The Effect of Vitamin D Supplementation to Parameter of Sarcopenia in Elderly People: a Systematic Review and Meta-Analysis

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ABSTRACT

Background

Vitamin D plays an essential role in promoting skeletal muscle metabolism. Several studies show that vitamin D may help the elderly prevent sarcopenia. Nevertheless, the outcome remains debatable. Our meta-analysis aimed to summarize the effect of vitamin D supplementation on sarcopenia-related parameters.

Methods

We searched PubMed, Cochrane, Springer, SAGE Journals, and Scopus abstracts on 10th December 2021 for relevant studies. We included articles that studied the effect of vitamin D on muscle mass, muscle strength, and physical performance. The aim was to measure the muscle mass, muscle strength, and physical performance both at baseline and at the end of the intervention.

Results

A total of 6,628 participants from 35 studies were included. Most of the studies used oral vitamin D, whereas only one study used intramuscular injection. The effect of vitamin D supplementation showed no effect on appendicular skeletal muscle mass (SMD = .05 [95% CI, .33 – .44], p = .79). Regarding muscle strength, vitamin D supplementation did not have a significant effect on muscle strength which is handgrip strength (p = .26). Respecting physical performance, vitamin D supplementation did not affect TUG (Timed Up and Go) (p = .45).

Conclusions

Vitamin D supplementation had minimal effect on sarcopenia-related parameters. Further research into understanding the role of Vitamin D in preventing the progressivity of sarcopenia still needs to be explored.

Key words: meta-analysis, myogenesis, sarcopenia, skeletal muscle, systematic review, vitamin D

INTRODUCTION

Vitamin D is a fat-soluble vitamin synthesized via cutaneous synthesis in response to exposure to sunlight and dietary intake, and it has significant effects on skeletal and extraskeletal health.(1) Vitamin D plays an essential role in promoting several actions including calcium absorption, bone metabolism, immune cell system, cardiovascular, neoplasms, and skeletal muscle metabolism.(1–3) As a result of the aging process, vitamin D insufficiency or deficiency is common among older individuals.(4,5) The risk for vitamin D insufficiency increases with aging due to a decreased ability of the skin to synthesize vitamin D, decreased vitamin D absorption in the intestine, and impaired hydroxylation in the liver and kidneys.(6–9) Inadequate nutritional quality due to limited intake of various foods among older adults may also contribute to vitamin D insufficiency.(10) Deficiency or insufficiency of vitamin D is associated with an increased risk of sarcopenia.(11)

Sarcopenia is a syndrome characterized by a gradual and general decline in the mass and function of skeletal muscle. It is strongly associated with physical impairment, poor quality of life, and mortality.(12) Regarding the diagnosis of sarcopenia, a consensus has been reached. Despite their differences, they share similar diagnostic criteria for sarcopenia, including muscle mass as quantity, muscle strength, and physical performance.(13,14) Sarcopenia affects 5–13% of individuals aged 60–70 and 11–50% of those older than 80.(15) These numbers suggest that loss of muscle mass and function is a serious and age-related problem in older people.

Some prevention and early interventions may be the key to limiting this decline and preserving muscle mass and function. Supplementation of vitamin D has shown to promote musculoskeletal health in the elderly. Vitamin D may help elderly people in maintaining or improving muscle mass, muscle function, and physical performance. Several studies have investigated the effectiveness of oral vitamin D supplementation in preventing sarcopenia in elderly

patients. Nonetheless, the results remain controversial. Our meta-analysis and systematic review aimed to summarize the effect of vitamin D supplementation on the parameters of sarcopenia in the elderly (muscle mass, muscle strength, and physical performance).

MATERIALS AND METHODS

Cochrane's methodology and PRISMA guidelines were used to perform this study. This study received no funding, and none of the authors disclosed competing interests. Our study protocol is recorded in the international prospective register of systematic reviews (PROSPERO registration number CRD42022299343).

The Strategy of Search

We performed a systematic search of several online databases (PubMed, Cochrane, Science Direct, Springer, SAGE Journals, and Scopus) on 10th December 2021, using the terms "(elderly OR older OR aged OR aging) AND (Vitamin D OR Vitamin D2 OR Vitamin D3 OR Ergocalciferol OR Cholecalciferol) AND (muscle strength OR muscle mass OR physical function OR physical performance)".

The inclusion criteria were randomized controlled trials (RCTs) or controlled trials which studied the effect of vitamin D on muscle mass, muscle strength, and physical performance. Case reports, case series, non-English studies, and non-human studies were excluded.

Study Selection

Two authors (H.B.P.P. and R.R.) independently screened the literature and identified relavant studies according to the inclusion and exclusion criteria. Disagreements were settled through discussion with the third author (N.H.S.).

Reports were included in this study if they satisfied all of the PICO criteria: 1) Population (P) consisted of male and/or female participants, elderly (aged $\geq$ 60 years or mean age $\geq$ 60 years) regardless of their baseline status; 2) Intervention (I) was supplementation of vitamin D (all doses and all forms), no length of follow-up restriction; 3) Comparison (C) was a placebo; 4) Outcomes (O) were muscle mass, muscle strength, and physical performance measured at baseline and the termination of intervention for both groups.

The Extraction of Data

Two authors (N.H.S. and R.R.) independently extracted the data from the selected studies using Microsoft Excel. The data included: the title of the journal, authors and years of publication, country/geographic areas, length of study, follow-up interval and frequency, randomization, source of bias, population (number of samples, age, sex, ethnicity, comorbidity, setting (outpatient/inpatient)), intervention (doses and forms of vitamin D supplementation, duration of intervention), outcomes (muscle mass, muscle strength, and physical performance, baseline and post-study serum (25(OH)D levels). Based on these data, subgroup analysis was predetermined.

