ORIGINAL ARTICLE

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Vitamin D and Muscle Health: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials

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ABSTRACT

The objective of this study was to investigate the effects of vitamin D supplementation versus placebo on muscle health. For this systematic review and trial-level meta-analysis of placebo-controlled trials, a systematic search of randomized controlled trials published until October 2020 was performed in Medline, Embase, and Google Scholar. We included studies in humans (except athletes) on supplementation with vitamin D2 or D3 versus placebo, regardless of administration form (daily, bolus, and duration) with or without calcium co-supplementation. The predefined endpoints were physical performance reported as timed up and go test (TUG; seconds), chair rising test (seconds), 6-minute walking distance (m), and Short Physical Performance Battery (SPPB; points). Furthermore, endpoints were maximum muscle strength (Newton) measured at handgrip, elbow flexion, elbow extension, knee flexion, and knee extension, as well as muscle (lean tissue) mass (kg). Falls were not included in the analysis. Cochrane Review Manager (version 5.4.1.) calculating mean difference (MD) using a random effect model was used. In total, 54 randomized controlled trials involving 8747 individuals were included. Vitamin D versus placebo was associated with a significantly longer time spent performing the TUG (MD 0.15 [95% confidence interval (CI) 0.03 to 0.26] seconds, $N = 19$ studies, $I^2 = 0\%$, $n = 5223$ participants) and a significant lower maximum knee flexion strength (MD −3.3 [−6.63 to −0.03] Newton, $N = 12$ studies, $I^2 = 0\%$, $n = 765$ participants). Total score in the SPPB showed a tendency toward worsening in response to vitamin D compared with placebo (MD −0.18 [−0.37 to 0.01] points, $N = 8$ studies, $I^2 = 0\%$, $n = 856$ participants). Other measures of muscle health did not show between-group differences. In subgroup analyses, including studies with low vitamin D levels, effects of vitamin D supplementation did not differ from placebo. Available evidence does not support a beneficial effect of vitamin D supplementation on muscle health. Vitamin D may have adverse effects on muscle health, which needs to be considered when recommending vitamin D supplementation. © 2021 American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: CLINICAL TRIAL; DXA; NUTRITION; SKELETAL MUSCLE; VITAMIN D

Introduction

Proximal muscle weakness and hypotonia are well-described symptoms accompanying rickets/osteomalacia.[1] Since 1922, when a healing effect of sun exposure on rickets was first described, vitamin D and muscle health has been associated.[2-4] Since the 1980s, when assays of 25-hydroxyvitamin D (25(OH)D) was developed as a marker of vitamin D status, multiple observational studies have supported the hypothesis of an inverse association between vitamin D status and muscle health.[5,6] Based on mainly observational data, it has literally been inscribed in existing medical guidelines that vitamin D improves muscle function in conditions with suboptimal vitamin D levels.[7,8]

However, randomized clinical trials (RCTs) have reported more ambiguous results, including both beneficial[9-12] and harmful effects.[13-16] Findings from RCTs have been summarized in a several meta-analyses (MA). Importantly, two of the trials reporting beneficial effects of vitamin D in patients with very low baseline 25(OH)D levels[17,18] were retracted in 2015 and 2017 as data turned out to be prefabricated.[19,20] MA of RCTs in non-athletes including the retracted data[21-24] have reported significant beneficial effects of vitamin D on muscle strength, either overall[23,24] or in subgroup analyses of those with low p-25(OH)D levels,[21,22] while all MA published after the retraction of the above-mentioned studies have shown neutral[25,26] or even harmful[27] effects of vitamin D supplementation.

So far, no published MA have reported summary estimates based on findings from only placebo-controlled RCTs with vitamin D (D3 or D2). No MA include summary estimates on frequently reported outcomes in terms of knee flexion, knee extension, elbow flexion, elbow extension, Short Physical Performance Battery (SPPB), chair rising test (CRT), and 6-minute

Received in original form March 30, 2021; revised form June 29, 2021; accepted July 4, 2021.
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Additional Supporting Information may be found in the online version of this article.
[Correction added on 25 August 2021, after first online publication: Reference 17 has been replaced]
Journal of Bone and Mineral Research, Vol. 36, No. 9, September 2021, pp 1651–1660.
DOI: 10.1002/jbmr.4412

walking distance (6MWD). Furthermore, subgroup analyses on, for example, bolus versus daily regimen have not been performed. Therefore, we performed a MA on the effect of vitamin D on selected muscle health outcomes, including only high-quality placebo-controlled RCTs with the intent to summarize effects of vitamin D with different dosing regimens and with different population characteristics such as age, comorbidity, and baseline 25(OH) levels.

