The Effects of Vitamin D on Skeletal Muscle Strength, Muscle Mass, and Muscle Power: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Context: There is growing evidence that vitamin D plays a role on several tissues including skeletal muscle.

Objective: The aim was to summarize with a meta-analysis, the effects of vitamin D supplementation on muscle function.

Data Sources: A systematic research of randomized controlled trials, performed between 1966 and January 2014 has been conducted on Medline, Cochrane Database of Systematics Reviews, Cochrane Central Register of Controlled and completed by a manual review of the literature and congressional abstracts.

Study Selection: All forms and doses of vitamin D supplementation, with or without calcium supplementation, compared with placebo or control were included. Out of the 225 potentially relevant articles, 30 randomized controlled trials involving 5615 individuals (mean age: 61.1 years) met the inclusion criteria.

Data Extraction: Data were extracted by two independent reviewers.

Data Synthesis: Results revealed a small but significant positive effect of vitamin D supplementation on global muscle strength with a standardized mean difference (SMD) of 0.17 ($P = .02$). No significant effect was found on muscle mass (SMD 0.058; $P = .52$) or muscle power (SMD 0.057; $P = .657$). Results on muscle strength were significantly more important with people who presented a 25-hydroxyvitamin D level <30 nmol/L. Supplementation seems also more effective on people aged 65 years or older compared to younger subjects (SMD 0.25; 95% CI 0.01 to 0.48 vs SMD 0.03; 95% CI -0.08 to 0.14).

Conclusions: Vitamin D supplementation has a small positive impact on muscle strength, but additional studies are needed to define optimal treatment modalities, including dose, mode of administration, and duration. **(*J Clin Endocrinol Metab* 99: 4336–4345, 2014)**

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Abbreviations: GRADE, grading of recommendations assessment development and evaluation; PRISMA, preferred reporting items for systematic reviews and meta-analysis; SMD, standardized mean difference.

Vitamin D, or calciferol, is a liposoluble prohormone available in two forms: vitamin D_2 and vitamin D_3. Many studies suggest that vitamin D is essential for bone health because of its role in the regulation of calcium and phosphate homeostasis (1). Currently, there is growing evidence that low serum concentration of 25-hydroxyvitamin D (25[OH]D) is also associated with many nonskeletal disorders, such as cardiovascular diseases, inflammation, infectious diseases, etc. (2). Moreover, vitamin D seems to play also a role on several tissues including skeletal muscle (3). Indeed, a recent review (4) developed four lines of evidence to support the role of vitamin D in muscle health. First, muscle manifestations, such as proximal muscle weakness, diffuse muscle pain, and gait impairments are defined to be well-known clinical symptoms of vitamin D deficiency (5–10). Second, a vitamin D receptor has been localized on muscle tissue (11). Third, several observational studies suggest a positive relationship between serum level of vitamin D and muscle function. Fourth, regarding the findings listed above, many researchers decided to investigate the effects of vitamin D supplementation on muscle function but results remains controversial. Consequently, two different meta-analyses that computed results of studies assessing the effects of vitamin D supplementation on muscle strength have been conducted in 2011. The first one (12), based on only three studies and focused only on people aged 65 and older, suggests that vitamin D supplementation could improve muscle strength. The second one (13), based on 12 studies and conducted on elderly subjects with baseline 25[OH]D concentration greater than 25 nmol/L, suggests no association between vitamin D supplementation and muscle strength. Because of the opposite results of these two meta-analyses, which focused only on specific groups of population and included a relatively restricted number of studies, it is difficult to conclude whether vitamin D supplementation has an effect on muscle strength for the global population. Moreover, muscle functions are not limited to muscle strength but comprises also muscle mass and muscle power and to date, no systematic review or comprehensive meta-analysis has addressed the role of supplementation of vitamin D on muscle mass and muscle power.

Vitamin D could be a simple and widely applicable public health intervention, especially in the field of musculoskeletal diseases. In view of the promising but inconclusive early results, a systematic meta-analysis that would summarize the results of randomized controlled trials assessing the effect of vitamin D supplementation on muscle function could be of a great public health interest. The main objective of this meta-analysis is therefore to compute results of randomized controlled studies performed on global population to assess the effect of vitamin D supplementation on muscle function, including muscle strength, muscle mass, and muscle power.

