05	128	10000 IU vit D 3x/wk	No exercise	6 months	HS	ASMM	Not deter-mined	Improved HS: + 3.2 %	Improved ASMM 3.1 %	Not measured
Kang et al., 2020[60]	Late middle-aged adults	58.38 ± 5.72	120	800 IU/day vit D + 20 g protein (50 % casein, 40 % whey, 10 % soy, 3000 mg leucine)	No exercise	12 weeks	HS, FMS	ASMM, ALM	SPPB	Not altered significantly	Improved ALM: + 1.2 %,	Not altered significantly
Negro et al., 2019[61]	Elderly adults	68 ± 4.6	38	1000 IU 2x/d vit D + Essen-tial Amino Acids (EAA)-based multi-ingredi-ent nutritional supplement – 5000 mg EAA, 1500 mg creatine, muscle restore complex	No exercise	12 weeks	MVC	ALM	Not deter-mined	Improved MVC: + 5.7 %	Improved ALM: + 1.7 %	Not measured
Verschueren et al., 2011[56]	Postmeno-pausal women	79.6	113	880 IU/day vit D (conven-tional), or 1600 IU/day vit D (high dose)	WBVT 3/ week or a no-training group	6 months	Isometric and dynamic strength (Nm) – isokinetic dynamom-etry	Muscle mass (cm)	Not deter-mined	Improved DKE: + 6.4 % WBVT DMS: + 7.9 % 1600 IU = + 8.1 % 880 IU = 6.3 %	Not altered significant-ly	Not measured

Abbreviations: ALM – appendicular lean mass; DMS – dynamic muscle strength; CRT – chair rising test; DKE – dynamic knee extensor; FMS: femoral muscle strength; HD – handgrip dynamometry; HS: handgrip strength; MS – muscle mass; MVC – maximal voluntary contraction; SMM – appendicular skeletal muscle mass; SMMI – skeletal muscle mass index; SPPB – short physical performance battery test; TLM – total lean mass; WBVT – whole body vibration training.

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the other trials analyzed and may have also contributed to the significant increase in muscle strength.

Muscle mass: Meanwhile, muscle mass improved in all vitamin D co-supplemented groups [59–61]. Chanet et al. [59], who co-supplemented vitamin D 800 IU vitamin D once per day with 21 g leucine-enriched whey protein, found a significant improvement in skeletal muscle mass index of 2.4 % from baseline. Kang et al. [60] supplemented 800 IU vitamin D plus 20 g protein (50 % casein, 40 % whey, 10 % soy, and 3000 mg leucine) found a 1.2 % improvement from baseline in lean body mass, while Negro et al. [61] reported a significant improvement of 1.7 % from baseline in appendicular lean mass. Interestingly, none of these groups which showed improvements in muscle mass included exercise as an interventional therapy. Taken together, it can be concluded that doses of 800 IU/day of vitamin D supplementation together with protein may have a beneficial effect in improving muscle mass between 1.2–2.4 % [59–61] independently of exercise. However, one needs to bear in mind that from these studies, the mixed effects of vitamin D and protein supplements have been obtained. Additional studies are needed to differentiate the effects between the two strategies, as it has been indicated that protein supplementation has a beneficial effect on improving [73] and preserving [74] muscle mass in older adults, while the evidence around the effect of vitamin D on muscle mass is rather inconclusive [75, 76].

Physical function: Data on the effect of combined vitamin D supplementation on physical function of non-sarcopenic individuals are sparse. However, Chanet et al. [59] and Kang et al. [60] measured physical function through the SPPB, but neither study saw any significant improvements from baseline compared to placebo. Additional research is needed to shed further light on this aspect.

Overall, the findings from the trials analyzed suggest that vitamin D alone may not be effective for the improvement of grip strength, muscle mass, or physical function in those non-sarcopenic individuals but at higher risk of developing the disease. Yet, when vitamin D is co-supplemented with protein, mixed effects appear to prevent or improve the decline of muscle mass. This may thereby potentially delay the onset of sarcopenia, at doses of 800–1,000 IU/day of vitamin D over 6–12 weeks [59–61]. However, there is still limited evidence available, and more research is required on the effect of vitamin D both alone and combined on sarcopenia measures in those at risk of developing sarcopenia.

