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SYSTEMATIC REVIEW

Creatine Supplementation and Lower Limb Strength Performance: A Systematic Review and Meta-Analyses

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Abstract

Background Creatine is the most widely used supplementation to increase strength performance. However, the few meta-analyses are more than 10 years old and suffer from inclusion bias such as the absence of randomization and placebo, the diversity of the inclusion criteria (aerobic/endurance, anaerobic/strength), no evaluation on specific muscles or group of muscles, and the considerable amount of conflicting results within the last decade.

Objective The objective of this systematic review was to evaluate meta-analyzed effects of creatine supplementation on lower limb strength performance.

Methods We conducted a systematic review and meta-analyses of all randomized controlled trials comparing creatine supplementation with a placebo, with strength performance of the lower limbs measured in exercises lasting less than 3 min. The search strategy used the keywords "creatine supplementation" and "performance". Dependent variables were creatine loading, total dose, duration, the time-intervals between baseline (T0) and the end of the supplementation (T1), as well as any training during supplementation. Independent variables were age, sex, and level of physical activity at baseline. We conducted meta-analyses at T1, and on changes between T0 and T1. Each meta-analysis was stratified within lower limb muscle groups and exercise tests.

Results We included 60 studies (646 individuals in the creatine supplementation group and 651 controls). At T1, the effect size (ES) among stratification for squat and leg press were, respectively, 0.336 (95 % CI 0.047–0.625, $p = 0.023$) and 0.297 (95 % CI 0.098–0.496, $p = 0.003$). Overall quadriceps ES was 0.266 (95 % CI 0.150–0.381, $p < 0.001$). Global lower limb ES was 0.235 (95 % CI 0.125–0.346, $p < 0.001$). Meta-analysis on changes between T0 and T1 gave similar results. The meta-regression showed no links with characteristics of population or of supplementation, demonstrating the creatine efficacy effects, independent of all listed conditions.

Conclusion Creatine supplementation is effective in lower limb strength performance for exercise with a duration of less than 3 min, independent of population characteristic, training protocols, and supplementary doses and duration.

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Key Points

Creatine supplementation is effective in lower limb strength performance.

The effectiveness of creatine supplementation is independent of population characteristic, training protocols, and supplementary doses and duration.

1 Introduction

Creatine is the most widely used supplement to increase strength performance [1]. However, results are conflicting despite an increasing number of publications. Previous meta-analyses investigating the effects of creatine supplementation on strength performance are more than 10 years old. These meta-analyses suffered from potential inclusion bias such as the absence of randomization [2, 3] and the diversity of the inclusion criteria (aerobic/endurance, anaerobic/strength) [2–4], resulting in a large or a small number of heterogeneous studies being reviewed [3, 4]. During maximal exercise, anaerobic metabolism is the predominant source of immediate energy. At the onset of anaerobic activity, stored phosphocreatine levels (the most immediate source of anaerobic metabolism) decrease via dephosphorylation to resynthesize ATP (adenosine triphosphate) from ADP (adenosine diphosphate). Creatine supplementation is supposed to enlarge the phosphagen pool within the muscle fibers. Anaerobic metabolism decreases until an equal contribution from the aerobic and anaerobic energy systems occurs approximately after 2–4 min [5]. Moreover, placebo effects have been demonstrated to be powerful in various conditions, including physical performance [6]. Finally, no meta-analysis to date has examined the effects of creatine supplementation on specific muscles or group of muscles.

Thus, we aimed to conduct a systematic review and meta-analyses of all randomized controlled trials comparing creatine supplementation with a placebo, with strength performance measured following exercises lasting less than 3 min. We performed meta-analyses stratifying muscles or group of muscles. Eventually, we further completed our analyses adding the double-blind design as an inclusion criterion. Specifically, this paper focuses on lower limb strength performances following creatine supplementation, because movement demands on the lower limbs are germane to multiple sporting pursuits.

2 Methods

2.1 Literature Search

We reviewed all randomized controlled trials comparing a creatine supplementation group with a control group. We used the following keywords: “creatine supplementation” and “performance”. The following databases were searched on 1 September 2014: PubMed, Cochrane Library, ScienceDirect, and EMBASE. The search was not limited to specific years and no language restrictions applied. To be included, the control group needed to receive a placebo during the supplementation period. The search strategy was inclusive of studies of healthy men or women, any age, any supplementation dose, any duration, with or without training (previously or during supplementation), and without a history of weight loss induced by a restrictive diet. The major inclusion criterion was a description of strength performance at baseline and following supplementation or placebo. In a further complementary analysis, group allocations had to be double-blind. The duration of exercise when performance was measured had to be less than 3 min. We also included articles reporting changes in performance. In the case of repeated and consecutive performances, we only took into account for our meta-analyses the first performance as it described the most anaerobic response. All eligible articles also had to report a statistical dispersion of results. In addition, reference lists of all publications meeting the inclusion criteria were manually searched to identify any further studies not found through electronic searching. The search strategy is described in Fig. 1. One author (CL) conducted all literature searches and collated the abstracts. Two authors (CL and FD) separately reviewed the abstracts and, based on the selection criteria, decided the suitability of the articles for inclusion. A third author (GN) was asked to review the article when consensus on suitability was not met. Then, all authors reviewed the eligible articles.