Materials and Methods

Searching and selection criteria

We performed a systematic literature review, identifying RCTs on effects of vitamin D supplementation on muscle strength/function. A literature search was performed in October 2020 at MEDLINE, Embase, and Google Scholar using the terms ''muscle strength'' OR ''muscle function'' OR ''muscle(s)'' AND ''vitamin D'' OR ''cholecalciferol.'' The article type was restricted to ''randomized (clinical) controlled trial'' and the use of vitamin D3 or D2. For Embase, we used the filter placebo. In addition, reference lists from the original studies and meta-analysis were scrutinized to identify additional eligible studies.

Inclusion criteria

Only double-blinded placebo-controlled English-language RCTs were included. Humans of all age groups were included when treated with vitamin D2 or vitamin D3 but not with active vitamin D analogues.

Calcium co-supplementation was allowed in both groups or in the vitamin D group alone, both not as comparator.

If a study included two vitamin D groups (different doses) but only one placebo group, we a priori included the placebo group and the group treated with the lowest dose of vitamin D. Sensitivity analyses were used to determine whether inclusion of the highest-dose group changed the pooled estimate.[28-34] In studies including two vitamin D groups (Pakistani versus Danish women[35] and depressive versus non-depressive individuals[11]) and similar two consecutive placebo groups, the two groups are registered as two separate studies, although published in one article.[11,35]

In factorial designs, including, for example, a group treated with exercise (± vitamin D),[13] we included the two groups treated with vitamin D versus placebo. Studies examining athletes were excluded, as those studies in general are more methodologically heterogenic and because training may exert an independent effect on muscle health,[36,37] complicating a direct comparison.

Effect parameters

We included studies assessing physical performance as reported as the timed up and go test (TUG; seconds), CRT, 10 replications (seconds), 6MWD (meters), and SPPB (points).

The maximum isometric muscle strength of handgrip and flexion/extension of the elbow and knee were also assessed, and finally we included muscle mass in terms of total lean tissue mass (kg) as reported by dual-energy X-ray absorptiometry (DXA).

All measures of force are reported in Newton. If data were reported as kg, data were multiplied by 9.81 to transform into Newton. If force in both the dominant and the non-dominant extremity was reported, we a priori chose the dominant or right extremity. If force was reported with the leg extension/flexion in both 60 and 90 degrees, we a priori reported data from the 60-degree positions.

In studies using a different regimen of administration, we chose oral supplementation, if available.[12]

In studies with non-daily treatment, subgroup analyses of the daily dose of supplementation are calculated as the total dose divided by the number of days from baseline to end of study.

Subgroup analyses were prespecified to assess whether vitamin D was modified by one or more of 17 different clinical characteristics in terms of serum 25(OH)D concentration <50 nmol/L as inclusion criteria, average serum 25(OH)D concentration <35 nmol/L (pragmatically defined to ensure a sufficient number of studies to be included in subgroups analysis), duration of intervention, clinical setting (healthy or comorbid), sex, menopausal state, children versus adults, age adults, calcium co-supplementation, vitamin D2 versus D3, dosing regimen (daily, weekly, bolus), dose, absolute increase in and end of study levels of 25(OH)D.

Risk of bias

Risk of bias was assessed using funnel plots and the Cochrane Collaboration risk of bias tool for randomized trials.[38] The tool included six domains to detect bias of selection (random sequence generation and allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome assessment), attrition (incomplete outcome data), and reporting (selective reporting). If the percentage of withdrawals and drop-outs combined with or if missing data for the effect parameter itself exceed 20% (30% in studies ≥3 years), the study was considered as high risk of attrition bias.

Statistics

Because most studies are reported in absolute numbers, data in the MA are recorded as absolute changes (end of study values minus baseline values) if assessable or alternatively absolute values at end of study. If published data were reported in percentage changes, the corresponding author was contacted twice per mail with an interval of 1 month in between and encouraged to send their data in absolute changes. We received data in absolute changes or absolute values from all,[11,13,15,16,30,39-42] except one study.[43]

We used Review Manager 5.4.1 for the statistical analysis and a priori chose mean difference and random effect model. Heterogeneity between studies was estimated by calculating the I^2 statistic.[44]

Excluded data

For three studies, we were not able to include data, as variability was reported as percentage of relative variation,[45] or range,[46] instead of SE/SD, or with an unreliable small SE.[47]

Results

Included studies

A flow chart of included articles is shown in Fig. 1.