The Risk of Bias

Three authors (N.H.S., H.B., and R.R.) independently evaluated the risk of bias in each RCT using The Cochrane risk of bias 2 (RoB2) assessment tool, regarding the following domain (i) randomization process; (ii) deviations from the intended interventions; (iii) missing outcome data; (iv) measurement of the outcome; (v) selection of the reported result. The criteria will each be judged as being 'low risk', 'high risk', and 'some concerns', and overall assessments of the quality of the study will be determined accordingly. Funnel plots were used to find any publication bias when there were enough studies to ensure the power of the test.

Statistical Analysis

This meta-analysis selected studies that reported sarcopenia parameters (muscle mass, handgrip strength (HGS) and Timed Up and Go (TUG) test. The data are presented as mean deviations and standard deviations (SDs). The median, sample size, range, and/or interquartile range were used to calculate the mean and standard deviation.[16,17] Weighted mean differences for vitamin D versus placebos/control were calculated by subtracting the mean of the outcome of interest at the end of the study from the mean at the baseline. SDs of the differences between standard errors and confidence intervals were calculated using a formula from the Cochrane Handbook,[18] and missing SDs were calculated by applying correlation coefficients of .90 for HGS, .80 for TUG. When none of the aforementioned methods permit the calculation of SDs from the report, the authors imputed missing data by borrowing SDs from one or more other studies.[19] Reported data with different measurement methods are excluded.

If a study included two vitamin D groups (different doses) but only one placebo group, we chose to include both the placebo group and the highest-dose vitamin D group. In factorial designs, for example, a group treated with exercise (± vitamin D), we included the two groups treated with vitamin D versus placebos.

If muscle strength was reported for both the dominant and nondominant extremities, we selected the dominant or right extremity. In studies using a different regimen of administration, we chose oral supplementation if available. If the measurements were at several different time points, we chose the longest time point.

After that, subgroup analyses based on vitamin D supplementation dosage were conducted. In non-daily treatment studies, the daily dose of supplementation is calculated by dividing the total dose by the number of days from baseline to the end of the study.[20] High-dose vitamin D is defined as 4000 IU of supplemental vitamin D per day.[21,22]

RevMan 5.4.1 version analysis software (www.cochrane.org) was utilized to conduct statistical analyses. Different unit-valued outcomes were evaluated as standardized mean differences (SMD) with a 95% confidence interval (CI), and the SMD was chosen for analysis. The mean difference values for a specified outcome in the same unit were assessed as mean

difference (MD) with a 95% confidence interval (CI) and the MD will be selected for analysis. The heterogeneity of results across trials will be assessed using the I^2 statistic. I^2 less than 25% is defined as low heterogeneity; I^2 within 25% to 50% is defined as moderate heterogeneity; and I^2 values greater than 50% are defined as high heterogeneity. Fixed-effects model was used when heterogeneity was low or moderate. However, a random-effects model was used when heterogeneity was high. All of the results will be presented as a forest plot.

RESULTS

Our preliminary article search returned 2,307 results. After duplicates and abstracts were excluded, 1,819 full-texts were identified and 103 studies were assessed for eligibility. The meta-analysis and systematic review included 35 studies. Figure 1 shows the flowchart for the included study.

Table 1 presents the characteristics of the 35 studies. Out of those 35 randomized controlled trials involving 6,628 participants, 3,303 were assigned as a control group and 3,325 were assigned as an intervention group. Vitamin D3 was used in 29 studies,[23–50] vitamin D2 in four studies,[51–54] alfacalcidol was used as supplementation in one study,[55] 1, 25 dihydroxy vitamin D in one study,[56] and a study did not report the type of vitamin D used.[57] The majority of studies supplemented participants with vitamin D orally, whereas only one study supplemented participants with intramuscular injection.[51] The doses used are evenly distributed below or above 4000 IU per day, and the treatment duration ranged from one to sixty months. There were six studies involving vitamin D supplementation at high doses.[28,31,44,48,50,57] There were 18 studies that included vitamin Deficiency individuals' serum 25(OH)D levels below 50 nmol/L,[23,25,27-30,33,35,36,38,40,42,44,45,49,51,52,54] and three studies did not report the baseline serum 25(OH)D levels[33,43,45]