2.2 Quality of Assessment

The Consolidated Standards of Reporting Trials (CONSORT) statement was used to check the quality of reporting [7]. The 25 items identified in the CONSORT criteria could achieve a maximal score of 37.

2.3 Statistical Considerations

Data were analyzed using STATA$^{®}$ version 13 (StataCorp LP, College Station, TX, USA, 2013). Heterogeneity in the study results was evaluated by examining forest plots,

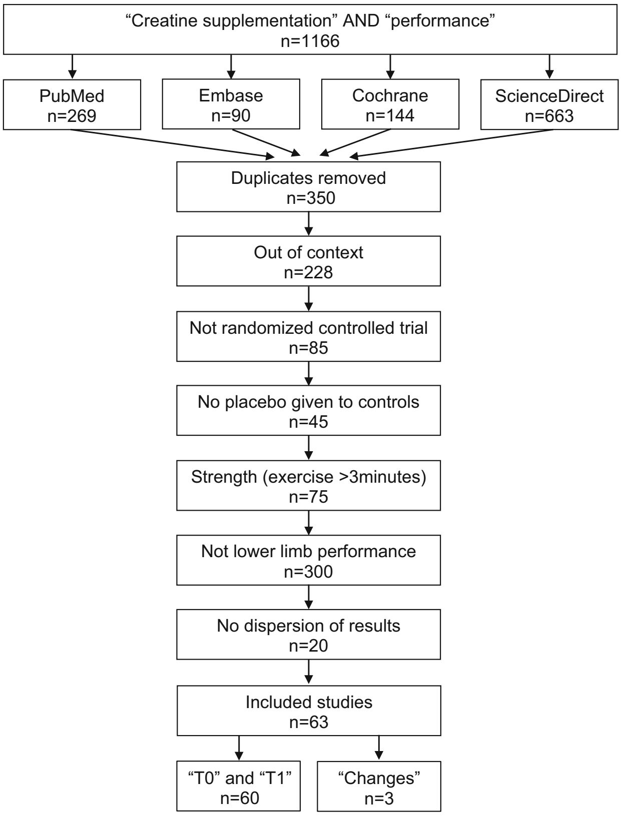

Fig. 1 Search strategy. *Changes* between T0 and T1, *T0* baseline, *T1* following supplementation

confidence intervals (CIs) and using formal tests for homogeneity based on the I^2 statistic. For example, a significant heterogeneity may be due to variability within characteristics of studies such as for participants (age, sex, trained or not, etc.), supplementation (loading dose, total dose, etc.), or training (type, number of repetitions, speed, etc.). Random effects meta-analyses (DerSimonian and Laird approach) were conducted when data could be pooled [8]. p Values <0.05 were considered statistically significant.

We conducted three meta-analyses based on the time of supplementation. First, a meta-analysis was performed at baseline (T0), in order to verify that the creatine supplementation group and the control group did not differ. Then, we conducted meta-analyses on data following the supplementation (T1). Finally, we conducted a third group of meta-analyses with the relative percentage changes (T1−T0)/T0 for both groups, adding some studies reporting only these changes.

Within each meta-analysis on lower limb strength performance, there was stratification for lower limb muscle groups (quadriceps, hamstrings, calves, and foot dorsiflexors). We also completed additional meta-analyses based on site-specific strength testing. Quadriceps performances were stratified by squat, leg press, leg extension, jump, and isokinetic exercises. Two meta-analyses were not stratified: maximal weight lifted in squat and maximal weight lifted in leg press.

We described our results calculating the effect size (ES) [standardized mean differences (SMDs)] of creatine supplementation for each dependent variable [8]. An ES is defined as a unitless measure of the efficacy of creatine centered at zero if the supplement effect is not different from the placebo. A positive ES denoted improved performance. A scale for ES has been suggested, with 0.8 reflecting a large effect, 0.5 a moderate effect, and 0.2 a small effect [9].

Meta-regression analyses were conducted to explore the influence of study characteristics on SMDs. The following characteristics were considered: sex of the participants (male vs. both sexes), age, physical status at baseline (sedentary, recreation, competitive), characteristics of creatine supplementation (loading dose, total dose, duration of supplementation), characteristic of training during supplementation (strength, aerobic, mixed, none), time between T0 and T1, and muscle groups (quadriceps, hamstrings, calves, and foot dorsiflexors). Results were expressed as regression coefficients and 95 % CI.

