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Review Article

The Effect of Vitamin D Supplementation on Muscle Mass, Muscle Strength and Muscle Function in the Elderly: A Systematic Review and Meta-Analysis

Samantha Harrison[1]*, Sudip Ghosh[1,2]

[1]Department of Allied Health Sciences, School of Allied Health and Life Sciences, De Montfort University, Leicester, UK
[2]Department of Health Sciences, College of Life Sciences, University of Leicester, Leicester, UK

***Correspondence**
Samantha Harrison
Department of Allied Health Sciences, School of Allied Health and Life Sciences, De Montfort University, Leicester, UK
E-mail:
Samantha.Harrison25@nhs.net

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ABSTRACT

Sarcopenia, the age-related loss of muscle mass, strength, and function is associated with falls and increased mortality. It is becoming a major public health concern due to its increase in prevalence, affecting over fifty million people worldwide. Due to the rising elderly population, this is expected to rise to over 200 million people by 2050. Mounting evidence supports the role of vitamin D in the stimulation of skeletal muscle fibre proliferation and differentiation. Therefore, vitamin D supplementation has the potential to prevent muscle loss and thus sarcopenia. Data from twenty-six randomised controlled trials including 6481 participants were summarised to investigate the effects of vitamin D supplementation on muscle mass, strength, and function in the form of balance, gait speed, and chair stand tests in the elderly population (≥60 years old). Results revealed that vitamin D supplementation had a significant positive effect on muscle mass (standardised mean difference (SMD) 0.27; 95% confidence intervals (CI) 0.12-0.42; *P* <0.001) and muscle strength (SMD 0.34; 95% CI -0.01 - 0.69; *P*=0.05). No significant effects were found for balance (SMD -0.06; 95% CI -0.19-0.08; *P*=0.40), gait speed (SMD 0.17; 95% CI -0.08–0.43; *P*=0.18), or chair stand tests (SMD 0.04; 95% CI -0.31–0.40; *P*=0.81) as markers for muscle function. These results suggest that vitamin D supplementation could have potential as a widely accessible cost-effective intervention for reducing sarcopenia. However, further studies are required to evaluate optimum modalities such as dose and treatment duration.

1. INTRODUCTION

Sarcopenia is the age-related loss of skeletal muscle mass and strength.[1] It is increasing in prevalence, affecting up to eighty-two percent of over eighty-year-olds.[2] In 2010, over 50 million people were thought to be affected by sarcopenia worldwide and with ever increasing populations, this is estimated to rise to over 200 million by 2050.[1] If low physical performance is also present, which can be measured via markers of muscle function, sarcopenia can be classified as severe.[3] The cut off values for the diagnosis of sarcopenia are summarised in Table 1. This reduction in muscle mass and strength results in reduced mobility, falls, functional impairment, and fractures, with falls in over sixty-five-year-olds costing the NHS £4.6 million per day.[4] Sarcopenia is therefore associated with increased morbidity, hospitalisation, and institutionalisation in addition to cardiac disease, respiratory disease, cognitive impairment, and

Table 1. Cut-off points for the diagnosis of sarcopenia categorised into tests which can be used to measure muscle strength, muscle quality and muscle performance. Adapted from Cruz-Jentoft et al[3].

Test	Cut-off points for men	Cut-off points for women
Cut-off points for low strength		
Grip strength	<27kg	<16kg
Chair stand	>15s for 5 rises	
Cut-off points for low muscle quality		
ASM	<20kg	<15kg
ASM/height^2	<7.0kg/m^2	<5.5kg/m^2
Cut-off points for low performance		
Gait speed	≤0.8m/s	
SPPB		≤8-point score
TUG		≥20s
400m walk test	Non completion or ≥6 min for completion	

ASM=Appendicular skeletal muscle. SPPB=Short physical performance battery. TUG=timed up and go.

mortality.[1] This places a burden on the individual, their family, and the healthcare system. The economic burden associated with sarcopenia has been estimated to cost the UK £2.5 billion per annum.[5]

The effects of vitamin D on muscle health have been demonstrated as early as 1945 where athletes felt that ultraviolet exposure positively impacted on their athletic function.[6] This was found to be due to the participation of vitamin D in myogenesis, cell proliferation and differentiation, which is further supported by the isolation of a vitamin D receptor on muscle tissue.[7] Therefore, vitamin D has the potential to maintain and improve muscle mass, strength, and function. Furthermore, vitamin D deficiency results in many muscle related side effects including proximal muscle weakness, myalgia, and gait abnormalities.[8]

Vitamin D is a group of fat-soluble steroids which play an essential role in the homeostasis of calcium and phosphate by stimulating their absorption in the intestine.[9] It has an extensive range of established roles including in skeletal growth and development, modulating the immune system[10], preventing cardiovascular complications, and regulating insulin production.[11] Within the body vitamin D3, also termed cholecalciferol, is converted into the active form calcitriol (Figure S1). Vitamin D3 can be synthesised in the presence of ultra-violet-B light, or it can be provided from dietary intake of meat, fish, and dairy products. The physiological level of vitamin D in the body ranges from 30-80ng/ml.[12] The NHS[12] recommends a daily intake of 10µg (400 IU) which should not exceed 100µg/day (4000 IU/day). Low vitamin D levels are common in elderly, with 40% to 100% of non-hospitalised US and European elderly classified as vitamin D deficient (<20ng/ml) or insufficient (20-30ng/ml).[13] This may be due to inadequate dietary intake, sun exposure, or hydroxylation by the liver or kidneys.