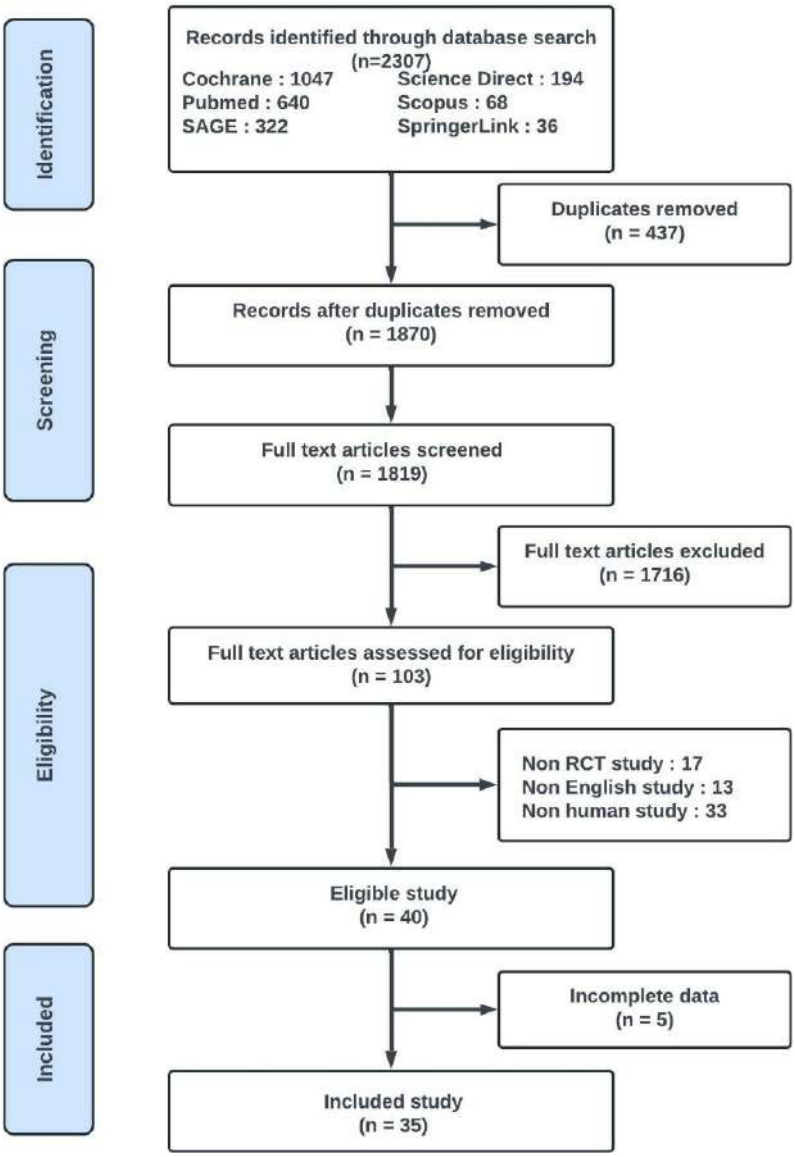

FIGURE 1. Flowchart of selection process for meta-analysis

TABLE 1 (part 1 of 4).
Baseline characteristics of included studies

No	*Study*	*Year*	*Sample Size (women, %)*	*Participants*	*Age (year) [mean (SD)]*	*Experimental*	*Control*	*Type of Vitamin D*	*Form and Dosage of Vitamin D*	*Study Duration*	*Serum 25(OH)D level at baseline (nmol/L) [mean (SD)]*	*Serum 25(OH) D level at end of study (nmol/L) [mean (SD)]*
1	Aloia[23]	2018	260 (100)	Healthy elderly black women with serum 25(OH)D between 20 and 65 nmol/L, age ≥60 years old	Median (IQR) C: 69 (65.4-73.4) I: 67.8 (65.1-71.5)	Vitamin D	Placebo	D3	Adjusted dose to maintain 25(OH) D>75 nmol/L), oral	3 years	C: 55.5 (6.9)[a] I: 53.5 (6.5)[a]	Mean (SE) C: 51 (2.7) I: 117 (2.9)
2	Bischoff-Ferrari[24]	2020	2157 (61.7)	Community-dwelling age >70 years old	C: 74.9 (4.4) I: 75.0 (4.5)	Vitamin D	Placebo	D3	2.000 IU / daily, oral	3 years	C: 56 (8.5)[a] I: 56 (8.4)[a]	NR
3	Bjerk[25]	2013	36 (0)	COPD patients	C: 68 (8) I: 67.6 (7)	Vitamin D	Placebo	D3	2.000 IU / daily, oral	6 weeks	C: 61 (10.5)[a] I: 56.5 (10.5)[a]	C: 55.25 (10.1)[a] I: 81.5 (8.2)[a]
4	Boxer[26]	2013	64 (48)	Patients with heart failure, age ≥50 years	C: 66 (10.4) I: 65.8 (10.6)	Vitamin D	Placebo	D3	50.000 IU / weekly, oral	6 months	C: 44.5 (22.5) I: 47.75 (23.25)	C: 45 (NR) I: 153.5 (NR)
5	Brunner[27]	2008	2347 (100)	Postmenopausal women	Mean (ranges) 62 (50-79)	Vitamin D + Calcium	Calcium	D3	400 IU / daily, oral	5 years	NR	NR
6	Bunout[28]	2006	48 (89)	Community-dwelling	C: 77 (4) I: 77 (5)	Vitamin D + Calcium	Calcium	D3	400 IU / daily, oral	9 months	C: 32.7 (6.75)[a] I: 31 (5.5)[a]	C: 36.25 (11.5)[a] I: 64.5 (16.25)[a]
7	Cavalcante[29]	2015	38 (100)	Postmenopausal women with type 2 diabetes	C: 62.32 (8.00) I: 62.16 (7.62)	Vitamin D	Placebo	D3	6.600 IU / weekly, oral	3 months	C: 57.27 (4.21)[a] I: 56 (3.98)[a]	C: 57.1 (3.88)[a] I: 57.45 (4.23)[a]
8	Ceglia[30]	2013	21 (100)	Mobility-limited women, aged > 65 years, with serum 25(OH)D levels 22.5 to 60 nmol/L.	C: 80 (5) I: 76 (4)	Vitamin D	Placebo	D3	4.000 IU / daily, oral	4 months	C: 48.3 (8.8) I: 43.6 (10.3)	C: 52.5 (17.1) I: 80.0 (11.5)
9	de Koning[31]	2019	155 (57.4)	Elderly aged 60–80 year who had clinically relevant depressive D symptoms, ≥1 functional limitations, and serum 25(OH)D between 15-70 nmol/L.	Median (IQR) C:67.3 (63.4-72.0) I: 67.8 (65.4-71.7)	Vitamin D	Placebo	D3	1.200 IU / daily, oral	1 year	Median (IQR) C:44 (36-55.25) I: 46 (32.5-57)	C: 43 (18) I: 85 (16)
10	Dhesi[32]	2004	123 (78)	Ambulatory fallers, age ≥65 years old	C:76.6 (6.1) I: 77.0 (6.3)	Vitamin D	Placebo	D2	600.000 IU single dose, intramuscular injection	6 months	Mean (95% CI) C: 25 (23.75-26.25)[a] I: 26.75 (25.5-28)[a]	Mean (95% CI) C: 31.5 (28.5-34.5)[a] I: 43.75 (41.25-46.25)[a]
11	el Hajj[33]	2019	115 (48.7)	Outpatient clinics with pre-sarcopenic and vit D deficient (serum25(OH)D < 20 ng/ml)	C: 73.56 (2.14) I: 73.05 (1.95)	Vitamin D	Placebo	D3	10.000 IU / 3 times a week, oral	6 months	C: 26.4 (3.14)[a] I: 25.325 (2.87)[a]	C: 39.275 (5.70)[a] I: 69.95 (2.82)[a]