Materials and Methods

Search strategy

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (14), we conducted a detailed literature search in English to identify all studies performed between 1966 and January 2014 assessing the effects of vitamin D supplementation on the muscle function. The following electronic databases were searched: Medline, Cochrane Database of Systematics Reviews, and Cochrane Central Register of Controlled Trials. The search strategy and MeSH search terms used are detailed in Supplemental Appendix 1. Additional studies were identified by a manual search of bibliographic references of extracted articles and existing reviews, by contacting experts in the field and by a manual search in the gray literature including abstracts presented from 2011 to 2013 in major meetings of nutrition, geriatrics, and bone research.

Study selection

Two authors (C.B., F.B.) independently made an initial screening of the titles and abstracts. They subsequently examined the full texts of the articles remaining after the initial screening stage to determine whether the studies met the inclusion criteria. All differences of opinion regarding selection of articles were resolved through discussion and consensus. In both rounds of title/abstract and full text review, studies were included according to some specific inclusion criteria (Table 1).

Studies were excluded if they were reviews, trials that were not randomized, duplicated studies, animal studies, studies that did not use a placebo or a control group, or used vitamin D as part of a complex nutritional supplementation regimen.

Table 1. Inclusion Criteria

	Inclusion Criteria
Design	Randomized controlled studies
Language	English
Participants	Humans, no age restriction
Intervention	Supplementation of vitamin D (all doses and all forms), no length of follow-up restriction
Comparator	Placebo or another standard treatment. The control group must be comparable to the treated group with the exception of vitamin D supplementation
Measures	Measure of muscle strength, muscle mass or muscle power before and after intervention for both groups
Date	From 1966 to January 2014

Methodological quality assessment

We used the system developed by Jadad (15) to evaluate methodological quality. Two authors (C.B., F.B.) independently assessed the quality of trials. The Jadad score can range from 0 to 5. Studies were considered of excellent quality if their Jadad score reached 5, of good quality if their score was 3 or 4 and of poor quality if their score was 1 or 2.

Data extraction

Articles selected for full review had the following data extracted: authors, date of publication, country where the study was realized, sample size, number and percentage of female included, mean age, age range, and type of population, before and after serum concentration of 25[OH]D, percentage of the subjects that completed the study, length of intervention, details of the interventions for the control and treated groups, type of vitamin D supplementation, mode of administration, treatment adherence, physical measure, measurement techniques, and results.

Muscle strength was defined as the amount of force a muscle can produce and was measured by grip strength, quadriceps muscle strength, and leg extension strength. Muscle mass was defined as the total of body lean mass measured by dual energy x-ray absorptiometry. Finally, muscle power was defined as the maximum force that a muscle or muscle group can generate in a minimum amount of time and was measured by leg peak power.

We paid particular attention to missing data. In order to include a maximum of studies in our meta-analysis, we systematically contacted authors or coauthors when information was missing in the full-text paper.

When the same study reported multi-measures of muscle strength, we deliberately chose to report, in the meta-analysis, only one of these results. We reported, in priority, the result of grip strength, if available, followed by the result of quadriceps strength, and finally, the result of the leg extension strength. Moreover, when one study managed three different groups to assess the difference between a placebo and two doses of vitamin D, we inserted arbitrary in the meta-analysis, the results of the group supplemented with the higher dose of vitamin D.

Grading of recommendations assessment development and evaluation (GRADE) was used to assess the quality of the evidence. The strength of the evidence for each outcome measurement was classed into one of four categories: high, moderate, low, and very low (16).

Statistical analysis

To provide a comparison between outcomes reported by the different studies, effect size as standardized mean difference (SMD) with 95% CIs was assessed for each outcome.

Regarding the supplementation protocols heterogeneity, since participant demographics and clinical settings differed greatly between studies, we assumed the presence of heterogeneity a priori, and we used random effects models (17). Results were examined for heterogeneity using Cochran's Q statistic and the I^2 statistic was used to quantify total variation across studies attributed to heterogeneity rather than sampling error (18).

Five meta-regressions were performed on baseline 25[OH]D levels, which changed during the study, age, length of study, and vitamin D dose to assess the effects of these different variables on the treatment effect. For doses-analyses, we excluded studies with intramuscular (IM) supplementation, with a direct supplementation of an active form of vitamin D (Alfacalcidol, 1·25 dihydroxyvitamin D) or with vitamin D_2.

Subgroup analyses were prespecified to assess whether the treatment effect was modified by one or more of eight different clinical characteristics (baseline 25[OH]D concentration, clinical settings, age, supplementation action, sex, length of intervention, dose of supplementation, study quality). A test of interaction was done on all subgroups to establish if the difference in effect size between subgroups was statistically significant.

Potential publication bias was explored by means of a funnel plot. We used the Begg's adjusted rank correlation test and the Egger's regression asymmetry test to detect publication bias.