Effect of combined vitamin D supplementation on sarcopenic participants

Muscle strength: Twelve trials [55, 62–72] were identified for vitamin D combined supplementation therapy on sarcopenic persons, and six of these studies [67–69, 71, 72] investigated exercise therapy as an additional treatment (▶ **Table 2**). Vitamin D in combination with other nutritional supplements in sarcopenic individuals showed improvements in handgrip strength in seven out of twelve studies [55, 62, 64–66, 68, 69] (▶ **Table 2**). Abe et al. [62] co-supplemented vitamin D at 800 IU/day with L-leucine and 6 g of either medium-chain triglycerides (MCTs) or long-chain triglycerides (LCTs). They found that right-hand grip strength improved by 13.1 % from baseline, but only in those participants who received vitamin D combined with MCTs. Although the net effect of vitamin D supplementation cannot be determined in this study, MCTs are believed to improve muscle function through the ghrelin/growth hormone axis and mitochondrial metabolism [77]. Meanwhile, Bo et al. [64] supplemented vitamin D at a dose of 702 IU/day, along with 22 g whey protein and vitamin E and reported a 9.8 % increase in handgrip strength from baseline (and a 13.7 % increase compared to the control group). Li et al. [65] studied the effect of nutritional supplementation composed of 250 IU vitamin D, 10 g whey protein, 300 mg EPA (Eicosapentaenoic Acid) and 200 mg DHA (Docosahexaenoic Acid, or rhodopsin) with or without exercise on muscle strength of sarcopenic patients. The study reported a 19.9 % increase in handgrip strength in response to the nutritional supplementation and a 14.3 % increase in response to exercise alone. Curiously, there was a 15 % increase in handgrip strength when supplementation was combined with exercise, ruling out any synergistic effects between supplementation and exercise. Since the study published by Gkekas et al. [47], three additional trials were published [66–68], which allowed further analysis of the effect of vitamin D supplementation on sarcopenic patients. Meanwhile, Nasimi et al. [66] administered participants a fortified yoghurt product with 1,000 IU/day vitamin D, 3 g beta-hydroxy beta-methyl butyrate (a leucine protein metabolite), and 500 mg vitamin C, and found a 30.5 % improvement in handgrip strength from baseline. Nilsson et al. [67] administered 1,000 IU/day vitamin D with 24 g whey protein, 16 g casein, 3 g creatine, and omega-3 containing fish oil to the intervention group (which contained sarcopenic and non-sarcopenic participants) and found significant improvements from baseline in handgrip strength by 7.8 %.

When examining the effect on sarcopenic patients alone who received the intervention in the sarcopenia subgroup analysis, muscle strength was not found to be significantly altered compared to the baseline, so it is likely that any significant change found in the normal analysis is due to improvements in non-sarcopenic participants. Rondanelli et al. [69] administered participants a combined supplement of 100 IU vitamin D, 22 g whey protein, and 10.9 g essential amino acids (including 4 g leucine) and found a 19.2 % increase in handgrip strength from baseline over 12 weeks. In a follow-up study, the same group of authors [68] found an improvement of 21.9 % in handgrip strength compared to baseline following a supplementation with 800 IU vitamin D twice daily, along with 20 g whey protein enriched with leucine. Takeuchi et al. [55] co-supplemented vitamin D at 500 IU/day with 10 g BCAA, and found an improvement in handgrip strength, namely an increase of 40.5 % from baseline. The study by Verlaan et al. [70] supplemented vitamin D at a dose of 800 IU/day, with 20 g whey protein and 3 g leucine, and indicated that handgrip strength was measured. However, they did not present the change from baseline in their results. So we were unable to include this in our analysis.

Taken together, these results indicate that when vitamin D is co-supplemented with protein (mainly whey, casein, BCAA, or leucine), a beneficial effect is evident for handgrip strength. In these studies, handgrip strength increased between 9.8–40.5 % when vitamin D was dosed between 100–1,000 IU/day. However, the large range of vitamin D dosage does not allow to determine accuracy of treatments. We have not been able to identify any correlation between vitamin D dosage and muscle strength on the above studies (see ▶ **Fig. 3**). This indicates that other parameters are possibly acting as interfering variables or that the handgrip strength test

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▶ **Table 2** The effects of vitamin D supplementation on the sarcopenia criteria in sarcopenic patients.