As NICE[14] estimate the cost of vitamin D supplementation in over sixty-five-year-olds to cost £20.70 per year, vitamin D supplementation may be an easily accessible cost-effective public health intervention which may potentially stop the progression of, or reverse, sarcopenia. However, results of two previous meta-analyses which looked at the effect of vitamin D on muscle strength have been contradictory[15,16] and only one meta-analysis has been conducted looking at both muscle mass and muscle strength.[8] Furthermore, only two meta-analyses have looked at the effect of vitamin D supplementation on markers of muscle function[15,17] with no meta-analyses addressing all three components of sarcopenia. Therefore, it is difficult to conclude whether vitamin D supplementation influences muscle mass, strength, and function. In lite of this information, a systematic meta-analysis that would summarise the data from randomised controlled trials (RCT) assessing the effect of vitamin D on all three components of sarcopenia would be beneficial to public health. Thus, the main aim of this meta-analysis is to compare data from RCT performed on elderly people over the age of sixty to evaluate whether vitamin D supplementation has a significant effect on muscle mass, strength, and function. This will be determined by comparing the values for appendicular muscle mass (AMM), grip strength, and markers for muscle function before and after an interval of vitamin D supplementation to see if they improve.

2. METHODS

2.1. Data Sources and Search Technique

A comprehensive study search was conducted, without language restriction, to identify articles from the year 2003 onwards. The electronic databases Google Scholar, PubMed and the Cochrane library were searched using the following key words: Vitamin D, cholecalciferol, supplementation, muscle mass, elderly, muscle strength, muscle function, sarcopenia.

2.2. Study Selection

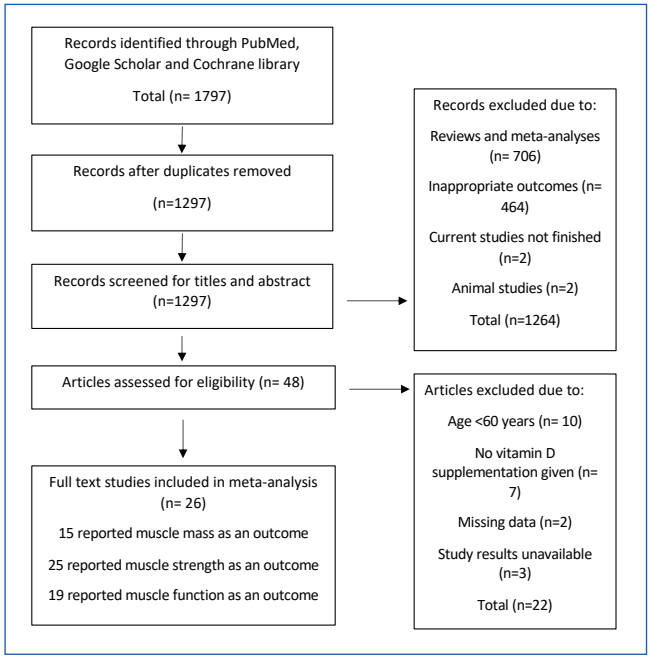
The inclusion and exclusion criteria used to select appropriate studies are outlined in Table 2. All

Table 2. Inclusion and exclusion criteria used to identify articles which generated data in the meta-analysis

Inclusion criteria	Exclusion criteria
• Randomised controlled trials • Humans aged sixty years and older (all male, all female, or a mixture) • Supplementation with vitamin D • Comparison with placebo or another standard treatment • Measures muscle mass and/or muscle strength and/or muscle function before and after intervention • Studies from year 2003 onwards	• Study on animals, or humans younger than sixty years old • Reviews or non-randomised trials • Studies that did not use a placebo or control group • Studies that look at vitamin D levels without giving supplementation • Studies conducted before the year 2003

methods of measurement of muscle mass, strength, and function were included in the study. Relevant studies were selected by screening abstracts as per the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Figure 1).

Figure 1. PRISMA flow chart of study selection
Fifteen out of twenty-six studies reported muscle mass, twenty-five out of twenty-six studies reported muscle strength, and nineteen out of twenty-six studies reported muscle function. Ten of these studies reported balance, nineteen studies reported gait speed and twelve studies reported chair stand tests as a measure of muscle function.



2.3. Data Extraction

The following information was extracted from articles identified for full review: authors, year of study, sample size, number of participants in intervention and placebo groups, intervention duration, units of vitamin D given, method of vitamin D, muscle mass, strength, and function measurements. Inclusion and exclusion criteria for the participants in each study selected were also extracted.

The number of participants in each study varied from 38 to 2694, with sixty-four percent of participants being female. The dose of vitamin D supplementation ranged from 100 IU/day to 1600 IU/day for a timeframe of 6 weeks to 18 months. The studies included were published between 2003 and 2019, with participants ranging from 60 to 90 years of age.

2.4. Measurement of Muscle Mass, Muscle Strength and Muscle Function

AMM was measured in fifteen studies. Sixty-seven percent of these studies used dual energy x-ray absorptiometry (DEXA) and the remaining third used bioelectrical impedance analysis (BIA). AMM was defined as the sum of lean mass in both arms and legs.

Muscle strength was measured via handgrip strength in nineteen out of twenty-five studies using a hydraulic hand dynamometer with the participant in a seated position. This was measured by one third of studies using the dominant hand only, and one third of studies using both hands. The remaining third did not report which hand was used. The maximum score of three measurements were reported by thirty percent of studies, the average score of two measurements were reported by thirty percent, and the remaining forty percent did not state the method of measurement. Knee extension was measured using an isokinetic dynamometer positioned at the ankle with the participant in a seated position in three out of twenty-five studies. The maximum value of three measurements was reported. The remaining three studies measured both handgrip strength and knee extension.

Muscle function was measured via short physical performance battery (SPPB) which consists of gait speed, chair stand, and balance tests. A score from 0 to 4 is given for each section, giving a maximum total of 12. A higher score indicates a higher level of physical performance.