For all results, a two-sided p value of 0.05 or less was considered as significant. All analyses were performed using the software package Comprehensive Meta Analysis, Biostat v2.

Results

Study characteristics

A total of 225 records were found in our initial search, restricted to 222 after removing duplicate studies. During the titles and abstracts screening stage, 165 of them were excluded. During the full-text review, 11 studies were identified as presenting incomplete or missing data. We contacted the authors of those studies and obtained the required data for nine of them. Consequently, during the full-text articles reviews, we excluded only two studies for incomplete data, instead of nine. After the full-text review, a total of 30 randomized controlled trials remained (Figure 1) (19–48). Out of them, 29 trials reported muscle strength as outcome (19–39, 41–48), six trials reported muscle mass as outcome (23, 24, 27, 38, 40, 47), and five reported muscle power as outcome (19, 24, 34, 36, 46).

Characteristics of the 30 studies are presented in Table 2. Out of those 30 randomized controlled trials involving 5615 participants, 72% were women and the mean age of the subjects was 61.1 (range: 10–99 years). Vitamin D_3 was used in 22 studies (19–25, 27–29, 31, 33–41, 43, 47) and vitamin D_2 in four studies (26, 42, 46, 48). Alfacalcidol was used as supplementation in three studies (32, 44, 45) and 1.25 dihydroxyvitamin D in one other (30). In 14 different studies (19, 25–27, 29, 30, 33, 37, 39, 42, 43, 45–47), participants received vitamin D-only supplementation, whereas in the 16 other trials (20–23, 28, 31, 32, 34–36, 38, 40, 41, 44, 48), they received combined vitamin D and calcium supplementation.

Only one study supplemented the participants with an IM injection (26). All other studies used an oral supplementation. Treatment duration lasted from 1 to 60 months.

Regarding the study quality assessment, a median score of 4 out of 5 points (P25 3; P75 5; mean 3.9 points) on the Jadad scale was found, reflecting that the studies were overall of good quality shown in Supplemental Table 5.

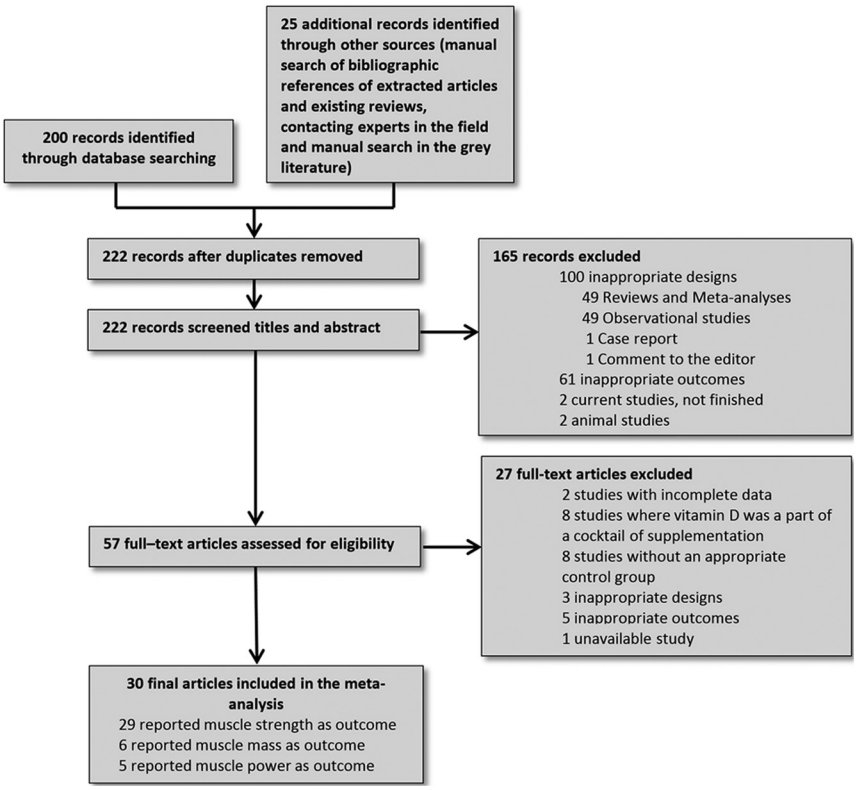


Figure 1. Flowchart of literature search.