Author, year	Population	Mean Age (Years)	Sample Size	Intervention	Exercise	Duration	Sarcopenia Indices			Hand grip strength	Lean mass	Physical function
							HS/MS	LM	PF			
Abe et al., 2016[62]	Elderly adults	86.6 ± 4.8	38	Arm 1–800 IU vit D + 1.2g L-leucine + 6 g MCTs	No exercise	3 months	HS	AC, CC	GS	Improved	Not altered significantly	Improved Arm 1 GS: + 12.5 %
				Arm 2–800 IU vit D + 1.2g L-leucine + 6 g LCTS						Arm 1 right HS: + 13.1 %		
Bauer et al., 2015 [63]	Elderly adults	77.7	380	800 IU vit D + 3 g leucine enriched 20 g whey protein	No exercise	13 weeks	HS	AMM	SPPB – GS, CS, balance	Not altered significantly	Improved AMM: ~ + 1.3 %	Not altered significantly
Bo et al., 2019 [64]	Elderly adults	73.23 ± 6.52	60	702 IU vit D + 22 g whey protein + vit E 2x daily	No exercise	6 months	HS	RSMM, BIA AMM (Kg)	GS, CS, TUG	Improved HS: + 9.8 %	Not altered significantly	Not altered significantly
Li et al., 2020 [65]	Elderly adults	Nutr: 70.04 Ex + nutr		250 IU vitamin D, 10 g whey protein + 300 mg EPA + 200 mg DHA	Aerobic & resistance exercise	12 weeks	Hand grip strength	ASMM, RSMI	GS	Improved	Improved:	Not measured
				3 study arms: Nutr; Ex; Nutr + Ex						HS:Nutr + 19.9 %	ASM: Nutr: + 4.7 %	
										Ex + 14.3 %	Ex: + 2.2 %	
										Nutr + Ex + 15.0 %	Nutr + Ex: + 3.5 %	
Nasimi et al., 2021 [66]	Elderly adults	71.0 (69.0, 73.5)	66	1000 IU/d vit D + 3 g beta-Hydroxy beta-Methyl Butyrate + 500 mg vit C (fortified yoghurt)	No exercise	12 weeks	HS	LBM, ALM, SMMI	GS	Improved HS: + 30.5 %	No significant change	Improved GS: + 10.7 %

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▶ **Table 2** Continued.

Author, year	Population	Mean Age (Years)	Sample Size	Intervention	Exercise	Duration	Sarcopenia Indices			Hand grip strength	Lean mass	Physical function
							HS/MS	LM	PF			
Nilsson et al., 2020 [67]	Elderly men	77.3 ± 2.8	45	1000 IU/d vit + 24 g whey protein + 16 g casein + 3 g creatine + omega-3 fish oil	3 d/wk whole body elastic band RE	12 weeks	LP, HS, IKE (kg)	TLM (kg), ASM (kg)	GS, STS, TUG, 4 m walk, 4 step stair climb, SPPB	Improved	Improved	Improved
				(M5)	HBRE					M5 group LP: 14.8 %,	Sarcopenia all:	STS: -8.3 %
										HS: 7.8 %,	TLM: 3.3 %	6 meter walk test: 7.4 %
										Sarcopenia: not significantly improved	ASM: + 4.3 %	4 step chair climb: -20.3 %
											M5: TLM 3.4 %	
											ALM: 4.1 %	
Rondanelli et al., 2016 [69]	Elderly adults	80.3 (80.77 ± 6.29)	130	100 IU/d vit D + whey protein 22 g/d + 10.9 g essential amino acids (including 4 g leucine)	Resistance and balance exercise	12 weeks	HS (kg)	RSMM	Not measured	Improved	Improved – RSMM = 3.2 %	Not measured
										HS: + 19.2 %		
Rondanelli et al., 2020 [68]	Elderly adults	81 ± 6	140	800 IU vit D 2x/d + 20 g whey protein-based supp enriched with leucine	Exercise program – balance and resistance training, 20 min 5x/wk	4–8 weeks	HS	AMM (g), SMMI (kg/m2)	GS, CS, TUG, SPPBNot measured	Improved	Improved	Improved GS: + 0.061 m/s/month
										HS: + 21.9 %	AMM: + 6.2 %	CS: + 28.2 %
											SMMI: + 6.4 %	TUG: + 12.4 %, SPPB: + 65.0 %
Takeuchi et al., 2019 [55]	Elderly adults	78.8 ± 5.1	68	500 IU vit D + 10 g BCAA 125ug	No exercise	8 weeks	HS	AC, (cm), CC (cm)		Improved	Improved:	Not measured
										HS: + 40.5 %	AC: + 5.8 %	
											CC: + 3.8 %	
Verlaan et al., 2018 [70]	Elderly adults	77.7	380	800 IU vit D + 20 g whey, 3 g leucine,	No exercise	13 weeks	HS	AMM kg,	SPPB, GS, CS	Not measured	Improved – AMM:	Not altered significantly

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▶ **Table 2** Continued.