TABLE 1 (part 2 of 4).
Baseline characteristics of included studies

No	*Study*	*Year*	*Sample Size (women, %)*	*Participants*	*Age (year) [mean (SD)]*	*Experimental*	*Control*	*Type of Vitamin D*	*Form and Dosage of Vitamin D*	*Study Duration*	*Serum 25(OH)D level at baseline (nmol/L) [mean (SD)]*	*Serum 25(OH) D level at end of study (nmol/L) [mean (SD)]*
12	Glendenning[34]	2012	686 (100)	Community-dwelling ambulant women, age >70 years old	C: 76.5 (4) I: 76.9 (4)	Vitamin D	Placebo	D3	150.000 IU / 3 months, oral	9 months	C: 66.5 (27.1) I: 65 (17.8)	C: 60.2 (26.3) I: 74.6 (25.8)
13	Grady[35]	1991	98 (54)	Community dwelling, age >69 years old	Median (ranges) 79.1 (70-97)	Vitamin D	Placebo	1,25-(OH) -D3	0.5 µg / daily, oral	6 months	C: 65.7 (51.4) I: 60.4 (35.3)	NR
14	Hangelbroek[36]	2019	22 (45.45)	Vitamin D deficient frail older adults (aged above 65), 25(OH)D 20-50 nmol/L.	C:74.1 (5.8) I: 71.8 (5.7)	Vitamin D	Placebo	D3	400 IU / daily, oral	6 months	C: 37.5 (11.9) I: 34.1 (9.3)	C: 43.8 (14.1) I: 87.3 (20.6)
15	Hansen[37]	2015	145 (100)	Postmenopausal women, age <75 years old	C: 61 (6) I: 60 (5)	Vitamin D	Placebo	D3	Loading dose 50.000 IU / daily (for 15 days), continued with 50.000 IU / 15 days, oral	1 year	C: 52.5 (3)[a] I: 52.5 (3)[a]	C: 45 (6)[a] I: 105 (8)[a]
16	Hewitt[38]	2013	56 (52)	Dialysis patients (CKD-5)	Median (ranges) 62 (20-86)	Vitamin D	Placebo	D3	50.000 IU / weekly for 8 weeks, then monthly for 4 months, oral	6 months	C: 40 (12.5)[a] I: 45 (12.5)[a]	C: 40 (17.5)[a] I: 87.5 (22.5)[a]
17	Janssen[39]	2010	70 (100)	Geriatric care, serum 25(OH)D concentration between 20 and 50 nmol/L, age >65 years old	C: 79.2 (6.7) I: 82.4 (6.4)	Vitamin D + Calcium	Calcium	D3	400 IU / daily, oral	6 months	C: 34.3 (11.5) I: 32.6 (11.6)	C: 41.6 (19.0) I: 77.2 (19.4)
18	Kenny[40]	2003	60 (0)	Community-dwelling, men aged ≥65 years old	C: 76 (5) I: 77 (4)	Vitamin D + Calcium	Calcium	D3	1.000 IU / daily, oral	7 months	C: 59 (18.75)[a] I: 65 (16.75)[a]	C: 56.5 (17)[a] I: 87.25 (13.75)[a]
19	Latham[41]	2003	222 (53)	Geriatric care	C: 80 (78-81) I: 79 (77-80)	Vitamin D	Placebo	D2	150.000 IU single dose, oral	6 months	Median (95% CI) C: 47.5 (40-52.5)[a] I: 37.5 (35-45)[a]	NR
20	Levis[42]	2016	113 (0)	Sedentary men	C: 73.0 (7.30) I: 71.8 (6.30)	Vitamin D	Placebo	D3	4.000 IU / daily, oral	9 months	C: 56.9 (5.3)[a] I: 57.6 (5.1)[a]	C: 59.9 (7.16)[a] I: 114.875 (12.75)[a]
21	Lips[43]	2010	213 (NR)	Community-dwelling, serum 25(OH)D concentration between 15 and 50 nmol/L, age ≥70 years old	C: 77.6 (6.6) I: 78.5 (6.2)	Vitamin D	Placebo	D3	8.400 IU / weekly, oral	16 weeks	C: 35.25 (5.5)[a] I: 34.25 (4.4)[a]	C: 35.25 (NR)[a] I: 65 (NR)[a]