Muscle strength

Out of the 30 randomized controlled trials, 29 involving 5533 subjects, reported muscle strength measures. Results show that vitamin D supplementation has a small, but significantly positive effect on global muscle strength with a SMD of 0.17 (95% CI 0.03–0.31; $P = .02$) (Figure 2A). We note, however, that heterogeneity is significant (Q-value = 125.4; $P < .001$; I^2 77.7%). Among the 29 randomized controlled trials, 16 studies reported grip strength results (21–23, 27–31, 34–37, 46, 47) and 19 studies reported lower limb muscle strength results (19–21, 23–26, 30, 31, 33, 34, 36, 38, 39, 41, 44–46, 48). Regarding the individual type of strength, results show no significant effect of vitamin D supplementation on grip strength (SMD 0.01; 95% CI −0.06 to 0.07; $P = .87$), but a significant positive effect on lower limb muscle strength (SMD 0.19; 95% CI 0.05–0.34; $P = .01$).

Subgroup analyses

Table 3 summarizes results of subgroups analyses. Supplementation of people who presented a 25[OH]D level < 30 nmol/L resulted in a significant higher improvement of their muscle strength compared to those who presented a 25[OH]D level ≥ 30 nmol/L ($P = .02$). Moreover, we also found higher SMDs for people who demonstrated an increase of their 25[OH]D concentration of at least 25 nmol/L within the duration of the study. This observation was confirmed by a meta-regression showing a significant association between changes in 25[OH]D concentration and changes in muscle strength [slope 95% CI = 0.01 (0.00; 0.01); $P = .01$] (Supplemental Figure 3. We note that, in subgroups analyses, we only found a significant intergroup difference for people who presented a change of their 25[OH]D concentration of more than 50 nmol/L within the duration of the study compared to others ($P < .01$).

Vitamin D supplementation of people aged 65 years or older resulted in a significant improvement of muscle strength (SMD 0.25; 95% CI 0.01–0.48), whereas supplementation of younger people did not (SMD 0.03; 95% CI −0.08 to 0.14). Intergroup difference is, however, insignificant ($P = .13$). In line with these results, we found that people institutionalized or hospitalized presented a greater standardized mean difference compared to community-dwellers (SMD 0.45 vs 0.05; $P < .01$). We also found that studies with a methodological quality above 4 points resulted in a significant improvement of muscle strength with an SMD of 0.22 (95% CI 0.03–0.41), whereas studies of lower quality did not (SMD 0.07; 95% CI −0.13 to 0.26).

Except for an apparent greater effect of vitamin D supplementation on muscle strength for only-women and only-men studies compared to mixed studies, we did not find any other significant difference between analyzed subgroups.

Muscle mass

Regarding the muscle mass, six studies have been included in the meta-analysis (23, 24, 27, 38, 40, 47) (Figure 2B).

The pooled SMD for vitamin D supplementation on muscle mass is 0.058 ($P = .52$) suggesting that vitamin D has no significant effect on muscle mass. Heterogeneity is not significant ($P = .395$).

Muscle power

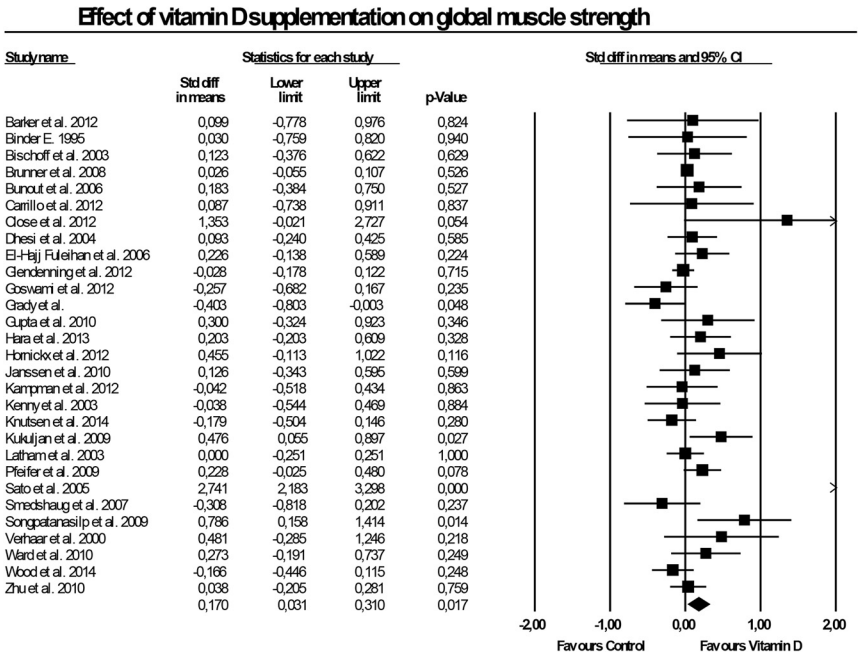
Five studies reported results on muscle power (19, 24, 34, 36, 46). The meta-analysis of these five studies does not show a significant result of vitamin D supplementation on muscle power (Figure 2C). No heterogeneity has been found in this meta-analysis ($P = .94$).