Author, year	Population	Mean Age (Years)	Sample Size	Intervention	Exercise	Duration	Sarcopenia Indices			Hand grip strength	Lean mass	Physical function
							HS/MS	LM	PF			
Yamada et al., 2019 [71]	Elderly adults	84.2 ± 5.5	112	800 IU vit D + 10 g whey protein	RE 2/wk + daily AHE	12 weeks	HS, KET (Nm)	AMM	5 m walking time, one leg stand, CS, GS	Improved –Knee extension torque – ex + nutr = + 17.5 %	Improved –(sarcopenic subgroup)	Improved – Max walking time in sarcopenic group
				4 arms: Ex + nutr, Ex alone,						Ex = + 1.8 %	Ex + nutr = + 10.5 %	Ex + nutr = –15.2 %
				Nutr alone, Control						Nutr = + 7.3 %	Ex = –5.3 %	Ex = –10.4 %
										Control = –13.6 %	Nutr = + 1.8 %	Nutr = –0.9 %
											Control = –12.7 %	Control = + 10.5 %
Zhu et al., 2019 [72]	Elderly adults	74.8 ± 6.9 (ex + nutr)	113	130 IU vit D + 8.61 g protein, 1.21 g B-methylb-tyrate, 0.21 g omega-3 fatty acid	90 min group training 2/wk + 1 AHE	12 weeks	HD, LE kg	Upper and lower limb muscle mass kg, ASM/height2 (kg/m2)	GS, CS	Improved	Improved – ExS LLMM: + 2.5 %	Improved –ExS CS: –26.6 %
		74.5 ± 7.1		3 arms						LE ExS: + 28.5 %	ExS ULMM: + 2.0 %	Ex CS = –22.8 %
		(ex alone)								LE Ex: + 24.2 %		5 chair stand: ExS –26.6 %

Abbreviations: AC – arm circumference; AHE – at home exercise; AMM – appendicular muscle mass; ASM – appendicular skeletal mass; CC – calf circumference; CS – chair stand test; DMS – dynamic muscle strength; Ex – exercise therapy; GS – gait speed; HBRE – home based resistance exercise; HS – handgrip strength; IKE – isometric knee extension; KET – knee extension torque; LE – leg extension strength; LP – leg press; LBM – lean body mass; MS – muscle strength; Nutr – nutrition supplement; RE – resistance exercise; RSMM – relative skeletal muscle mass; SMMI – skeletal muscle mass index; SPPB – short physical performance battery test; STS – sit to stand; TLM – total lean mass; TUG – timed up and go test.