Characteristics of included studies

Fifty-four randomized placebo-controlled clinical trials with 8747 unique individuals are included in this MA (Table 1). Supplemental Table S1 shows a more detailed description of included

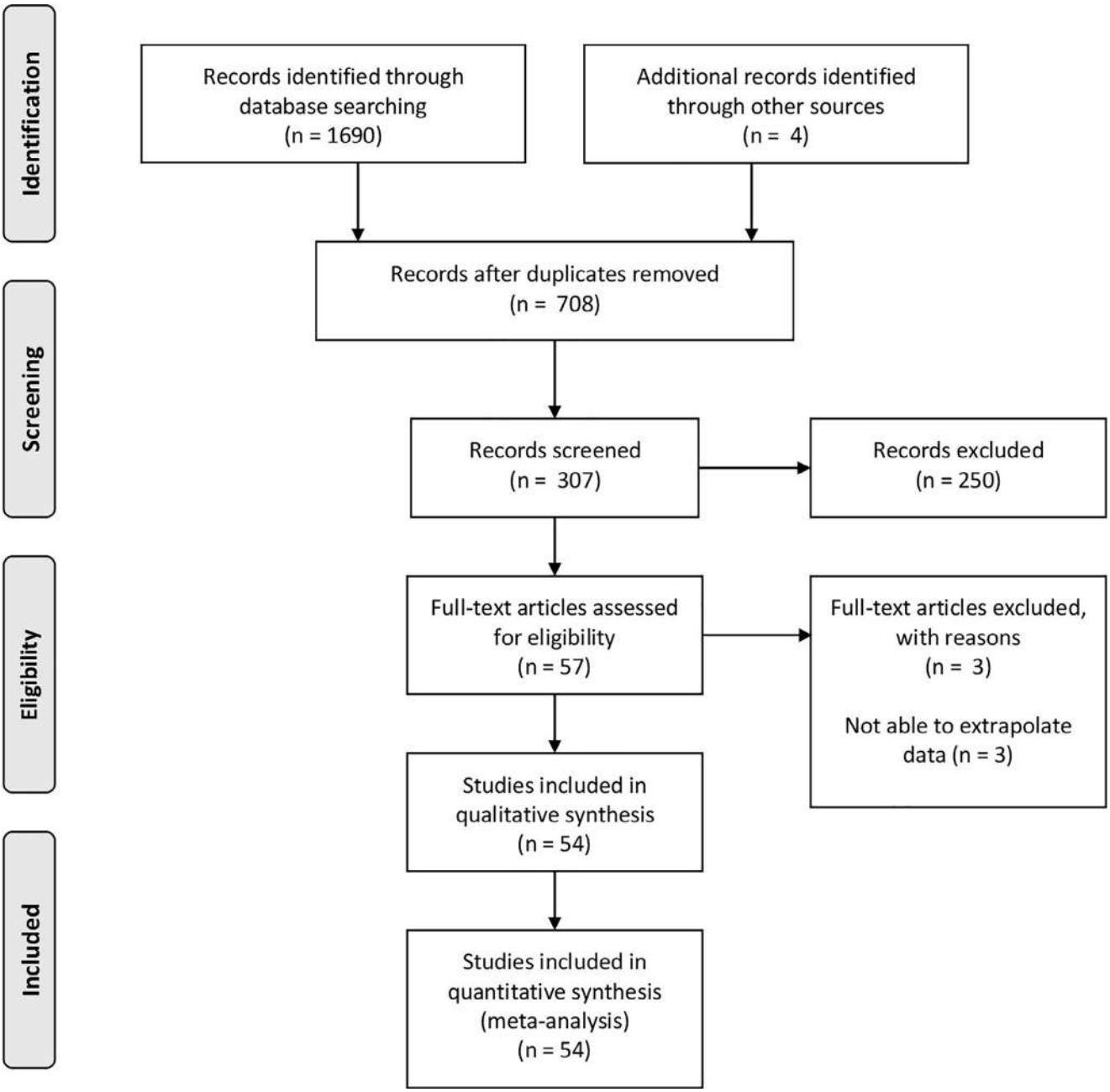

Fig. 1. PRISMA flow diagram.

studies. Most studies included data on handgrip strength and the TUG test (Table 2) in mostly postmenopausal women or in patients with different comorbidities. On the other hand, data in men and children are sparse. The doses used are equally distributed below or above 1000 IU/d and duration of treatment ranged from 1 to 60 months (median 6 [IQR 3 to 12] months).