Table 2. Study and Participants Characteristics

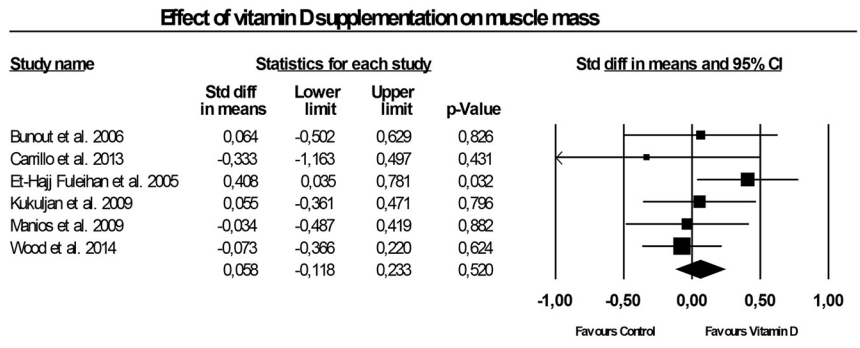
Study, Year	N (women, %)	Participants	Mean Age (y)	Baseline 25[OH]D (nmol/L)	Study Duration (months)	Supplementation	Type of Vitamin D	Dose of Vitamin D (IU)	Outcome	25[OH]D after Treatment (nmol/liter)	Trial Quality[a]
Barker 2012 (19)	20 (50)	Active males and females	28.6 (18–45)	80.4	1	Vit D only	D_3	4000 IU/day	Strength Power	126.3	3
Binder 1995 (20)	25 (36)	Institutionalized	87.9 (NR)	56.8	2	Vit D + Ca	D_3	100000 IU once + 50 000 IU/week	Strength	81.6	2
Bischoff 2003 (21)	62 (100)	Geriatric care	85.3 (63–99)	29.8	3	Vit D + Ca	D_3	800 IU/day	Strength	65.4	5
Brunner 2008 (22)	2364 (100)	Postmenopausal women	62.4 (50–79)	NR	60	Vit D + Ca	D_3	400 IU/day	Strength	NR	4
Bunout 2006 (23)	48 (90)	Community-dwelling	77 (≥70)	31.8	9	Vit D + Ca	D_3	400 IU/day	Strength Mass	64.4	5
Carrillo 2013 (24)	23 (52)	Overweight and obese adults	26.1	48.2	3	Vit D + Ca	D_3	4000 IU/day	Strength Mass Power	83.4	3
Close 2012 (25)	10 (0)	Healthy adults	NR	NR	2	Vit D only	D_3	5000 IU/day	Strength	NR	4
Dhesi 2004 (26)	139 (78)	Ambulatory fallers	76.8 (≥65)	25.8	6	Vit D only	D_2	600000 IU once	Strength	43.7	5
El-Hajj Fuleihan 2006 (27)	117 (100)	Healthy children and adolescents	13.3 (10–17)	34.9	12	Vit D only	D_3	2000 IU/day	Strength Mass	94.8	5
Glendenning 2012 (28)	686 (100)	Older postmenopausal women	76.7 (>70)	NR	3	Vit D + Ca	D_3	150000/3 months	Strength	NR	3
Goswami 2012 (29)	86 (100)	Young Asian students	21.8 (NR)	23.2	6	Vit D only	D_3	60000/week during 6 weeks + 60000 twice/month during 4 months	Strength	74.63	5
Grady 1991 (30)	98 (54)	Community-dwelling	79.1 (70–97)	62.9	66	Vit D only	1·25[OH]$_2$D		Strength	NR	3
Gupta 2010 (31)	40 (40)	Healthy volunteers	31.55 (20–40)	23.2	6	Vit D + Ca	D_3	60000 IU/week (8 weeks) + 60000 IU/months (4 months)	Strength	56	4