2.5. Data Synthesis and Analysis

The meta-analysis was performed using the programme Review Manager (RevMan) 5.4.1. All outcomes in all studies were included in the analysis, using a random-effects model. The mean, standard deviation (*SD*), and number of participants in each study arm were used to calculate the standardised mean difference (SMD) with 95% confidence intervals (CI) for AMM, muscle strength and the three components of muscle function. The mean difference and 95% CI were reported in eight studies rather than the *SD* so could not be put into RevMan in their current form. The *SD* was calculated from the CI using the formula in Figure S2.[18] Further comparisons were made between studies to investigate whether participant age, the dose of vitamin D given, and the duration of treatment had any effect on these outcomes. Statistical analysis for heterogeneity included the chi^2 test for heterogeneity and the I^2 statistic to quantify the total variation attributed to heterogeneity across the studies involved. Outcomes were presented as forest plots.

2.6. Ethics

Ethical approval was not required as the published data consist of continuous or dichotomous data rather than raw data. Ethical considerations for the original trials are outlined below. All research involving human subjects must comply with the declaration of Helsinki[19] and any trials generating data from the composition of muscle must adhere to the human tissue act.[20]

Each trial requires evidence of informed consent for each participant.[21] This would involve providing a participant information sheet including adequate details of the study, what is required of the participant, and the risks and benefits of the study before obtaining consent. Participants should also be made aware that they can withdraw from the study at any time in order to respect autonomy. Data collected from participants should be protected via appropriate procedures for confidentiality and anonymisation to ensure accessing, obtaining, and storing data complies with data protection legislations.[22]

Each study will also need to consider how fair their research method is and ensure that no individual or group is being discriminated against. This is overcome by using double blind, randomised trials which ensures there is minimal bias in the group selection.

Furthermore, each study would need to consider safety. This involves ensuring the participants are fit to take part in the study and minimising any potential harm to the participants and researchers. In placebo-controlled trials it is vital to ensure no harm will come to individuals who are not receiving the intervention. If any harm is anticipated individuals in this group should receive a standard intervention in comparison to the treatment group.[20]

Cochrane's risk of bias tool for randomised trials[23] was used to assess the level of bias of each RCT. Nineteen trials were considered low risk overall due to being low risk in all categories. However, there were concerns of bias in seven studies due to missing outcome data (Table S1).

3. RESULTS

Twenty-six studies were investigated to determine if supplementation of vitamin D in the elderly had a significant impact on the three key components of sarcopenia: muscle mass, strength, and function. The comparisons made between studies included AMM via DEXA and BIA, muscle strength via handgrip strength and knee extension, and muscle function via a combination of balance, gait speed, and chair stand tests. Further comparisons were made between studies to investigate whether participant age, the dose of vitamin D given, and the duration of treatment had any effect on these outcomes.

3.1. Muscle Mass

Fifteen out of twenty-six RCT, including 1475 participants, reported AMM as an outcome measure. Results showed that vitamin D supplementation had a significant positive effect on AMM in the elderly (Figure 2A) with a SMD of 0.27 (95% CI 0.12-0.42; *P* <0.001). However, heterogeneity was also significant (Chi^2= 26.97; *P*=0.02; I^2=48%). Among these fifteen RCT, ten reported AMM via DEXA and five via BIA. Regarding the method of AMM measurement, results showed vitamin D supplementation had a significant positive effect on AMM when measured by DEXA (SMD 0.21; 95% CI 0.09-0.33; *P* <0.001) but no significant effect when measured by BIA (SMD 0.39; 95% CI -0.05-0.82; *P*=0.08).

3.2. Muscle Strength

Twenty-five studies, including 4562 participants, reported results on muscle strength. Meta-analysis of these twenty-five studies (Figure 2B) showed that vitamin D supplementation had a significant positive effect on muscle strength in the elderly (SMD 0.34; 95% CI -0.01-0.69; *P*=0.05). Results showed significant heterogeneity within these twenty-five studies (Chi^2=690.01; *P* <0.00001; I^2=97%).

3.3. Muscle Function

Muscle function was reported as a combination of balance (Figure 3A), gait speed (Figure 3B) and chair stand tests (Figure 3C). Ten studies reported balance, nineteen studies reported gait speed and twelve studies reported chair stand tests including 904, 3882 and 1646 participants respectively. Results showed vitamin D supplementation had no significant effect on any aspects of muscle function. No heterogeneity was found in the meta-analysis for balance (*p*=0.72). However, significant heterogeneity was found within the meta-analysis for gait speed (Chi^2=222.53; *P* <0.0001; I^2=92%) and chair stand tests (Chi^2=111.48; *P* <0.00001; I^2=90%).

3.4. Further Comparisons

Further comparisons were made (Table S2) between studies to estimate the effect size of participant age, the dose of vitamin D given, and the duration of treatment.

Supplementation of vitamin D in participants between the age of 60 and 69 years had a significant positive effect on both AMM (SMD 0.32, 95% CI 0.13–0.52; *P*=0.001) and muscle strength (SMD 0.51, 95% CI 0.22–0.79; *P*=0.0004) whereas supplementation in participants aged 70 and over had no significant effect on AMM (SMD 0.13, 95% CI -0.15–0.43; *P*=0.34) or muscle strength (SMD 0.29, 95% CI -0.52–1.10; *P*=0.49).

Results showed that supplementation of ≥1000 IU/day of vitamin D had a significant positive effect on AMM (SMD 0.60, 95% CI 0.16–1.04; *P*=0.008) but no significant effect on muscle strength (SMD 0.28, 95% CI -0.46–1.02; *P*=0.46). Supplementation of <1000 IU/day of vitamin D had a significant positive effect on AMM (SMD 0.16, 95% CI 0.02–0.30; *P*=0.03) and

significant effect on muscle strength (SMD 0.52, 95% CI 0.22–0.82; *P*=0.0006).