TABLE 1 (part 3 of 4).
Baseline characteristics of included studies

No	*Study*	*Year*	*Sample Size (women, %)*	*Participants*	*Age (year) [mean (SD)]*	*Experimental*	*Control*	*Type of Vitamin D*	*Form and Dosage of Vitamin D*	*Study Duration*	*Serum 25(OH)D level at baseline (nmol/L) [mean (SD)]*	*Serum 25(OH) D level at end of study (nmol/L) [mean (SD)]*
22	Momosaki[44]	2019	97 (29.89)	Aged 20 years or older, suffering from first hemiparetic stroke, underwent rehabilitation	C: 65.6 (11.7) I: 67.6 (11.7)	Vitamin D	Placebo	D3	2.000 IU / daily, oral	8 weeks	NR	NR
23	Moreira-Pfrimer[45]	2009	46 (73)	Institutionalized elderly, age ≥60 years old	Median (ranges) C:78 (63–92) I: 78.5 (62–94)	Vitamin D + Calcium	Calcium	D3	150.000 IU / month for 2 months and then 90.000 IU/month in the following 4 months, oral	6 months	Median (ranges) C: 39.5 (20.3-68.8) I: 45.9 (20.3-84.8)	Median (ranges) C: 51.8 (23.5-107.8) I: 86.6 (52.3-106.5)
24	Pfeifer[46]	2009	228 (75)	Healthy ambulatory women and men, serum 25(OH)D level below 78 nmol/L, age ≥70 years	C: 77 (4) I: 76 (4)	Vitamin D + Calcium	Calcium	D3	800 IU / daily for 12 months, oral	12 months	C: 54 (19) I: 55 (18)	C: 57 (20) I: 84 (18)[b,c]
25	Pirotta[47]	2015	26 (42.3)	Community-dwelling (≥60 yr.), 25(OH) D<60	C: 66.1 (4.0) I: 71.5 (5.7)	Vitamin D	Placebo	D3	2.000 IU / daily, oral	10 weeks	C: 48.5 (11.1) I: 46.4 (11.4)	Mean, CI 95% C: 47.3 (-5.8, 3.4) I: 82,5 (26.3, 42.2)
26	Rafiq[48]	2017	50 (50.48)	COPD patients	Median (IQR) C: 61 (58-66) I: 64 (61-66)	Vitamin D	Placebo	D3	1.200 IU / daily, oral	6 months	C: 40.6 (17.0) I: 42.3 (15.2)	C: 52.9 (29.8) I: 95.1 (25.1)[b]
27	Sakalli[49]	2012	60 (48)	outpatient clinic, age >65 years old	70.1 (4.3)	Vitamin D	Placebo	NR	300.000 IU single dose, oral	4 weeks	C: 53 (18.5)[a] I: 52.25 (23.75)[a]	C: 52.5 (8.75)[a] I: 67.5 (30)[a]
28	Setiati[50]	2018	88 (100)	Older women at geriatric clinic (age ≥60 years) with HGS ≤22 kg.	Median (min-max) C: 70 (64-84) I: 70 (61-88)	Vitamin D	Placebo	Alfacalcidiol	0.5 µg / daily, oral	90 days	Median (min-max) C: 93.75 (42.5-165)[a] I: 105 (47.5-240)[a]	Median (min-max) C: 95.875 (36-155.25)[a] I: 97.75 (44-247.75)[a]
29	Shea[51]	2019	100 (36)	Community-dwelling adults	C: 69.2 (6.2) I: 70.1 (7.4)	Vitamin D	Placebo	D3	800 IU / daily, oral	1 year	C: 52 (6.9)[a] I: 49 (6.6)[a]	C: 49.5 (7.3)[a] I: 81.35 (5.1)[a]
30	Smedshaug[52]	2007	60 (65)	Institutionalized	C: 82 (7.6) I: 82.8 (7)	Vitamin D in cod liver oil	Cod liver oil	D3	400 IU / daily, oral	1 year	C: 49.9 (34.8) I: 49.3 (26.5)	C: NR I: 70.4 (NR)
31	Uusi-Rasi[53]	2015	183 (100)	Community dwelling, age 70-80 years old	C: 74.1 (3.0) I: 73.8 (3.1)	Vitamin D	Placebo	D3	800 IU / daily, oral	2 years	C: 67.75 (7.5)[a] I: 66 (6.9)[a]	C: 69.375 (7.4)[a] I: 92.5 (7.4)[a]
32	Vaes[54]	2018	52 (44.2)	Community-dwelling (pre-or frail) older adults	C: 73.7 (6.2) I: 74.8 (6.7)	Vitamin D	Placebo	D3	800 IU / daily, oral	6 months	Mean, CI 95% C: 38.1 (32.5, 43.8) I: 36.3 (30.6, 42.0)	Mean, CI 95%, changes C: 47 (2.0, 15.9) I: 71 (28.6, 42.7)

TABLE 1 (part 4 of 4).
Baseline characteristics of included studies

No	*Study*	*Year*	*Sample Size (women, %)*	*Participants*	*Age (year) [mean (SD)]*	*Experimental*	*Control*	*Type of Vitamin D*	*Form and Dosage of Vitamin D*	*Study Duration*	*Serum 25(OH)D level at baseline (nmol/L) [mean (SD)]*	*Serum 25(OH) D level at end of study (nmol/L) [mean (SD)]*
33	Witham[55]	2010	96 (35)	Systolic heart failure with serum 25(OH) D concentration <50 nmol/L, age ≥70 years old	C: 80.6 (5.7) I: 78.8 (5.6)	Vitamin D	Placebo	D2	100,000 IU at baseline and 10 weeks, oral	20 weeks	C: 23.7 (8.9) I: 20.5 (10.0)	C: 25 (NR) I: 40 (NR)
34	Wood[56]	2014	181 (100)	Postmenopausal women	63.8 (2.2)	Vitamin D	Placebo	D3	1.000 IU / daily, oral	1 year	NR	NR
35	Zhu[57]	2010	261 (100)	Community-dwelling ambulant elderly, aged 70 to 90, serum 25(OH) D levels < 60 nmol/L	C: 77 (4.8) I: 76.8 (4.2)	Vitamin D + Calcium	Calcium	D2	1.000 IU / daily, oral	1 year	C: 44.25 (13)[a] I: 45.25 (12.5)[a]	C: 45 (13.5)[a] I: 60 (14)[a]

[a]Calculated to nmol/L using coefficient of 2.5
[b]p< .001 significantly different versus baseline
[c]p< .001 significantly different versus baseline
C = Control group; I = Intervention group; NR = Not Reported.

The Risk of Bias

The overall risk of bias in included studies is considered low. High-risk bias was present in deviations from intended interventions,[26,34] missing outcome data,[26] and selection of the reported result.[39,42]

Muscle Mass

Forest plots of muscle mass analysis are shown in Figure 2. Four studies have been pooled in this analysis and reported the differences in muscle mass between pre- and post-vitamin D supplementation. Three hundred and ninety-nine participants were pooled, with 199 participants in the vitamin D group and 200 participants in the control group.[33,37,51,54] Two studies used standard doses of vitamin D,[51,54] and the other studies used high-dose supplementation of vitamin D.[33,37]

Three studies used kilogram (kg) as a unit of measurement.[33,51,54] One study used kilogram per square meter (kg/m²) as a unit of measurement.[37] Two studies measured muscle mass after six months of vitamin D supplementation,[33,54] and two others measured after one year of vitamin D supplementation.[37,51]

According to the Asian Working Group for Sarcopenia (AWGS) () 2019, cutoffs for height-adjusted muscle mass are: dual-energy X-ray absorptiometry (DXA), < 7.0 kg/m^2 in men and < 5.4 kg/m^2 in women; and for bioimpedance analysis (BIA), < 7.0 kg/m^2 in men and < 5.7 kg/m^2 in women.[58] Whereas, in the European Working Group on Sarcopenia in Older People (EWGSOP2) definition, low muscle mass for both DXA and BIA was expressed by muscle mass with cut-off points for men < 20 kg and women < 15 kg, and height-adjusted muscle mass with cut-off points for males < 7.0 kg/m^2 and females < 5.5 kg/m^2.[14]