Hara 2013 (32)	94 (100)	Postmenopausal osteoporotic women	67.7 (55–75)	45.7	4	Vit D + Ca	1-hydroxycholecalciferol	1 μg/day	Strength	NR	3
Hornikx 2010 (33)	49 (24)	COPD patients	68 (≥50)	42.4	3	Vit D only	D_3	100000 IU/month	Strength	127.3	3
Janssen 2010 (34)	70 (100)	Geriatric care	80.8 (≥65)	34.4	6	Vit D + Ca	D_3	400 IU/day	Strength Power	77.2	4
Kampman 2012 (35)	68 (71)	Multiple sclerosis ambulatory patients	40.5 (18–50)	56.4	22	Vit D + Ca	D_3	20000 IU/week	Strength	123.2	5
Kenny 2003 (36)	60 (0)	Community-dwelling	76.5 (65–87)	62.4	6	Vit D + Ca	D_3	1000 IU/day	Strength Power	87.1	5
Knutsen 2014 (37)	146 (75)	Healthy immigrants	37.5 (18–50)	27	4	Vit D only	D_3	1000 IU/day	Strength	52	5
Kukuljan 2009 (38)	89 (0)	Community-dwelling	61 (50–79)	80.6	18	Vit D + Ca	D_3	800 IU/day	Strength Mass	NR	2
Latham 2003 (39)	243 (53)	Geriatric care	79.5 (77–81)	42.4	6	Vit D only	D_3	300000 IU once	Strength	59.9	5
Manios 2009 (40)	82 (100)	Postmenopausal women	61.3 (55–65)	NR	12	Vit D + Ca	D_3	300 IU/day	Mass	NR	2
Pfeifer 2009 (41)	242 (74.5)	Community-dwelling	76.5 (70–94)	54.5	20	Vit D + Ca	D_3	800 IU/day	Strength	84	4
Sato 2005 (42)	96 (100)	Women after stroke	74.1 (NR)	24.5	24	Vit D only	D_2	1000 IU/day	Strength	83.4	5
Smedshaug 2007 (43)	60 (65)	Institutionalized	82.4 (NR)	46.6	12	Vlt D only	D_3	400 IU/day	Strength	70.4	3
Songpatanasilp 2009 (44)	42 (100)	Postmenopausal women	70.7 (65–84)	24.3	3	Vit D + Ca	1-hydroxycholecalciferol		Strength	NR	5
Verhaar 2000 (45)	27 (100)	Geriatric care	75.7 (≤70)	18.2	6	Vit D only	1-hydroxycholecalciferol		Strength	27.8	1
Ward 2010 (46)	72 (100)	Healthy children and adolescents	13.8 (12–14)	18.0	12	Vit D only	D_2	150000 IU/3 months	Strength Power	56	5
Wood 2014 (47)	196 (100)	Postmenopausal women	63.8 (60–70)	33.8	12	Vit D only	D_3	1000IU/day	Strength Mass	75.7	4
Zhu 2010 (48)	261 (100)	Community-dwelling	76.9 (70–90)	44.7	12	Vit D + Ca	D_2	1000 IU/day	Strength	60	5