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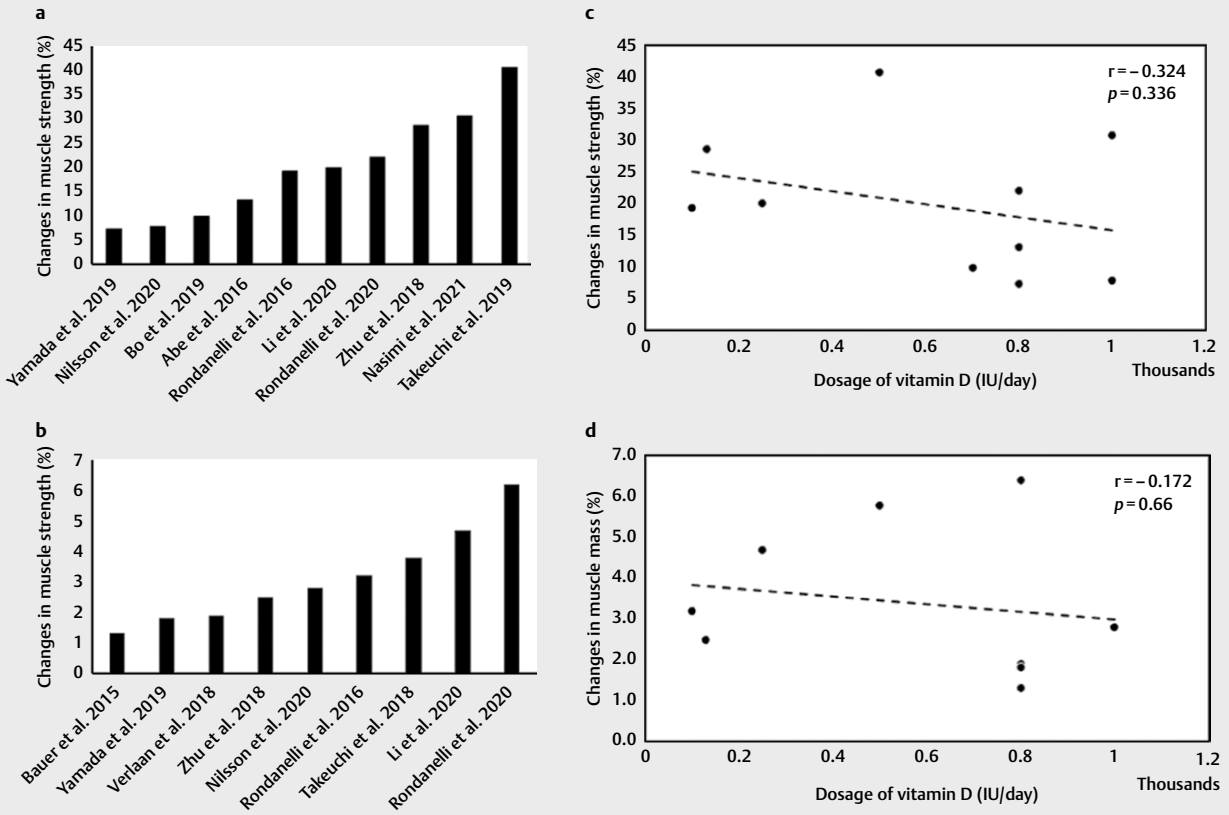

▶ **Fig. 3** Relative changes of muscle mass and strength. (A-B) Percent changes in muscle strength and mass respectively among trials from non-vitamin D deficient patients respectively. Percent changes were calculated by the authors to the best of our ability based on the original data published in individual trials. (C-D) Vitamin D dosage does not correlate with observed changes in muscle strength and mass (Pearson correlation coefficients).

was not standardized among different research environments. Dosage recommendations for handgrip strength improvements are difficult to determine based on these studies due to the large data variability. The supplement with the smallest dose of vitamin D at 100 IU/day [69] showed a greater improvement in handgrip strength than other studies that used higher doses of vitamin D [62, 67], indicating that co-supplemented nutrients had a more significant impact in improving strength than vitamin D. The smaller dose of 500 IU/day [55] appeared to exert the greatest impact on handgrip strength, but this combined effect may be attributed to the co-supplementation with 10 g BCAA, as it has been shown that protein supplementation alone improves muscle strength in older adults [22].

Three studies showed no significant improvements in handgrip strength [63, 71, 72]. Nilsson et al. [67], Yamada et al. [71] and Zhu et al. [72] instead reported significant improvements in lower limb muscle or knee extension strength. However, only three trials measured lower limb or knee extension strength; therefore, the evidence is rather sparse limiting the interpretation of these data. Yamada et al. [71] found a 7.3 % increase from baseline in knee extension strength with 800 IU/day of vitamin D plus 10 g whey protein. When supplementation was combined with exercise knee extension strength increased by 17.5 % from baseline, while the knee extension strength of the control group decreased by 13.6 %. Zhu et al. [72] studied the effect of supplementation with 130 IU/day of vitamin plus: 8.61 g protein, 1.21 g B-methylbutyrate, 0.21 g omega-3 fatty acid, with or without exercise on leg extension strength. They reported a 28.5 % increase (from baseline) in strength in response to supplementation plus exercise training for 12 weeks, and an increase of 24.2 % in response to exercise training alone. Finally, in the trial by Nilsson et al. [67] (where participants were supplemented with 1,000 IU/day vitamin D) muscle strength on the leg press improved by 14.8 %, while knee extension strength did not change significantly. Taken together, these trials indicate that vitamin D plus protein supplementation may increase limb strength even when handgrip strength tests did not show improvement. However, there appears to be a discrepancy in the results as there was a greater increase with 130 IU/day of vitamin D [72] than 800 IU/day vitamin D [71] and 1,000 IU/day vitamin D [67], indicating that the effect may be due to the co-supplemented protein. Another contributing factor may have been the age of the participants, as in the trial by Zhu et al. [72] the participants were 10 years younger than in the trial by Yamada et al. [71]. There is some evidence to suggest that younger individuals respond better to protein supplementation, as it has been indicated that older adults have blunted response to anabolic stimuli [78, 79].