The baseline level of muscle mass between vitamin D and the placebo group was comparable in three studies.[37,51,54] However, a study conducted by El Hajj *et al*. had a remarkable difference in the baseline of muscle mass between the vitamin D and placebo group.[33]

Compared with the placebo, vitamin D supplementation did not affect appendicular skeletal muscle mass (SMD = .05 [95% CI, -.33 – .43], p = .79). In subgroup analysis, neither the standard dose nor the high dose of vitamin D supplementation showed muscle mass improvement. However, heterogeneity was high (p = .02; I^2 = 71%)

Muscle Strength

Muscle strength was represented by handgrip strength. Forest plots of muscle strength analysis are shown in Figure 3. Compared with the control group, vitamin D supplementation did not have a significant effect on muscle strength (handgrip strength) (p = .26).

Handgrip Strength

Nineteen studies were included in this analysis. Four thousand four hundred and forty (4,440) participants were pooled, with 2,249 participants in the vitamin D group and 2,191

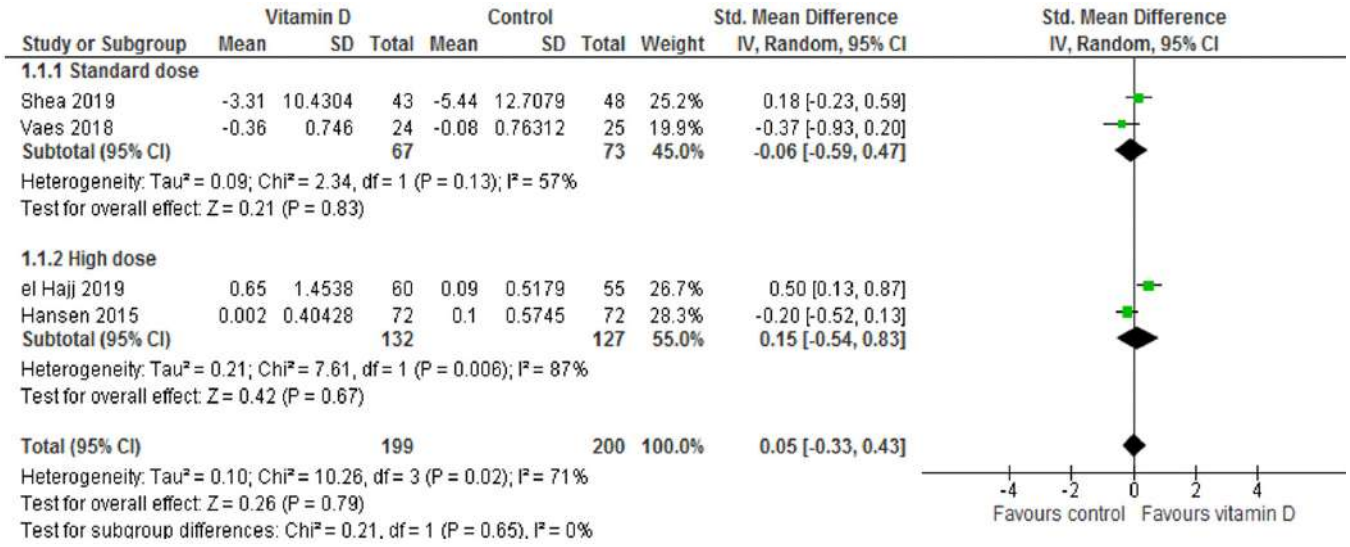

FIGURE 2. Forest plots skeletal muscle mass

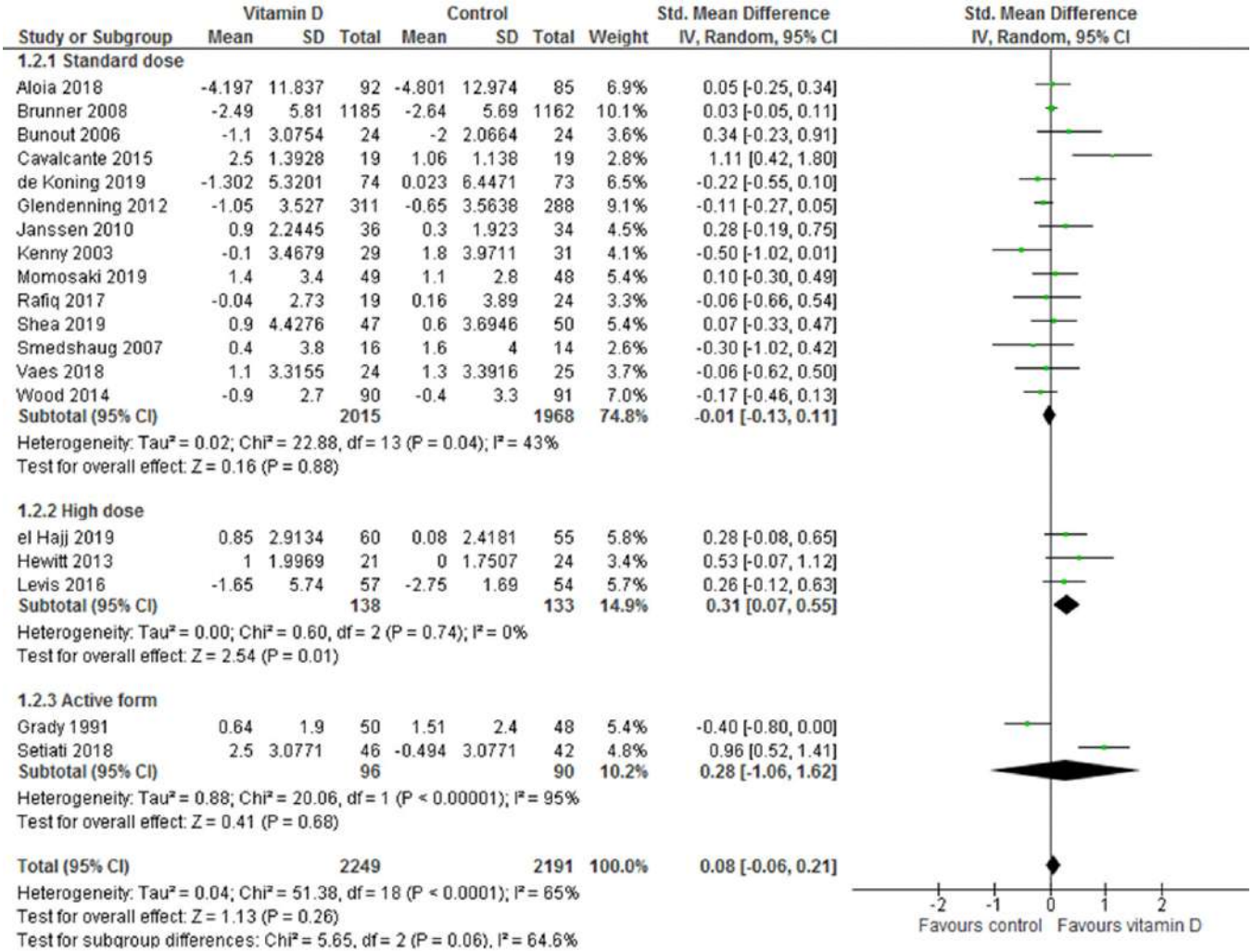

FIGURE 3. Forest plots handgrip strength

participants in the control group. Fourteen studies used a standard dose of vitamin D,[23,27,28,29,31,34,39,40,44,48,51,52,54,56] three studies used high-dose supplementation of vitamin D,[33,38,42] and two studies used an active form of vitamin D.[35,50]

All of the studies, except the study from Aloia *et al*.[23] and Grady *et al*.[35], used kg as a unit of measurement.[27,28,29,31,33,34,38,39,40,42,44,48,50,51,52,54,56] There was a different trace between AWGS 2019 and EWGSOP2 in the normal level of handgrip strength. AWGS 2019 stated that the normal level of handgrip strength is 18 kg in women and 28 kg in men.