Although most studies include vitamin D–replete individuals, 17% of the population of this MA focused on only subjects with 25(OH)D levels below 50 nmol/L (Table 1). Studies with a mean baseline 25(OH)D level below <35 (Table 1), <30,[9,29,48-52] or <25 nmol/L[9,48-51] represented 23%, 11.8%, and 7.6% of the population of this MA, respectively. No studies had average baseline 25(OH)D levels ≤20 nmol/L.

Risk of bias

As visualized in Supplemental Fig. S9, the overall risk of bias in included studies is considered low. High-risk bias was mainly present in attrition bias, primarily due to dropout rates exceeding 20% in some studies.[33,49,53-57]

Table 1. Overview Included Studies

	No. of studies	No. of study participants
Included studies[9,11-16,28-35,39-42,45,48-57,60-65,67-73,83-91]	54	8747
Effect parameter		
Handgrip[9,11,13,15,16,28-31,33,35,39,40,42,48,49,51,53,55,57,65,68-70,72,83-88,90,91]	35	5946
Elbow extension[15,16,39,53]	4	235
Elbow flexion[15,16,39,53,86]	5	636
Knee extension[13,15,16,33-35,39,42,52-55,61,62,64,67,72,73,84]	20	1624
Knee flexion[15,16,34,39,42,53-55,61,67,72,73]	12	765
Timed up and go[11-13,15,16,32,33,39,40,42,50,54,62,67,73,83,85,87]	19	5223
Chair rising test[13,15,16,29,32,39,41,42,83,87,88]	11	3112
6-minute walking distance[9,41,48-50,54,56,64,65]	9	796
Short Physical Performance Battery[40-42,60,63,88-90]	8	856
Total lean mass [14-16,30,35,42,45,51,71,90,91]	12	1201
Studies with 25(OH)D <50 nmol/L as inclusion criteria[15,33,42,49,50,56,57,61,65,86,89-91]	13	1496
Serum 25(OH)D concentration <35 nmol/L at baseline[9,15,28-31,33,48-52,57,86,89]	15	2014
Length of intervention ≥26 weeks[9,11,13,14,16,30,32,33,39-42,45,48,49,51-54,56,57,61,62,65,68,72,73,83,85,87,88,90]	33	6823
Comorbid individuals[11-13,16,33,39,40,42,50,51,53,54,56,57,60-65,68,69,71-73,92]	27	2242
Men only[55,87,88]	3	201
Postmenopausal women only[11,13-15,28,32,33,41,45,60,70,73,83,85,91]	16	5233
Children only[30,31,49]	3	393
Calcium co-supplementation[9,33,67,68,71,73,83,85,87]	9	4180
Vitamin D2[50,52,73,91]	4	503
Daily therapy[11,13,15,16,28,29,31-35,39-42,45,55,56,60,61,63,65,67,69,71,72,83,84,87,88,90]	33	5529
Dose of supplementation ≤1000 IU/d[13,28-33,42,45,54,61,70,73,84,85,87,90]	17	4723
Increase in 25(OH)D ≥50 nmol/L[11,15,41,48,49,56,57,61,64,65,67,68,86,88,93]	15	1488
End of study levels of 25(OH)D ≥100 nmol/L[11,16,34,41,54-57,63,64,67,68,88]	14	972

Table 2. Mean Difference of Maximum Muscle Strength, Physical Performance, and Muscle Mass

Effect parameter	No. of studies	No. of participants	Mean difference (95% confidence interval)	*p* Value	Forest plot (Fig. no.)
Physical performance					
Timed up and go test[a] (s)	19	5223	0.15 (0.03, 0.26)	**0.01**	2
Short Physical Performance Battery (points)	8	856	−0.18 (−0.37, 0.01)	0.06	S1
Chair rising test[a] (s)	11	3112	−0.07 (−0.21, 0.06)	0.31	S2
6-minute walking distance (m)	9	796	−3.18 (−11.35, 4.99)	0.45	S3
Maximum muscle strength (N)					
Handgrip	35	5946	0.56 (−1.50, 2.62)	0.60	S4
Elbow extension	4	235	−4.00 (−10.19, 2.20)	0.21	S5
Elbow flexion	5	636	−1.93 (−8.68, 4.82	0.25	S6
Knee extension	20	1624	1.26 (−2.85, 5.37)	0.55	S7
Knee flexion	12	765	−3.33 (−6.63, −0.03)	**0.05**	3
Muscle mass (kg)					
Total lean mass	12	1201	−0.06 (−0.32, 0.19)	0.63	S8

[a]A positive mean difference favors placebo (longer time spent performing the test). Significant results are shown in bold.