The duration of vitamin D supplementation ranged from 6 weeks to 18 months. Results showed that supplementation of vitamin D for ≥6 months had no significant effect on AMM (SMD 0.08, 95% CI -0.15–0.30; *P*=0.50) or muscle strength (SMD 0.41, 95% CI -0.09–0.91; *P*=0.11). However, when supplementation is given for <6 months, results showed a significant positive effect on AMM (SMD 0.37, 95% CI 0.18–0.56; *P*=0.0001) and muscle strength (SMD 0.46, 95% CI 0.12–0.80; *P*=0.008).

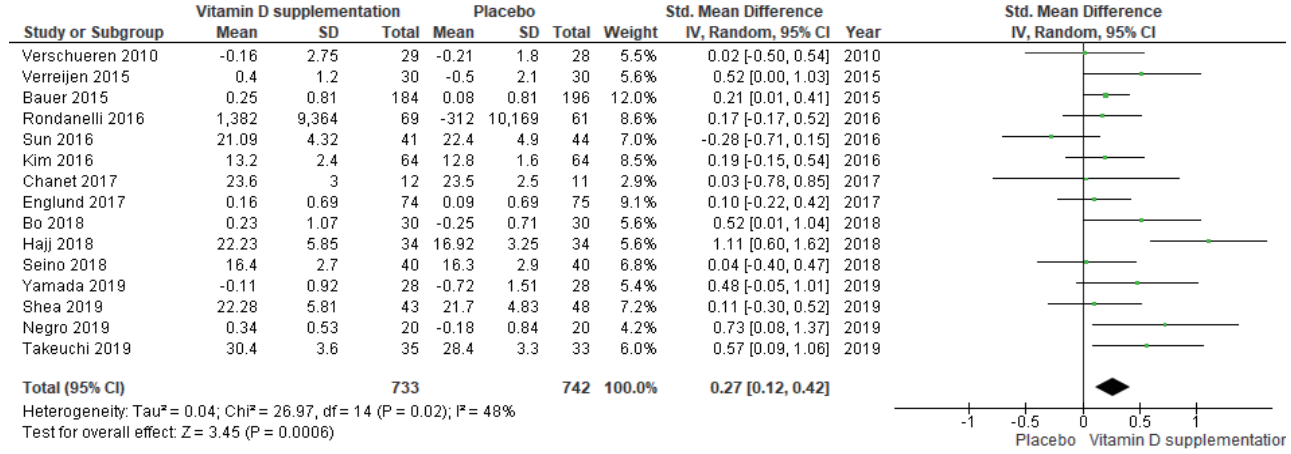
4. DISCUSSION

4.1. Principal Findings

The pooled results from 26 RCTs showed that 100–1600 IU of vitamin D in the elderly led to a statistically

Figure 2. Forest plots of summary standardised mean difference for (A) appendicular muscle mass, and (B) muscle strength.
This information is represented as a forest plot with the overall SMD represented as a diamond.
A- the overall SMD for AMM is 0.27 with 95% confidence intervals (CI) of 0.12-0.42. The outcome significantly favours vitamin D supplementation (*P* <0.001).
B- The overall SMD is 0.34 (95% CI -0.01–0.69). This significantly favours vitamin D supplementation (*P*=0.05).

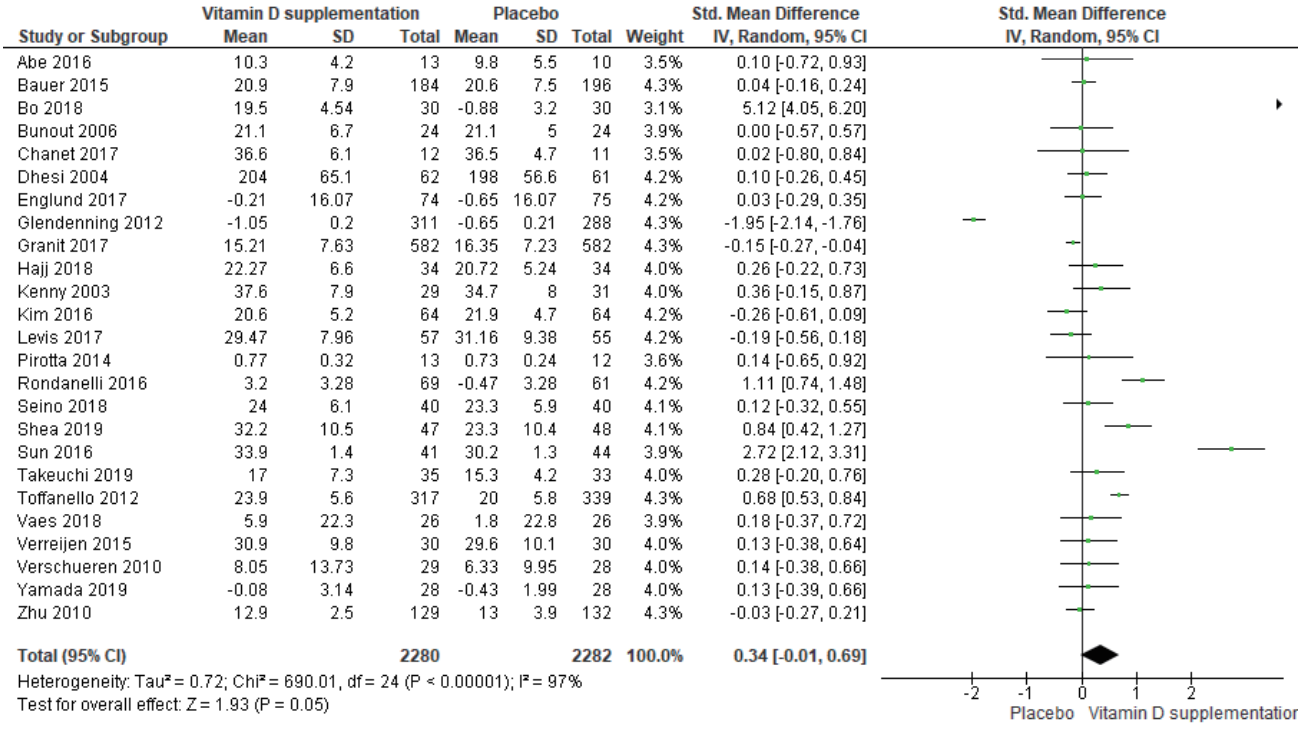
A)