[13] However, EWGSOP2 stated that the normal level of handgrip strength is 16 kg in women and 27 kg in men.[14] One study from Grady et al.[25] did not state clearly their normal baseline of the unit of measurement. Five studies had a lower baseline level of handgrip strength compared to others.[29,39,44,50,52]

The mean difference in handgrip strength favored vitamin D supplementation rather than placebos. However, this result was not statistically significant (SMD = 0.08 [95% CI, -0.06 – 0.21], p = .26). Interestingly, the subgroup of high-dose vitamin D supplementation showed a significant increase in handgrip strength compared to the placebos (SMD = 0.31 [95% CI, 0.07 – 0.55], p = .01). However, there was significant heterogeneity among studies in HGS (I^2 = 65 %, p < .0001).

Physical Performance

Physical performance was represented with TUG test. Forest plots of physical performance analysis are shown in Figure 4. The overall results from the random effects model indicated that supplemental vitamin D did not affect TUG compared with placebos (p = .45).

Timed Up and Go

Fifteen studies were included in this analysis. Two thousand three hundred and forty-four (2,344) participants were pooled, with 1,176 participants in the vitamin D group and 1,168 participants in the control group. Twelve studies used a standard dose of vitamin D,[28,31,34,37,39,40,41,46,53,54,55,57] two studies used high-dose supplementation of vitamin D,[26,49] and one study used an active form of vitamin D.[50] All of these studies used the second (s) as a unit of measurement. Low performance is defined by TUG $\geq$ 20 s, according to EWGSOP2.[14] There was only one study that had a low baseline of TUG.[52]

DISCUSSION

This meta-analysis and systematic review summarized the effects of vitamin D supplementation relative to placebos on