Physical performance

Compared with placebo, vitamin D supplementation significantly increased the time spent performing the TUG test with a mean difference of 0.15 (95% confidence interval [CI] 0.03 to 0.26) seconds, $N = 19$ studies, $I^2 = 0\%$, $n = 5223$ participants (Table 2 and Fig. 2). As shown in Supplemental Table S2, all 17 subgroup analyses for the TUG test showed no intergroup differences.

Total score in the SPPB showed a tendency toward a worsening in patients treated with vitamin D compared with placebo, with a mean difference of –0.18 (−0.37 to 0.01) points, $N = 8$ studies, $I^2 = 0\%$, $n = 856$ participants (Table 2 and Supplemental Fig. S1).

Vitamin D supplementation did not affect performance of the CRT and 6MWD (Table 2 and Supplemental Figs. S2 and S3).

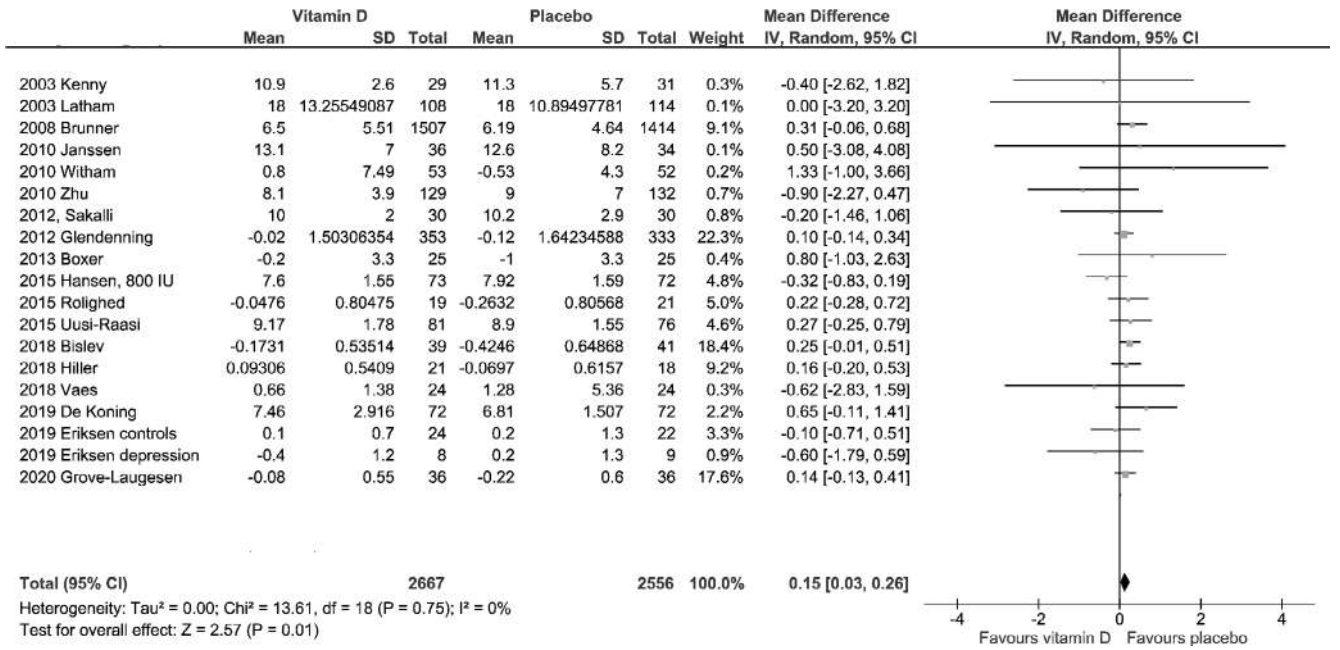

Fig. 2. Forest plot timed up and go.