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Muscle mass: In terms of muscle mass, ten studies showed improvement [55, 63–65, 67–70, 72]. Measurements of muscle mass varied between studies and were measured by either appendicular muscle mass (AMM) or appendicular skeletal muscle mass (ASMM) [63–65, 67, 68, 70, 71], relative skeletal muscle mass index (SMMI) or relative skeletal muscle mass (RSMM) [64, 66, 68, 69], total lean mass (TLM) [67], or calf circumference [55]. Bauer et al. [63], in the PROVIDE study, co-supplemented 800 IU/day vitamin D with 20 g whey protein enriched with 3 g leucine, 9 g carbohydrates, and 3 g fat, and found an estimated 1.3 % increase in AMM from baseline (as calculated by us from a results bar graph), and a 1.0 % gain compared to the control group. Rondanelli et al. [68] also reported a 6.3 % improvement in AMM from baseline and a 6.5 % increase in SMMI. Verlaan et al. [70] also found improvements in AMM by 1.9 % from baseline. Yamada et al. [71] reported significant improvements in AMM in the exercise plus nutrition group in the sarcopenic subgroup (however, due to insufficient sample size in the sarcopenia subgroups these findings may be subject to type 2 error), in which AMM improved by 10.5 % from baseline. Nutrition alone showed a significant improvement of 1.8 % from baseline, while, interestingly, exercise alone was not effective in preventing the loss of muscle mass, and this group showed a decrease of 5.3 % from the baseline measurement. Zhu et al. [72] reported a significant improvement in exercise-supplementation-group of 2.1 %, which was significant when compared to the placebo group and exercise-alone group. Li et al. [65] found improvement in AMM by 4.7 % from baseline in response to nutrition alone, by 3.5 % in response nutrition plus exercise and a 2.2 % in response to exercise alone. Nilsson et al. [67] found that muscle mass in the sarcopenic subgroup analysis significantly improved from baseline when sarcopenic participants received the vitamin D combined nutritional supplement. TLM improved by 3.4 % from the baseline, while ALM improved by 4.1 % from the baseline. In the study by Bo et al. [64], RSMM increased significantly from compared to the control group by 3.1 %, yet the difference of 1.4 % from baseline was not found to be a significant increase.

Rondanelli et al. [69] found that RSMM improved by 3.2 % from baseline. Takeuchi et al. [55] reported an increase in calf circumference of 3.8 %. Meanwhile, muscle mass was unaltered in the intervention populations of three studies [62, 64, 66]. These results indicate that vitamin D plus protein supplementation results in significant improvements in muscle mass. This is supported by the conclusions of a recent meta-analysis [47] regarding the beneficial effect of vitamin D supplementation in combination with other nutritional supplements in improving muscle mass and strength. However, the trial by Abe et al. [62] did not find improvements. There is a large range of muscle mass increase from 1.3–10.5 % at doses of vitamin D 100–1,000 IU/day. The largest increase in muscle mass was found by Yamada et al. [71], when 800 IU vitamin D was supplemented with 10 g whey protein plus exercise for 12 weeks. A large increase also seen with Rondanelli et al. [68] who administered 800 IU vit D 20 g whey plus exercise; the smaller effect may be due to the shorter dosage time period of 4–8 weeks. From this analysis, 800 IU/day vitamin D may be the most optimal dose to see the greatest improvements in muscle mass (when coupled with exercise). However, the evidence is still slightly unclear as significant improvements were found by Rondanelli et al. [69] despite participants receiving the smallest dose of 100 IU/day vitamin D. Here, it is arguable that the increase in muscle mass may have been brought about by the 22 g whey protein supplemented in the study [69].