Study or Subgroup	Vitamin D supplementation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Verschueren 2010	-0.16	2.75	29	-0.21	1.8	28	5.5%	0.02 [-0.50, 0.54]	2010
Verreijen 2015	0.4	1.2	30	-0.5	2.1	30	5.6%	0.52 [0.00, 1.03]	2015
Bauer 2015	0.25	0.81	184	0.08	0.81	196	12.0%	0.21 [0.01, 0.41]	2015
Rondanelli 2016	1,382	9,364	69	-312	10,169	61	8.6%	0.17 [-0.17, 0.52]	2016
Sun 2016	21.09	4.32	41	22.4	4.9	44	7.0%	-0.28 [-0.71, 0.15]	2016
Kim 2016	13.2	2.4	64	12.8	1.6	64	8.5%	0.19 [-0.15, 0.54]	2016
Chanet 2017	23.6	3	12	23.5	2.5	11	2.9%	0.03 [-0.78, 0.85]	2017
Englund 2017	0.16	0.69	74	0.09	0.69	75	9.1%	0.10 [-0.22, 0.42]	2017
Bo 2018	0.23	1.07	30	-0.25	0.71	30	5.6%	0.52 [0.01, 1.04]	2018
Hajj 2018	22.23	5.85	34	16.92	3.25	34	5.6%	1.11 [0.60, 1.62]	2018
Seino 2018	16.4	2.7	40	16.3	2.9	40	6.8%	0.04 [-0.40, 0.47]	2018
Yamada 2019	-0.11	0.92	28	-0.72	1.51	28	5.4%	0.48 [-0.05, 1.01]	2019
Shea 2019	22.28	5.81	43	21.7	4.83	48	7.2%	0.11 [-0.30, 0.52]	2019
Negro 2019	0.34	0.53	20	-0.18	0.84	20	4.2%	0.73 [0.08, 1.37]	2019
Takeuchi 2019	30.4	3.6	35	28.4	3.3	33	6.0%	0.57 [0.09, 1.06]	2019
Total (95% CI)			**733**			**742**	**100.0%**	**0.27 [0.12, 0.42]**	

Heterogeneity: Tau² = 0.04; Chi² = 26.97, df = 14 (P = 0.02); I² = 48%
Test for overall effect: Z = 3.45 (P = 0.0006)

B)



Study or Subgroup	Vitamin D supplementation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abe 2016	10.3	4.2	13	9.8	5.5	10	3.5%	0.10 [-0.72, 0.93]
Bauer 2015	20.9	7.9	184	20.6	7.5	196	4.3%	0.04 [-0.16, 0.24]
Bo 2018	19.5	4.54	30	-0.88	3.2	30	3.1%	5.12 [4.05, 6.20]
Bunout 2006	21.1	6.7	24	21.1	5	24	3.9%	0.00 [-0.57, 0.57]
Chanet 2017	36.6	6.1	12	36.5	4.7	11	3.5%	0.02 [-0.80, 0.84]
Dhesi 2004	204	65.1	62	198	56.6	61	4.2%	0.10 [-0.26, 0.45]
Englund 2017	-0.21	16.07	74	-0.65	16.07	75	4.2%	0.03 [-0.29, 0.35]
Glendenning 2012	-1.05	0.2	311	-0.65	0.21	288	4.3%	-1.95 [-2.14, -1.76]
Granit 2017	15.21	7.63	582	16.35	7.23	582	4.3%	-0.15 [-0.27, -0.04]
Hajj 2018	22.27	6.6	34	20.72	5.24	34	4.0%	0.26 [-0.22, 0.73]
Kenny 2003	37.6	7.9	29	34.7	8	31	4.0%	0.36 [-0.15, 0.87]
Kim 2016	20.6	5.2	64	21.9	4.7	64	4.2%	-0.26 [-0.61, 0.09]
Levis 2017	29.47	7.96	57	31.16	9.38	55	4.2%	-0.19 [-0.56, 0.18]
Pirotta 2014	0.77	0.32	13	0.73	0.24	12	3.6%	0.14 [-0.65, 0.92]
Rondanelli 2016	3.2	3.28	69	-0.47	3.28	61	4.2%	1.11 [0.74, 1.48]
Seino 2018	24	6.1	40	23.3	5.9	40	4.1%	0.12 [-0.32, 0.55]
Shea 2019	32.2	10.5	47	23.3	10.4	48	4.1%	0.84 [0.42, 1.27]
Sun 2016	33.9	1.4	41	30.2	1.3	44	3.9%	2.72 [2.12, 3.31]
Takeuchi 2019	17	7.3	35	15.3	4.2	33	4.0%	0.28 [-0.20, 0.76]
Toffanello 2012	23.9	5.6	317	20	5.8	339	4.3%	0.68 [0.53, 0.84]
Vaes 2018	5.9	22.3	26	1.8	22.8	26	3.9%	0.18 [-0.37, 0.72]
Verreijen 2015	30.9	9.8	30	29.6	10.1	30	4.0%	0.13 [-0.38, 0.64]
Verschueren 2010	8.05	13.73	29	6.33	9.95	28	4.0%	0.14 [-0.38, 0.66]
Yamada 2019	-0.08	3.14	28	-0.43	1.99	28	4.0%	0.13 [-0.39, 0.66]
Zhu 2010	12.9	2.5	129	13	3.9	132	4.3%	-0.03 [-0.27, 0.21]
Total (95% CI)			**2280**			**2282**	**100.0%**	**0.34 [-0.01, 0.69]**