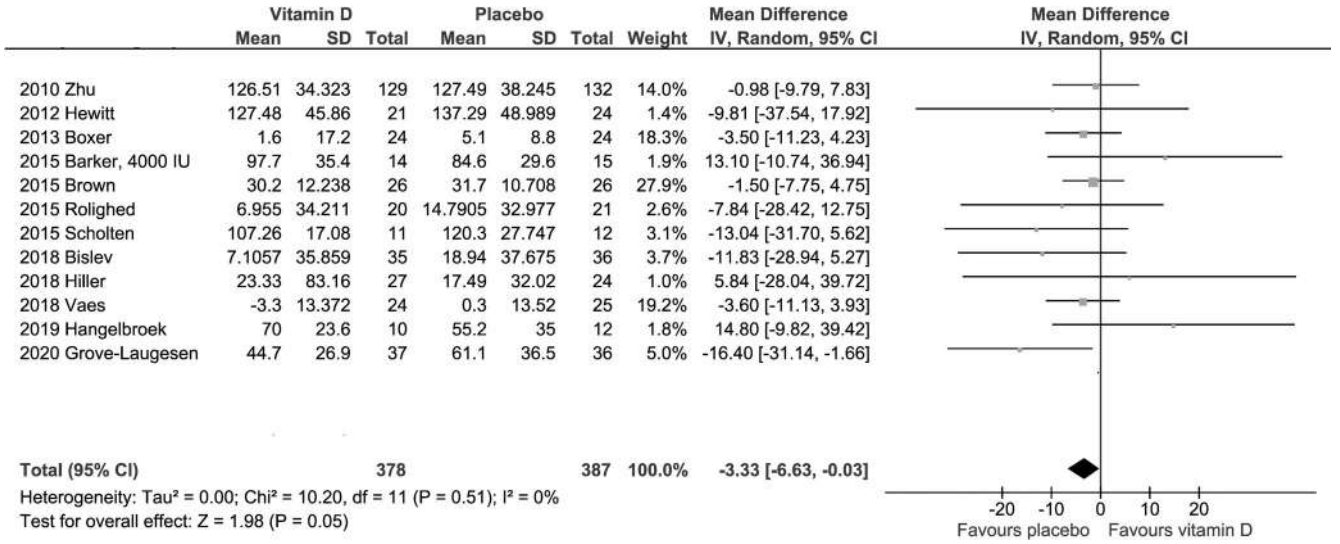

Fig. 3. Forest plot knee flexion.

Subgroup analyses for CRT, 6MWD, and SPPB revealed no intergroup differences (Supplemental Tables S3–S5).

Maximum muscle strength

Compared with placebo, vitamin D lowered knee flexion strength by −3.33 (−6.63 to −0.03) Newton, $N = 12$ studies, $I^2 = 0\%$, $n = 636$ participants (Table 2 and Fig. 3), whereas no significant effects were found at strength at handgrip, elbow flexion/extension, or knee extension (Table 2 and Supplemental Figs. S4–S7).

Subgroup analyses of the five measures of maximum muscle strength (Supplemental Tables S6–S10) only revealed a between-group difference at handgrip between children (6.7 N) and adults (−0.1 N) (Supplemental Table S6) and at elbow flexion if stratified by end-of-study 25(OH)D levels below (0.70 N) or above (−16.4 N) 100 nmol/L (Supplemental Table S8).

Muscle mass

Vitamin D supplementation did not affect total lean tissue mass (Table 2 and Supplemental Fig. S8). Subgroup analyses

revealed a between-group difference when stratified into average baseline 25(OH)D levels below (0.4 kg) or above (−0.2 kg) 35 nmol/L, respectively (Supplemental Table S11).

Data exploring

In studies using two different doses of vitamin D and one placebo group, using the highest dose (instead of the lowest dose) for calculations, findings were not changed on effects of vitamin D supplementation on the TUG,[32] CRT,[29,32] handgrip strength,[28-31] knee flexion strength,[34] or lean tissue mass.[30] Nor were results changed by using standard mean difference to calculate effects.

On all 10 effect parameters, there were no differences between subjects treated with or without calcium co-supplementation, daily versus non-daily therapy, intervention </≥ 26 weeks, dosages (</≥1000 or </≥2800), or use of vitamin D2 versus D3 (Supplemental Tables S2–S11). Restricting analysis to subjects treated with vitamin D3 versus placebo or subjects treated with vitamin D without calcium versus placebo did not affect the main findings of negative effects on TUG (Supplemental Table S2) or knee flexion (Supplemental Table S10). Restricting analyses to studies using daily administration, the findings on TUG (Supplemental Table S2) were still significant and negative, $p = 0.03$, whereas the negative findings on knee flexion did not reach statistical significance, $p = 0.11$ (Supplemental Table S10).

In included studies published until 2014 (the last published MA including the retracted Sato studies[21,22,24]), none of the effect parameters were significant. However, looking at studies published 2015 and later, the time spent performing the TUG were still significantly increased (MD 0.15 [0.01 to 0.28] seconds, $p = 0.03$, $N = 10$ studies, $n = 788$ participants), while the negative finding on knee flexion no longer reached statistical significance (MD –4.04 [−9.10 to 1.01] N, $p = 0.12$, $N = 9$ studies, $n = 411$ participants), $p = 0.12$.