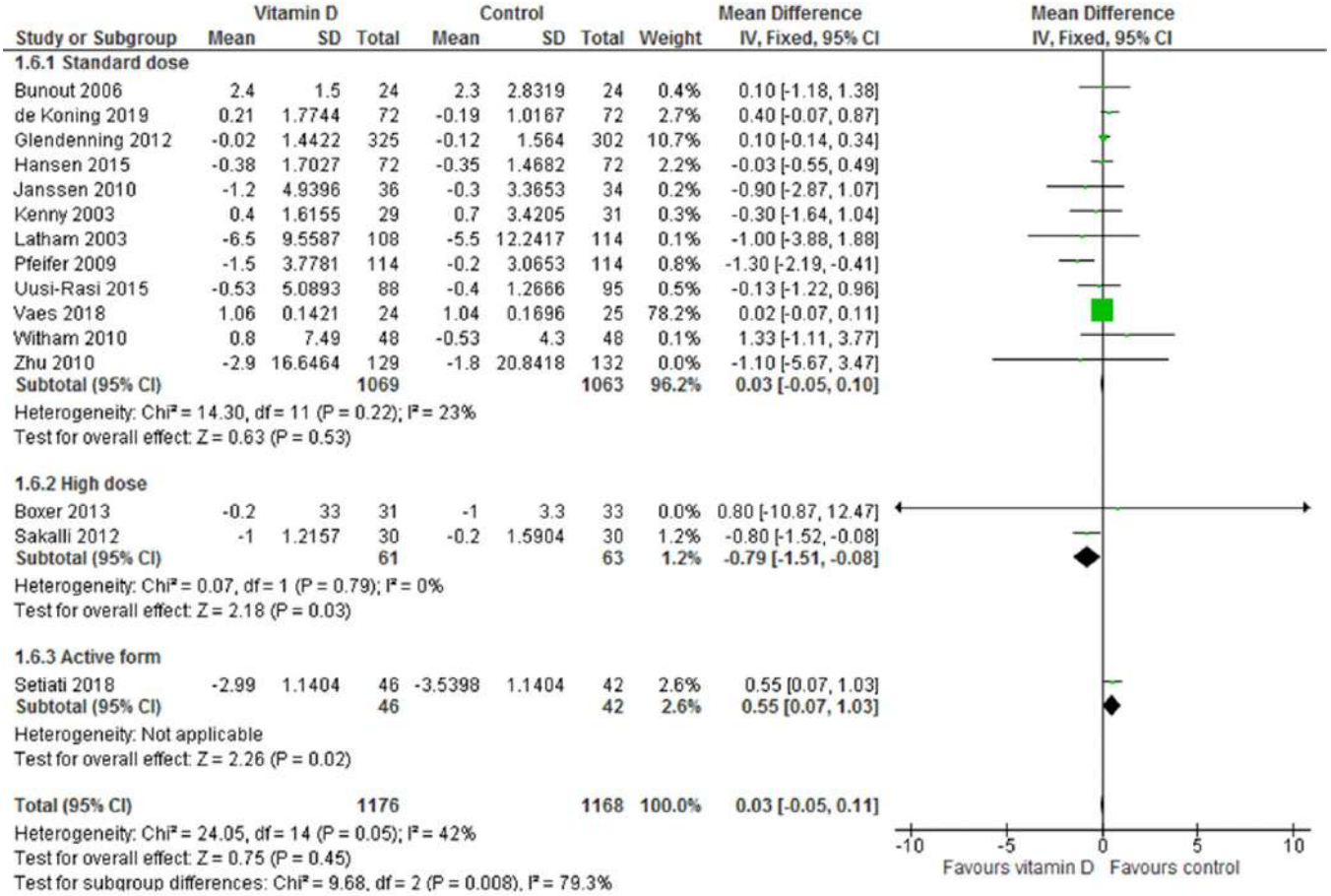

FIGURE 4. Forest plots physical performance

sarcopenia parameters (muscle mass, muscle strength, and physical performance) in the elderly. The results of 35 randomized controlled trials showed that vitamin D supplementation has no beneficial effects on muscle mass, muscle strength, or physical performance. Currently, this study is the largest meta-analysis of RCTs assessing vitamin D supplementation regarding its dose in the elderly population.

Evaluation and measurement of muscle mass are valuable diagnostic parameters for sarcopenia.[13,14] Despite the study from El Hajj *et al*. that showed that a high dose of vitamin D supplementation significantly improved skeletal muscle mass.[33] However, our findings indicate that neither the standard nor the high dose of vitamin D supplementation increases muscle mass.

Monitoring muscle strength is the most important aspect of sarcopenia evaluation.[13] HGS (handgrip strength) is a simple, quick, and inexpensive tool that is reportedly reliable for diagnosing sarcopenia and is widely used to represent overall muscle strength.[14,13,59-61] Although the results of our meta-analysis indicated that vitamin D supplementation had no significant effects on muscle strength, there were a few exceptions (e.g., handgrip strength). However, our research demonstrated that vitamin D supplementation at high doses significantly improves HGS. Furthermore, additional analysis of vitamin D supplementation at the standard dose in individuals with a lower HGS at baseline revealed an improvement, although it was not statistically significant. This finding contradicted previous studies of meta-analyses conducted by Prokopidis *et al*., Stockton *et al*., and Rosendahl-Riise *et al*. which concluded that supplementation with vitamin D did not significantly improve muscle strength in older adults.[58,62,63] Another meta-analysis by Beaudart *et al*. found that vitamin D supplementation improved general muscle strength; however, these studies included young adults and did not focus on the elderly.[64]

Physical performance has been defined as the objective measurement of total body function, mobility, and balance. This term encompasses not only muscle functions, but also central and peripheral nervous system functions.[65,66] In response to vitamin D supplementation, there were no significant changes in overall physical performance as determined by our meta-analysis. Nevertheless, additional analysis in our study revealed that vitamin D supplementation at high doses also significantly improves TUG.

TUG test and HGS improvement with high-dose vitamin D supplementation raise the question of whether a higher dose of vitamin D supplementation is required for significant improvement in older populations. This may be due to decreased vitamin D receptors (VDR) in the elderly.[6] A decrease in VDR has been linked to a decrease in mitochondrial oxidative phosphorylation capacity, an essential driver of muscle regeneration.[67] Therefore, elderly individuals require higher vitamin D dosages to compensate for the loss of VDR. Unfortunately, few studies have evaluated vitamin D supplementation at high doses. Vitamin D supplementation at high doses may require further investigation.

Vitamin D is one of the essential supplements for sarcopenia, according to the International Clinical Practice Guidelines for Sarcopenia (ICFSR), along with high-protein nutritional interventions and exercise training. However, vitamin D supplementation alone is not recommended due to insufficient evidence.[66] Our recent findings also indicate that vitamin D supplementation itself would not improve sarcopenic parameters immediately. When vitamin D levels in patients with sarcopenia are low (20 ng/mL), supplementation may be considered.[68]

In terms of etiology, sarcopenia has numerous risk factors, such as oxidative stress, inflammation, the aging process, an inadequate diet, a sedentary lifestyle, metabolic disorders, and genetic factors.[69,70] Thus, the management of sarcopenia may provide less optimal results if assessed only from one risk factor. According to our research, in vivo supplementation with vitamin D had generally no significant effects on muscle mass, muscle strength, or physical performance. However, the effect of vitamin D in vitro on sarcopenia muscles is still unknown because of limited research. Yang *et al*., and Wagatsuma *et al*., found that vitamin D consumption affects the myogenesis process in muscle cells, making it a viable treatment option for sarcopenia.[69,71] Thus, it is necessary to investigate vitamin D's effects on sarcopenia muscles in vitro.

CONCLUSION

Our systematic review and meta-analysis demonstrate that vitamin D supplementation had minimal effects on sarcopenia-related parameters. Further research concerning the role of Vitamin D in preventing the progressivity of sarcopenia still needs to be explored.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood the *Canadian Geriatrics Journal*'s policy on conflicts of interest disclosure and declare there are none.

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