Heterogeneity: Tau² = 0.72; Chi² = 690.01, df = 24 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.93 (P = 0.05)

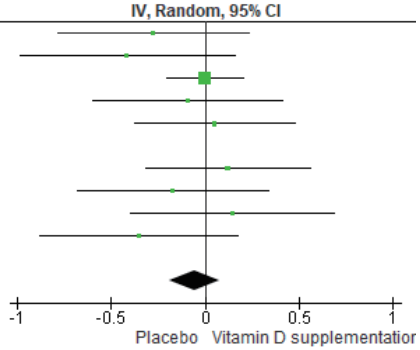
SD=standard deviation, Std=standardised, CI=confidence intervals.

Figure 3. Forest plots of summary standard mean difference for (A) balance, (B) gait speed and (C) chair stand tests
This information is also represented as a forest plot with the overall SMD represented as a diamond.
A- the overall SMD for balance is -0.06 with 95% confidence intervals (CI) of -0.19-0.08. The outcome favours placebo rather than vitamin D supplementation. However, this is not statistically significant (*P*=0.40).
B- The overall SMD for gait speed is 0.17 (95% CI -0.08–0.43). This favours vitamin D supplementation but is not statistically significant (*P*=0.18).
C- The SMD is 0.04 (95% CI -0.31–0.40). This result favours vitamin D supplementation but is not statistically significant (*P*=0.81)

A)

Study or Subgroup	Vitamin D supplementation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Kenny 2003	13.5	11.5	29	16.6	10.8	31	6.8%	-0.27 [-0.78, 0.23]	2003
Bunout 2006	137.2	32.9	24	153.9	45.2	24	5.3%	-0.42 [-0.99, 0.16]	2006
Bauer 2015	0	1	184	0	1	196	43.3%	0.00 [-0.20, 0.20]	2015
Verreijen 2015	0.04	0.1	30	0.05	0.11	30	6.8%	-0.09 [-0.60, 0.41]	2015
Sun 2016	3.96	0.16	41	3.95	0.22	44	9.7%	0.05 [-0.37, 0.48]	2016
Chanet 2017	4	0	12	3.8	0.4	11		Not estimable	2017
Seino 2018	5.5	1	40	5.4	0.6	40	9.1%	0.12 [-0.32, 0.56]	2018
Bo 2018	-1.36	2.43	30	-0.86	3.29	30	6.8%	-0.17 [-0.68, 0.34]	2018
Vaes 2018	1.06	0.14	26	1.04	0.13	26	5.9%	0.15 [-0.40, 0.69]	2018
Yamada 2019	-0.28	6.69	28	1.93	5.64	28	6.3%	-0.35 [-0.88, 0.18]	2019
Total (95% CI)			**444**			**460**	**100.0%**	**-0.06 [-0.19, 0.08]**	

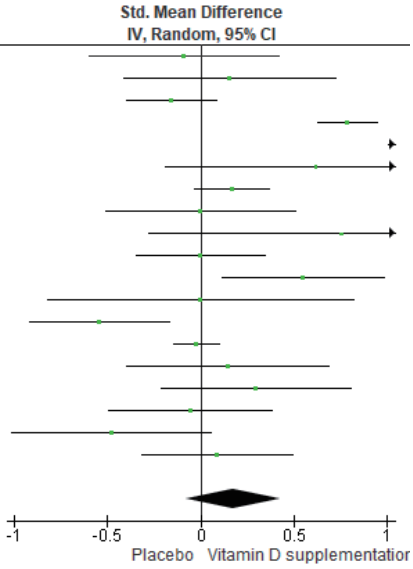
Heterogeneity: Tau² = 0.00; Chi² = 5.34, df = 8 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)



B)

Study or Subgroup	Vitamin D supplementation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Kenny 2003	10.9	2.6	29	11.3	5.7	31	5.1%	-0.09 [-0.59, 0.42]	2003
Bunout 2006	814.6	142.6	24	790.7	157.1	24	4.9%	0.16 [-0.41, 0.72]	2006
Zhu 2010	8.1	3.9	129	9	7	132	6.1%	-0.16 [-0.40, 0.09]	2010
Toffanello 2012	0.7	0.18	317	0.55	0.2	339	6.3%	0.79 [0.63, 0.95]	2012
Glendenning 2012	-0.02	0.08	325	-0.12	0.09	302	6.3%	1.18 [1.01, 1.35]	2012
Pirotta 2014	1.74	0.25	13	1.51	0.45	12	3.9%	0.62 [-0.19, 1.42]	2014
Bauer 2015	0.07	0.12	184	0.05	0.12	196	6.2%	0.17 [-0.04, 0.37]	2015
Verreijen 2015	0.11	0.25	30	0.11	0.21	30	5.1%	0.00 [-0.51, 0.51]	2015
Abe 2016	0.698	0.497	9	0.374	0.232	7	3.1%	0.76 [-0.28, 1.79]	2016
Kim 2016	1.2	0.2	64	1.2	0.2	64	5.8%	0.00 [-0.35, 0.35]	2016
Sun 2016	1.1	0.19	41	0.97	0.27	44	5.4%	0.55 [0.11, 0.98]	2016
Chanet 2017	1.1	0.2	12	1.1	0.2	11	3.8%	0.00 [-0.82, 0.82]	2017
Levis 2017	0.63	0.16	57	0.71	0.13	56	5.6%	-0.54 [-0.92, -0.17]	2017
Granit 2017	22.14	14.51	529	22.48	14.53	529	6.4%	-0.02 [-0.14, 0.10]	2017
Vaes 2018	-0.1	0.13	26	-0.12	0.14	26	5.0%	0.15 [-0.40, 0.69]	2018
Bo 2018	0.14	0.15	30	0.08	0.24	30	5.1%	0.30 [-0.21, 0.80]	2018
Seino 2018	1.37	0.2	40	1.38	0.17	40	5.4%	-0.05 [-0.49, 0.38]	2018
Yamada 2019	-0.64	1.64	28	0.2	1.81	28	5.0%	-0.48 [-1.01, 0.05]	2019
Shea 2019	4.28	1.61	46	4.16	1.04	48	5.5%	0.09 [-0.32, 0.49]	2019
Total (95% CI)			**1933**			**1949**	**100.0%**	**0.17 [-0.08, 0.43]**	