Post hoc analysis of participants with "very low" average 25(OH)D levels arbitrarily defined as 25(OH)D ≤30 or ≤25 nmol/L, respectively, did not change any results, except the subgroup analysis of total lean mass, which no longer differed. In the vitamin D–deficient group (25(OH)D ≤25 nmol/L), available estimates showed no significant effects for the TUG (MD 1.33 [−1.00 to 3.66] seconds, $N = 1$ study,[50] $n = 105$ participants), 6MWD (MD –4.84 [−14.09 to 4.40] meters, $N = 4$ studies,[9,48-50] $n = 314$ participants), handgrip strength (MD 2.75 [−8.66 to 14.15] Newton, $N = 4$ studies,[9,48,49,51] $n = 333$ participants), or total lean mass (MD 2.30 [−0.71 to 5.31] kg, $N = 1$ study,[51] $n = 115$ participants).

Discussion

This MA does not support a beneficial effect of vitamin D supplementation on muscle function, strength, or mass. On the contrary, our analyses suggest overall adverse effects of vitamin D supplementation on muscle health in terms of an increased time spent performing the TUG, a decrease in maximum muscle strength at knee flexion, and a tendency toward a reduced score of the SPPB.

Our findings are in contrast with most observational studies. Observational studies do, however, not prove causative effects of vitamin D, and findings may be prone to reverse causality. Vitamin D is synthesized in the skin in response to sunlight exposure. People with open-air activities may have increased 25(OH)D levels due to exposure of their skin to sunlight, and physical efforts related to outdoor activities may improve muscle function.[58]

Placebo-controlled RCTs are needed, as investigation of muscle function demands cooperation from the patients and may show improvement of results over time, a well-described phenomenon called learning effect.[59] This is a systematic bias in the interpretation of beneficial effects of vitamin D on muscles if no control group is included.

Findings from individual RCTs have previously been combined in several MA. Unfortunately, several previously published MA have included data from studies by Sato and colleagues, which later have been retracted because of scientific fraud.[17-20] 20) Since the retraction of two Sato articles in 2015−17, no MA have reported beneficial effects of vitamin D on summary estimates of muscle health.[25-27] Looking at effect parameters of available data published before the retraction (null findings) and after the retraction (negative effect on the TUG) suggests that both retracted fake data as well as new RCTs reporting negative effects of vitamin D may count for the discrepancy between older and new MAs.

MA reporting summary estimates of vitamin D on SPPB and knee flexion do not exist, but disadvantageous effects of vitamin D supplementation on the TUG test have been reported in a MA from 2016 including community-dwelling older persons.[27] Nevertheless, recently published MA are characterized by a huge (>90%) heterogeneity,[26,27] as a consequence of differences in vitamin D dosing regimens, type of supplement, calcium co-supplementation, participant demographics, and clinical settings.[25-27] In the present MA, we were able to reduce the heterogeneity by using strict criteria for inclusion of studies in pooled analyses.

Most available studies report effects on handgrip strength, as a handheld dynamometer is inexpensive and easy to use. However, grip strength is less reproducible compared with the isodynamic "muscle chairs" and the physical performance tests, as reflected in the highest study heterogeneity ($I^2 = 30\%$). Both the TUG and the SPPB reflect a combination of balance/coordination, speed gait, and lower leg strength, and may contain more clinically relevant information.

Subgroup analyses of, for example, baselines levels of 25(OH)D, residential status, and vitamin D regimen are extremely important, as it becomes more evident that vitamin D may only exert beneficial effects in individuals who "need it." Although most studies include vitamin D–replete individuals, 17% of the individuals in this MA are included based on vitamin D insufficiency (ie, <50 nmol/L), ensuring that all individuals suffer from low p-25(OH)D levels at inclusion. Nevertheless, subgroup analyses revealed no effect on the summary estimate and neither did similar analyses in the 23%, 11.8%, and 7.6% of the population with mean baseline 25(OH)D levels below <35, ≤30, or ≤25 nmol/L, respectively.

This in contrast to subgroup analyses of existing MA suggesting a beneficial effect in patients with comorbidity and/or with old age,[21,22,24] as well as if supplementation is sustained for more than 3 months with dosages above 1000 IU/d to raise plasma 25(OH)D levels >80 nmol/L.[26]

A more pronounced effect of vitamin D in institutionalized persons compared with community dwellers has also been suggested.[24] Available data did not enable subgroup analysis on institutionalized people, as only one placebo-controlled study included institutionalized elderly, and the author of that study did not respond to our request to provide findings in

absolute values.[43] Although not completely comparable, a large number of studies investigated comorbid patients reported as (pre)frail[33,42,60-62] or with different diseases such as chronic obstructive pulmonary disease,[63-65] heart failure,[54,56,66] chronic kidney disease,[10,57] depression,[11,40] and neurologic,[67-69] endocrine,[16,39,51,70,71] or other diseases.[12,72,73] Subgroup analyses in the comorbid group of patients did not show any differences compared with healthy participants.

