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 To summarize with a meta-analyse 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<0.02). No significant effect was found on muscle mass (SMD 0.058; p>0.52) or muscle power (SMD 0.057; p>0.657). 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 versus 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.

Vitamin D, or calciferol, is a liposoluble prohormone available in two forms: vitamin D2 and vitamin D3. 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-hydroxyvio-
Vitamin D (25[OH]D) is also associated with many non-skeletal 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 concordance 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 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 (CB and FB) made independently 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

<table>
<thead>
<tr>
<th>Table 1. Inclusion criteria</th>
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<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td>Design</td>
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<tr>
<td>Language</td>
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<tr>
<td>Participants</td>
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<tr>
<td>Comparator</td>
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<tr>
<td>Measures</td>
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<td>Date</td>
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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.

**Methodological quality assessment**

We used the system developed by Jadad (15) to evaluate methodological quality. Two authors (CB and FB) independently assessed the quality of trials. The Jadad score can range from zero to five. Studies were considered of excellent quality if their Jadad score reached five, of good quality if their score was three or four and of poor quality if their score was one or two.

**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 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 I² 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, 25(OH)D levels changes during 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 D₂.

Subgroups 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 D₃ was used in 22 studies (19–25, 27–29, 31, 33–41, 43, 47) and vitamin D₂ 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 supple-
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Quality evaluation was conducted using Jadad criteria (21), fully described in Table 2. The end points, participants’ characteristics, and other key information are shown in Table 3. The GRADE analysis was used to assess the quality of evidence (22). The quality of evidence was graded as low (1), moderate (2), high (3), and very high (4). The quality of evidence was lower than expected due to the small number of studies (23) included in the meta-analysis but also to the small number of subjects included 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 this meta-analysis. Regarding muscle mass and muscle power, our GRADE analysis showed a low level of evidence. This is likely to change this estimate (Table 4).

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).

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 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.

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 3. Subgroups analyses

<table>
<thead>
<tr>
<th>Serum 25(OH)D concentration</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30nmol/liter</td>
<td>710</td>
<td>9</td>
<td>0.47 (-0.07; 1.01)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥ 30nmol/liter</td>
<td>1763</td>
<td>17</td>
<td>0.06 (-0.05; 0.16)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical settings</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-dwelling</td>
<td>4901</td>
<td>21</td>
<td>0.05 (-0.04; 0.15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Institutionalized or hospitalized</td>
<td>632</td>
<td>8</td>
<td>0.45 (-0.16; 1.07)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 yr</td>
<td>3221</td>
<td>11</td>
<td>0.03 (-0.08; 0.145)</td>
<td>0.13</td>
</tr>
<tr>
<td>≥ 65 yr</td>
<td>2302</td>
<td>17</td>
<td>0.25 (0.01; 0.48)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplementation</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D alone</td>
<td>1359</td>
<td>14</td>
<td>0.06 (-0.01; 0.13)</td>
<td>0.7</td>
</tr>
<tr>
<td>Vitamin D + calcium</td>
<td>4174</td>
<td>15</td>
<td>0.25 (-0.08; 0.59)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women only</td>
<td>4173</td>
<td>13</td>
<td>0.29 (0.01; 0.05)</td>
<td>0.21</td>
</tr>
<tr>
<td>Men and women</td>
<td>1201</td>
<td>13</td>
<td>0.02 (-0.10; 0.15)</td>
<td></td>
</tr>
<tr>
<td>Men only</td>
<td>159</td>
<td>3</td>
<td>0.38 (-0.17; 0.93)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Length of intervention</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 26 weeks</td>
<td>1157</td>
<td>10</td>
<td>0.13 (-0.06; 0.33)</td>
<td>0.72</td>
</tr>
<tr>
<td>≥ 26 weeks</td>
<td>4376</td>
<td>19</td>
<td>0.17 (-0.01; 0.36)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Dose of supplementation</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1600 IU/day</td>
<td>3337</td>
<td>10</td>
<td>0.04 (-0.08; 0.15)</td>
<td>0.90</td>
</tr>
<tr>
<td>≥ 1600 IU/day</td>
<td>1367</td>
<td>11</td>
<td>0.02 (-0.08; 0.13)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Change of 25(OH)D concentration</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25 nmol/liter</td>
<td>904</td>
<td>8</td>
<td>0.06 (-0.07; 0.20)</td>
<td>0.23</td>
</tr>
<tr>
<td>≥ 25 nmol/liter</td>
<td>1335</td>
<td>15</td>
<td>0.27 (-0.04; 0.57)</td>
<td></td>
</tr>
<tr>
<td>&lt; 50 nmol/liter</td>
<td>1783</td>
<td>17</td>
<td>0.06 (-0.04; 0.15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>≥ 50 nmol/liter</td>
<td>456</td>
<td>6</td>
<td>0.56 (-0.24; 1.36)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of studies</th>
<th>Subtotal (n)</th>
<th>Number of studies</th>
<th>SMD (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 points</td>
<td>1171</td>
<td>10</td>
<td>0.07 (-0.13; 0.26)</td>
<td>0.42</td>
</tr>
<tr>
<td>≥ 4 points</td>
<td>4362</td>
<td>19</td>
<td>0.22 (0.03; 0.41)</td>
<td></td>
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</table>

SMD = Standardized Mean Difference

Table 4. Evidence quality and recommendation grade

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nb. of studies</th>
<th>Study design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strength</td>
<td>29</td>
<td>RCT</td>
<td>No serious</td>
<td>Seriousa</td>
<td>Seriousb</td>
<td>No serious</td>
<td>No assessedc</td>
<td>Moderate</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>6</td>
<td>RCT</td>
<td>No serious</td>
<td>No serious</td>
<td>Seriousb</td>
<td>No serious</td>
<td>No assessedc</td>
<td>Low</td>
</tr>
<tr>
<td>Muscle power</td>
<td>5</td>
<td>RCT</td>
<td>No serious</td>
<td>No serious</td>
<td>Seriousb</td>
<td>No serious</td>
<td>No assessedc</td>
<td>Low</td>
</tr>
</tbody>
</table>

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 coauthors 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 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.

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Author’s contributions: CB, OB, JP AND JYR conceived the study. VR gave support on methodology. CB and FB collected the data and disagreements were solved in presence of JS. CB performed statistical analysis and interpreted data with OB, SG and EC. All authors commented on the drafts and approved the final draft. CB is the manuscript’s guarantor.

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**Take-home points:** This systematic review and meta-analysis summarises 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.; Effects may be more important with people presenting a baseline 25[OH]D concentration lower than 30 nmol/L, with people institutionalised or hospitalized and with people aged 65 years or older.

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