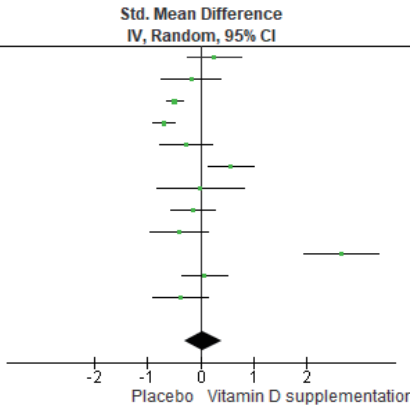
Heterogeneity: Tau² = 0.26; Chi² = 222.53, df = 18 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.34 (P = 0.18)



C)

Study or Subgroup	Vitamin D supplementation Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Kenny 2003	13.4	10.6	29	11.4	2	31	8.3%	0.26 [-0.25, 0.77]	2003
Bunout 2006	12	2.2	24	12.6	4.3	24	8.0%	-0.17 [-0.74, 0.39]	2006
Toffanello 2012	12.4	3.5	317	16.4	10.8	339	9.8%	-0.49 [-0.65, -0.34]	2012
Bauer 2015	-2.5	1.7	184	-1.2	2.05	196	9.6%	-0.69 [-0.89, -0.48]	2015
Verreijen 2015	-2.4	4	30	-1.4	3.1	30	8.3%	-0.28 [-0.78, 0.23]	2015
Sun 2016	3.46	0.71	41	3.17	0.14	44	8.7%	0.57 [0.14, 1.01]	2016
Chanet 2017	10.6	1.4	12	10.6	1.9	11	6.5%	0.00 [-0.82, 0.82]	2017
Levis 2017	14.27	3.92	41	14.82	3.92	45	8.7%	-0.14 [-0.56, 0.28]	2017
Vaes 2018	1	0.17	26	1.07	0.17	26	8.1%	-0.41 [-0.96, 0.14]	2018
Bo 2018	12.79	3.73	30	-1.21	6.28	30	7.2%	2.68 [1.97, 3.38]	2018
Seino 2018	6.1	1.5	40	6	1.1	40	8.7%	0.08 [-0.36, 0.51]	2018
Yamada 2019	-0.85	5.08	28	0.63	1.97	28	8.2%	-0.38 [-0.91, 0.15]	2019
Total (95% CI)			**802**			**844**	**100.0%**	**0.04 [-0.31, 0.40]**	

Heterogeneity: Tau² = 0.33; Chi² = 111.48, df = 11 (P < 0.00001); I² = 90%
Test for overall effect: Z = 0.24 (P = 0.81)



SD=standard deviation, Std=standardised, CI=confidence intervals.

significant improvement in muscle mass and a marginally significant improvement in muscle strength. There were no statistically significant effects on muscle function. A significant positive effect on muscle mass and strength was observed on participants aged 60-69 but there were no significant effects on participants aged ≥70. Although the increase in AMM was seen as significant with DEXA and non-significant with BIA, the confidence intervals for BIA are wider than for DEXA, hence less significant, which is likely due to a smaller sample size. As the estimates for AMM are similar there is no evidence of a difference between DEXA and BIA. These positive effects were especially observed with treatment duration <6 months. Results suggest dosing of vitamin D ≥1000 IU/day positively impacted AMM whereas <1000 IU/day positively impacted muscle strength. However, these results should be interpreted with caution as no interaction term was fitted in the sub-group analyses.

4.2. Comparison with Previous Studies

Previous meta-analyses looking at the effect of vitamin D supplementation on muscle strength are contradictory. Three studies[14,25,26] which also focused on the elderly population reported no significant effect of vitamin D supplementation on muscle strength. In comparison, three other studies[8,16,27] which looked at all age groups rather than concentrating on the elderly reported a significant increase in muscle strength in response to vitamin D supplementation. However, one of these studies[25] only found a significant effect when baseline serum vitamin D levels were <25nmol/l which classifies participants as vitamin D insufficient.[28] When summarising these results, it can be concluded that studies looking solely at the elderly population all reported no significant effect of vitamin D supplementation on muscle strength, whereas studies looking at participants of all ages reported a significant positive effect of vitamin D supplementation on muscle strength. Although the results of these previous studies contradict the significant positive effect of vitamin D on muscle strength found in this current analysis, when the studies included were analysed according to age, the results showed that adults aged 60-69 years had a significant increase in muscle strength whereas adults aged ≥70 years had no significant effect in response to vitamin D supplementation. Thus, these results support the idea that there may be a cut-off age above which the effects of vitamin D are reduced.

Only one previous meta-analysis has been conducted on the effect of vitamin D supplementation on AMM[8] which showed no significant effect. This contradicts the current finding that vitamin D supplementation significantly increases AMM despite both using DEXA as a measurement. However, this previous meta-analysis only contained six studies with 538 participants and included participants of all ages. This current study is the first to assess the benefits of vitamin D supplementation on AMM exclusively in the elderly population.