Recently, a discussion on "more is not always better" emerged. Trials testing high doses of vitamin D have shown harmful effects in terms of impaired muscle function[15,16] and an increased risk of falls and fractures.[74-78] Whether the increased risk of falls and fractures is caused by impaired muscle health is currently unknown. For some effect parameters (elbow and knee extension/flexion and 6MWD), at least half of the included participants used moderate to high dosages of vitamin D (>2800 IU/d) (Supplemental Tables S4 and S7–S10), and it is possible that the negative finding on knee flexion is due to the dosage used. The subgroup analysis showing reduced elbow flexion with an end-of-study 25(OH)D level above 100 nmol/L supports this hypothesis. Subgroup analyses in the studies reporting negative effects on the TUG (Supplemental Table S2) or the SPPB (Supplemental Table S5) do, however, not support this theory, as the dosages used were substantial lower.

In existing literature, muscle mass is reported in different ways. We included total lean tissue mass as assessed by DXA, as most available studies use this measure to report muscle mass. Of note, this MA included 12 studies with a total of 1201 individuals and showed no effect on muscle mass in terms of changes in total lean tissue mass in response to vitamin D supplementation.

Interestingly, the retracted Sato studies were the first RCT to report increased size and number of type II fibers in response to vitamin D.[18] This has been reproduced in one RCT,[60] while no changes were found in the most recent RCT.[79] After completion of the literature search for this MA, data from the VITAL trial were published.[80] The VITAL study included 771 participants ≥50 years, who received a daily supplement of 2000 IE vitamin D3 (versus placebo) for 2 years and in agreement with our findings showed no effects on lean mass or other measures of body composition.[80] Nevertheless, the study investigated participants with mean vitamin D levels of 69 nmol/L, while subgroup analyses of this MA suggest a beneficial effect in participants with low (<35 nmol/L) 25(OH)D levels (Supplemental Table S11).

After completion of the literature search, data from the DO-HEALTH trial were published, reporting effects of a daily supplementation with 2000 IU of vitamin D3 ($n = 1076$) versus no vitamin D ($n = 1081$) on the SPPB in adults ≥70 years.[81] In the study, data were evaluated after 1 to 3 years of supplementation, showing a tendency ($p = 0.05$) toward a reduction in the SPPB after 1 but not after 2 and 3 years of supplementation.[81]

Our study has several strength as well as limitations. In a systematic review and MA including a large number of placebo-controlled studies reporting multiple outcomes with no or relatively low (handgrip strength, elbow flexion strength, and total lean mass) heterogeneity, the study ranges on the top of clinical evidence. In clinical evidence-based medicine, systematic reviews and MAs based on multiple RCTs are considered the highest level of scientific evidence.[82]

However, the approach of a trial-level MA does not answer all questions, as the summary estimate of a trial-level MA is not better than the individual studies included. The average treatment duration was only 6 months. Although some studies treated up to 60 months,[83] available data therefore need to be interpreted acknowledging the relative short treatment duration in most studies. No studies included participants with very low levels of vitamin D (≤20 nmol/L) and available data do therefore not allow for conclusions on patients with severe vitamin D deficiency, although this subgroup of participants is of most interest to study. Furthermore, we did not assess falls.

Whether small decreases in physical performance or muscle strength are clinically important is unknown, but we find it fair to conclude that the common statement that vitamin D protects muscle health lacks clinical evidence. Adverse effects may even be present. Given the enormous public interest in vitamin D supplementation, we need to be aware of uncritical use of vitamin D. Identifying safe repletion regimens is warranted.

Disclosures

All authors state that they have no conflicts of interest.

Acknowledgments

We acknowledge biostatistician Niels Trolle, Aarhus University, for invaluable help planning the design and data selection. Furthermore, we owe a special thanks to the authors responding to our request for sending us their data in absolute values.

Authors' roles: LBand LR participated in the study design. LB collected the data. All authors analyzed and interpreted the data and take responsibility for the integrity of the data analysis. LB, DG and LR wrote the manuscript. All authors revised and approved the final version of manuscript.

Author Contributions

Diana Grove-Laugesen: Conceptualization; data curation; formal analysis; supervision; validation; writing - original draft; writing-review & editing. **Lars Rejnmark:** Conceptualization; data curation; formal analysis; supervision; validation, writing - original draft; writing-review & editing.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4412.

Data Availability Statement

The data that support the findings of the study are available from the corresponding author upon reasonable request.

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