Physical function: Muscle function has been assessed differently among trials by various approaches including walking speed, gait speed, TUG test, SPPB, five times sit-to-stand test, chair stand test, 5-min walking time. Six studies reported significant improvements in physical function of sarcopenic patients [62, 66–68, 71, 72]. Abe et al. [62] found an increase in walking speed of 12.5 % from baseline, while Nasimi et al. [66] found a 10.7 % improvement in 4-min gait speed. Nilsson et al. [67] found improvements in the sarcopenic subgroup analysis in the 6-metre walk test of 7.4 % from baseline, and improvements in the 4-step chair climb test of 20.3 % from the baseline measurement. Rondanelli et al. [68] found improvements of 28.0 % in the chair stand test, 12.5 % in the TUG test, and 65.0 % in SPPB, without any improvements in the 4-min gait speed test. Yamada et al. [71] found a 10.4 % improvement in 5-min walking time in response to a 12-week exercise training program from baseline, 15.2 % improvement in response to exercise training plus supplementation (i. e. 800 IU/day of vitamin D plus 10 g whey protein), while supplementation alone resulted in significantly higher test time by 5.6 % from baseline. This study failed to report any improvements in one leg stand and 5 chair stand tests. Of note, in the placebo group the time worsened by 10.5 % from baseline. Zhu et al. [72] found an improvement in the five-chair stand test by a 22.8 % in response to exercise training and a 26.6 % in response to exercise training plus supplementation (i. e. 130 IU/day of vitamin plus: 8.61 g protein, 1.21 g B-methylbtyrate, 0.21 g omega-3 fatty acid) from baseline. However, there were not any cumulative effects of exercise plus supplementation on muscle function. Physical function was not assessed in two trials [55, 69]. Overall, the evidence for the effect of vitamin D on physical function is limited. Half of the trials included in this review investigating sarcopenic participants failed to measure physical function at all or did not report improvements in physical function [55, 63–65, 69, 70]. However, discrepancies in the use of measured aspects of physical function among trials and inconsistent results on the role of vitamin D perplex the comparison and interpretation of findings. As a result, there is not abundant evidence that vitamin D consistently improves physical function in sarcopenic individuals, especially as any improvements found [62, 66–68, 71, 72] may well be attributed to additional variables such as exercise training or co-supplemented protein.

Conclusions

To the best of our knowledge, there have been no published trials to date on the effect of vitamin D as the sole intervention against sarcopenia. There are sparse clinical data on non-sarcopenic individuals, indicating that vitamin D alone has a subtle beneficial effect on leg extension strength at doses between 880–1600 IU/day without improving handgrip strength or muscle mass. When vitamin D is co-administered with other supplements such as protein, mixed effects appear to prevent the decline of muscle mass, possibly delaying the onset of sarcopenia in non-sarcopenic individuals, at doses of 800–1,000 IU/day vitamin D over 6–12 weeks. In

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sarcopenic individuals, vitamin D between 100–1,000 IU/day co-supplemented with protein results in increased handgrip strength between 9.8–40.5 %. However, there is no strong clinical evidence that vitamin D dosage correlates with the changes in muscle strength or in mass. To fully assess the role of vitamin D, appropriate experimental design is needed, allowing the unmasking of possible mixed effects with other parallel interventions such as exercise training regimes or supplementation of other substances such as protein. This would allow direct comparisons among trials. In addition, studies on optimal dosage of vitamin D supplementation may shed light on its role against sarcopenia.

Potential sources of discrepancy among studies may derive from the experimental design, such as an age-dependent blunted anabolic response, the use of various measures of physical function, the level of exercise, and most importantly the co-administration of other substances providing mixed effects on sarcopenic indices. The use of multiple assessment tools for muscle function among different research environments as a source of variability can be ruled out by introducing more standardized approaches such as the SPPB that combines the results of the gait speed, chair stand and balance tests [75, 80]. Future studies should follow appropriate experimental design with reproducible cutting-off points, reliable tests, and suitable control groups to dissect the net effect of vitamin D in sarcopenia. A field of increasing interest is that of nutrigenetics and nutrigenomics, which examines how genetic variations interact with nutritional habits. Vitamin D may represent a suitable candidate of such epigenetic and transcriptional regulation of the human genome [81]. However, research in this field is expanding and the role of nutritional epigenomics in sarcopenia remains to be established, which could improve our understanding on treatment optimization and disease prevention [82].

Conflict of Interest

The authors declare that they have no conflict of interest.

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