Muir and Montero-Odasso[15] reported that supplementation of vitamin D had no significant effect on two components of muscle function: balance and gait speed. This is further supported by Tarbizi et al[24] who also reported no significant effect of vitamin D supplementation on gait speed. These results are consistent with the results reported in this current analysis. However, these meta-analyses did not explore the effect of vitamin D supplementation on chair stand tests as a marker of muscle function. When vitamin D supplementation was paired with resistance exercise training significant improvements in all aspects of SPPB were seen[29] which were not seen with vitamin D supplementation alone. Furthermore, vitamin D supplementation in athletes resulted in a significant increase in muscle function whereas supplementation in non-athletes produced mixed results[30] suggesting vitamin D supplementation alone is insufficient to see significant improvements in muscle function.

4.3. Limitations

Significant heterogeneity was found in the meta-analyses for muscle mass, muscle strength and the gait speed and chair stand components of muscle function. This may be due to the number of studies included in the meta-analyses and the variability observed between supplementation protocols and procedures. However, this heterogeneity was presumed, and a random-effect model was applied. Furthermore, no dose-response effect was found within this meta-analysis. This is also likely due to the variability in supplementation protocols across the studies included.

There are limited studies published on the effects of vitamin D supplementation on muscle in the elderly. Only ten studies were included in the meta-analysis for balance, and only twelve studies were included in the meta-analysis for chair stand tests. These numbers are quite small and thus more good quality studies are required to determine the effect of vitamin D supplementation on muscle function.

Nineteen studies used gait sped as a measure of muscle function. Nine of these studies did not specify how the gait speed was measured, four of these studies used 4-meter walk, three of these studies used 5-meter walk, and the remaining three studies used 6-meter walk. This variability in method may have significantly affected the outcome and may contribute to the heterogeneity seen in the data.

All studies interpreted findings objectively using BIA, DEXA, handgrip strength, leg extension strength, or

SPPB. However, the values reported varied between the average score of two trials, the maximum score of three trials and the use of the dominant hand or both hands. This variability in reporting of data contributes to the heterogeneity seen between studies and thus a standardised measurement should be used to ensure the data are comparable.

Funnel plots for all outcomes showed little asymmetry, suggesting that there is no significant publication bias. For muscle strength and chair stand tests there is a study with extreme results (Bo et al, 2018), and removing this as a sensitivity analysis led to a statistically non-significant pooled estimate for both metrics. This extreme value is likely to be due to differences in population, intervention, or study quality rather than misreporting.

Finally, one person screened all article abstracts for full evaluation which could have introduced bias, and screening for bias identified five studies with a moderate risk due to missing outcome data which could contribute to variations in reporting. Therefore, this study could be improved by having articles screened by two independent evaluators and including a larger number of studies in the analysis.

4.4. Future Application

Based on the studies included in this meta-analysis, supplementation of vitamin D resulted in a significant increase in AMM and muscle strength and had no significant effect on all markers of muscle function in the elderly. These results may be of great public health interest due to the known association between low muscle mass and strength, functional impairment, increased morbidity, and mortality.[32,33]

Supplementation of vitamin D significantly increased AMM and muscle strength in individuals aged 60-69 but had no significant effect on individuals aged ≥70. Previous research[8,15,16,25] showed that vitamin D supplementation had no significant effect on muscle strength in the elderly but significantly improved muscle strength in the adult population. These results suggest that at a certain age, the effects of vitamin D supplementation on muscle are lost. This may be due to the natural decline in muscle with age[34,35] which at this cut-off value may become too significant to be compensated by vitamin D supplementation. Furthermore, with advancing age, the concentration of 7-dehydrocholesterol, the precursor of vitamin D3, declines in the epidermis[36] and the absorption of cholecalciferol from the gut also declines with age.[37] Therefore, these results may be influenced by an insensitivity to metabolising vitamin D with advancing age.

The results of this study showed that the increase in AMM and muscle strength were seen within the first six months of treatment. This may be due to there being more actin and myosin cross-bridges[38] as muscle mass increases, increasing the power that the muscle can generate, and therefore increasing muscle strength., However this suggests muscle mass and strength only increases to a certain extent above which supplementation makes no difference. Although this study showed no significant effect of vitamin D supplementation on muscle function, the maximum treatment duration was only eighteen months. Previous research[39,40] suggests greater muscle mass and strength are associated with improved physical function. Thus, perhaps a longer period of supplementation is required for these effects to be seen.

In addition to physical tests, previous research[41] has shown an inverse association between increased inflammatory markers and muscle strength. This paves the way for future research to evaluate the influence of molecular aspects such as inflammatory markers, growth factors, and serum vitamin D levels on muscle outcomes.

Further research is required to determine optimum parameters for supplementation such as dose, method of administration and treatment duration which optimises both AMM and muscle strength, in addition to confirming the age range in which maximum benefit of vitamin D supplementation is gained. Further studies with longer treatment durations and studies combining vitamin D supplementation with resistance exercise training are also required to determine if these factors have any effect on muscle function.

5. CONCLUSION

Results showed that vitamin D supplementation increased AMM and muscle strength but had no effect on all aspects of muscle function in the elderly population. This may lead to an improvement in mobility due to bulking and strengthening of the quadriceps muscles and thus a reduction in falls and fall related complications such as fractures, hospitalisation, and subsequent frailty in the elderly. These results suggest that vitamin D supplementation could have potential as a widely accessible cost-effective public health intervention for reducing muscle loss and thus sarcopenia. Therefore, vitamin D supplementation as a preventative of falls would provide a financial benefit and would increase quality of life of the elderly as it will reduce the psychological thoughts associated with falls such as anxiety as well as physical complications such as fractures. Thus, maintaining independence.

CONFLICTS OF INTEREST

There is no conflict of interest.

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