Abbreviation: NR, not reported.

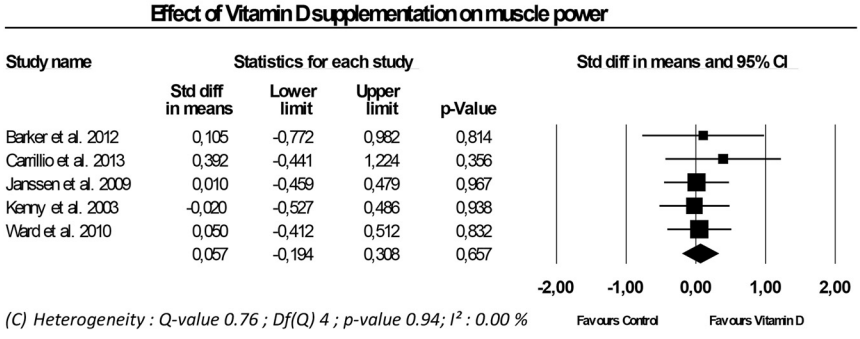
[a] Quality evaluation was conducted using Jadad criteria.



(A) Heterogeneity : Q-value 125.37 ; Df(Q) 28 ; p-value 0.001; I^2 : 77.67



(B) Heterogeneity : Q-value 5.17 ; Df(Q) 5 ; p-value 0.39; I^2 : 3.34



(C) Heterogeneity : Q-value 0.76 ; Df(Q) 4 ; p-value 0.94; I^2 : 0.00 %

Figure 2. Effect of vitamin D supplementation on global muscle strength (A), muscle mass (B), and muscle power (C). (A) Heterogeneity: Q-value 125.37; Df(Q) 28; *P*-value .001; I^2: 77.67. (B) Heterogeneity: Q-value 5.17; Df(Q) 5; *P*-value .39; I^2 3.34. (C) Heterogeneity: Q-value 0.76; Df(Q) 4; *P*-value .94; I^2 0.00%

GRADE analysis

Our GRADE analysis showed a moderate evidence quality for muscle strength. The main reason for the reduced level of evidence is the small sample size in some studies and the presence of heterogeneity in this meta-analysis. Regarding muscle mass and muscle power, our GRADE analysis showed a low level of evidence. This is mainly due to the restricted number of studies included in this meta-analysis, but also to the small number of subjects in some of these studies. Future researches on muscle strength, muscle mass, and muscle power are likely to have an important impact on our confidence in the estimate of effect and are likely to change this estimate (Table 4).

Discussion

Principal findings

The aim of this meta-analysis was to assess the effect of vitamin D supplementation on muscle function. Pooled results from the 29 identified randomized controlled trials have shown a small but positive significant effect of vitamin D supplementation on muscle strength. These results could be of a great public health interest because of the well-known correlation between, on the one hand, low muscle strength, and, on the other hand, functional impairments (49, 50), affected quality of life (QOL) (51) and mortality (52).

Positive effects on muscle strength are especially observed on lower limb muscles. These results are interesting insofar they can explain the significant effect of vitamin D on falls observed in three different meta-analyses (53–55). Indeed, quadriceps strength is recognized to be a significant predictor of incident falls (56).

Concerning muscle mass and muscle power, no significant effect of vitamin D was found. However, only six studies for muscle mass and five studies for muscle power with a total of only 538 and 245 subjects have been included, respectively, in the meta-analysis on muscle mass and muscle power. Given this small number of included studies, results must be interpreted with caution. Sufficient good quality studies are lacking to enable a clear assessment of the impact of vitamin D on muscle mass and muscle power.

Table 3. Subgroups Analyses

	Subtotal (n)	Number of Studies	SMD (95% CI)	*P* Value
Serum 25(OH)D concentration				
<30 nmol/L	710	9	0.47 (−0.07; 1.01)	.02
≥30 nmol/L	1763	17	0.06 (−0.05; 0.16)	
Clinical settings				
Community-dwelling	4901	21	0.05 (−0.04; 0.15)	<.01
Institutionalized or hospitalized	632	8	0.45 (−0.16; 1.07)	
Age				
<65 y	3221	11	0.03 (−0.08; 0.145)	.13
≥65 y	2302	17	0.25 (0.01; 0.48)	
Supplementation				
Vitamin D alone	1359	14	0.06 (−0.01; 0.13)	.7
Vitamin D + calcium	4174	15	0.25 (−0.08; 0.59)	
Sex				
Women only	4173	13	0.29 (0.01; 0.05)	.21
Men and women	1201	13	0.02 (−0.10; 0.15)	
Men only	159	3	0.38 (−0.17; 0.93)	
Length of intervention				
<26 weeks	1157	10	0.13 (−0.06; 0.33)	.72
≥26 weeks	4376	19	0.17 (−0.01; 0.36)	
Dose of supplementation				
<1600 IU/day	3337	10	0.04 (−0.08; 0.15)	.90
≥1600 IU/day	1367	11	0.02 (−0.08; 0.13)	
Change of 25(OH)D concentration				
<25 nmol/L	904	8	0.06 (−0.07; 0.20)	.23
≥25 nmol/L	1335	15	0.27 (−0.04; 0.57)	
<50 nmol/liter	1783	17	0.06 (−0.04; 0.15)	<.01
≥50 nmol/L	456	6	0.56 (−0.24; 1.36)	
Quality of studies				
<4 points	1171	10	0.07 (−0.13; 0.26)	.42
≥4 points	4362	19	0.22 (0.03; 0.41)	

Comparison with previous studies

Our findings can be compared to results of the meta-analyses of Stockton et al (13) and Muir et al (12), but several methodological differences between their meta-analyses and ours can be observed. We have found a larger number of studies, thus provided a bigger sample and hence more representative results. Indeed, when data were missing in the paper, we systematically contacted authors or coauthors of the paper to obtain these data, which enabled us to include 30 studies in our meta-analysis, instead of 3 for Muir et al (12) and 12 for Stockton et al (13). Contrary to Stockton et al (13), we also decided to exclude studies that used vitamin D as part of a complex nutritional supplementation regimen because of the impossibility to report only effects of vitamin D. Moreover, unlike these two authors, when a study presented results of two different measurements of muscle strength, we decided to report only one of these results to avoid an artificial increase of the statistical power in the meta-analysis.

Regarding subgroup analyses, like Stockton et al (13), we have found a possibly greater effect of vitamin D supplementation in subjects with a baseline 25[OH]D level below 30 nmol/L.

Although for bone health, vitamin D seems more efficient when combined with calcium, we have found no significant difference between a simple supplementation of vitamin D and a supplementation of vitamin D combined with calcium. The role of calcium on muscle func-

Table 4. Evidence Quality and Recommendation Grade

Outcome	No. of Studies	Study Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Evidence Quality
Muscle strength	29	RCT	Not serious	Serious[a]	Serious[b]	Not serious	Not assessed[c]	Moderate
Muscle mass	6	RCT	Not serious	Not serious	Serious[b]	Not serious	Not assessed[c]	Low
Muscle power	5	RCT	Not serious	Not serious	Serious[b]	Not serious	Not assessed[c]	Low

[a] A significant heterogeneity was observed in this meta-analysis. [b] Wide confidence intervals around the estimate of the effect were observed for most studies. [C] Not assessed because of methodological issues (high heterogeneity observed in the meta-analysis on muscle strength and limited number of studies included in the meta-analyses on muscle mass and muscle power).

tion is yet not clear but this result does not seem to suggest an additional effect of calcium on muscle strength.

Regarding the age subgroup, we suggest a possible better effect on subjects aged 65 years or older. Moreover, effect on muscle strength seems also more important in frail people compared to community-dwelling people. These results could be an incentive to perform interventional studies with vitamin D in the field of older people's musculoskeletal diseases, such as sarcopenia.

Strength and limitations

We have used the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (14) to perform our research, to ensure as much as possible, a good quality to our research. Thanks to a rigorous research of published and unpublished studies, and thanks to the contact we have made with authors or co-authors when information was missing in the full-text paper, we have included a higher number of studies in our meta-analysis than other authors (12, 13). We have defined clear inclusion criteria and have carefully ensured that the treated group was strictly comparable to the control group, with the exception of vitamin D supplementation. The 30 randomized controlled trials identified with this method and included in the meta-analysis showed a median score of quality of 4 out of 5 points, reflecting a high methodological quality.

Our study has also some limitations. Despite our efforts to include all potentially interesting studies in our meta-analysis, we have been obliged to exclude two studies because their authors did not answer our request for more information. Even if it is not the case for the meta-analysis on muscle mass and muscle power, we found a significant heterogeneity in the meta-analysis on muscle strength. This could be explained by the large number of studies included in the meta-analysis and by the variability observed between the different protocols of supplementation. However, we have presumed this heterogeneity in the statistical methodology and used a random effect model in our analyses. We also regret to be unable to find any dose effect in this meta-analysis but this is probably due, once again, to the variability of the different protocols of supplementation across studies. To avoid an artificial increase of the statistical power in the meta-analysis, we have arbitrary chosen to report only the result of the group supplemented with the higher dose of vitamin D. This choice was however not determinative in view of the nonsignificant results of the dose-effect meta-regression. Regarding the study quality assessment, we have to acknowledge that, despite its large use, the Jadad score is not perfect and that another quality scale could have been used. Moreover, because of the limited number of studies included in the meta-analyses on muscle mass and muscle power and because of the high heterogeneity observed in the meta-analysis on muscle strength, we were unable to measure the potential publication bias by the Begg's adjusted rank correlation and the Egger's regression asymmetry tests (57). Finally, only six studies were included in the muscle mass analysis and five in the muscle power analysis. This number is quite small and more good quality studies are needed to make a clear statement about the effect of vitamin D supplementation on these variables.

Conclusion

Based on the studies included in this meta-analysis, vitamin D supplementation has a small, but positive, impact on global muscle strength, more specifically on the lower limb. These results could have a positive public health interest, especially in the field of musculoskeletal diseases. However, no impact was found on muscle mass and muscle power. Our meta-analysis suggests that vitamin D could improve muscle strength, but additional studies are needed to define optimal treatment modalities, including dose, mode of administration, and duration.

Take-home points: This systematic review and meta-analysis summarizes results from 30 randomized controlled trials assessing effect of vitamin D supplementation on muscle function on the general population providing the most comprehensive synthesis on this issue so far. Vitamin D supplementation has a small, but significant positive effect on global muscle strength, but no effect on muscle mass and muscle power. The effects may be more important with people presenting a baseline 25[OH]D concentration lower than 30 nmol/L, with people institutionalized or hospitalized and with people aged 65 years or older.

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