3 Results

3.1 Overview of Studies Included

An initial search produced a possibility of 1166 articles (Fig. 1). Selection criteria and removal of duplicates reduced these articles to 60 randomized controlled trials comparing T0 and T1 lower-limb strength performances of less than 3 min between a creatine supplementation group and a placebo group. Three additional studies reported only changes between T0 and T1. All studies were written in English.

3.2 Quality of Articles

Quality assessment of the 60 included studies reporting T0 and T1 data, as outlined by the CONSORT criteria, varied from 22 to 65 % where a higher percentage infers a higher quality of scientific reporting [7]. Of the studies, 61 % have a score exceeding 50 %. Fifty-five of the 60 studies described double-blinding to the supplementation. Overall, the studies performed best in the discussion section and worst in the methods section. Most of the studies described ethical approval. Of the studies, 50 % did not report any conflict of interest, 25 % were funded by creatine manufacturers, and 25 % did not provide any information regarding funding.

3.3 Characteristics of Individuals

3.3.1 Sample Size

In total in these 60 studies, 646 individuals in the creatine supplementation group were compared with 651 individuals in the placebo group.

3.3.2 Sex

The proportion of females remained low (26 %), with eight studies restricted to only women [10–16]. A further two studies failed to report participants' sex [17, 18]. In total, 538 males and 109 females were in the creatine supplementation group, and 537 males and 114 females in the placebo group.

3.3.3 Age

Regardless of whether age was expressed as a median or a mean value, reported study participants' ages ranged between 16 and 72 years [19, 20].

3.3.4 Physical Activity

In six of the 60 studies, the type of physical activity was not specified [21–25]. Most studies recruited recreationally trained populations (43 %) and competitive athletes (37 %), whereas the remaining studies were conducted on sedentary individuals (11 %). The physical status of the population was not reported in 9 % of the studies.

3.4 Characteristics of Intervention

3.4.1 Type of Supplementation

Several types and forms of creatine are available. The most common type of creatine examined in 56 of the 60 studies was creatine monohydrate. However, three other types of supplementation were found in four studies: polyethylene glycosylated creatine [26], creatine pyruvate [27], and creatine phosphate [28, 29].

3.4.2 Loading Dose

For all studies, the mean loading dose for creatine supplementation was 20.5 ± 9.7 g/day. More than 80 % of studies described a loading dose for the supplementation. The most common loading duration was between 5 and 7 days. The frequency of daily loading varied between one and seven times [30]. However, the loading dose was most regularly divided into three to four times per day with 5 g per dose.

3.4.3 Maintenance Dose

Only 40 studies had a maintenance dose that varied between 1.25 and 22 g/day [26, 31]. The quantity of maintenance dose was more variable between studies than the loading dose. Participants took the maintenance dose once daily.

3.4.4 Total Dose of Supplementation

The mean total dose was 271.6 ± 224.8 g across the studies' duration. Participants were supplemented for between 5 [14, 20, 28, 32–39] and 98 days [21].

3.4.5 Time Between Baseline (T0) and the End of the Supplementation (T1)

The duration between T0 and T1 ranged from 6 to 98 days [21, 40].

3.4.6 Training

More than 80 % of studies declared that the supplementation (creatine or placebo) was associated with sports training, whether it was specific or not for the study. Participants trained for endurance, strength, or both. Among the 58 studies for which the training status was reported, 39 % of participants performed strength training during the trial, 6.3 % took part in aerobic training, and 27 % participated in mixed training (endurance and strength). Only ten studies reported no training. The frequency of training per week was mainly three times per week.

3.5 Outcome and Aim of the Studies

All studies shared similar outcomes with varying degrees of clarity. The key dependent variables of the studies were muscle strength and body composition (body weight, lean body mass, percentage of fat free mass, total body water). Additional outcomes were heterogeneous but included tiredness and recovery capacity during exercises, functional capacity, cardiovascular function, systemic inflammation, muscle fiber area, and adverse events.

3.6 Study Designs

All studies were randomized placebo-controlled trials. The majority of studies were double-blind. Only five studies were single-blind randomized trials [36, 41–44]. One study supported a crossover design [45] with 42 days of wash-out period.

3.7 Stratification

With our inclusion criteria, 16 studies reported total weight lifted in kg for leg press and 11 studies reported maximal weight lifted in kg during a squat, allowing us to complete two meta-analyses. We then conducted a meta-analysis on quadriceps performances stratified on global tasks for leg press ($n = 19$ studies) and squat ($n = 12$), leg extension ($n = 19$), jump ($n = 22$), and isokinetic ($n = 13$) tests. The next level of our meta-analysis targeted lower-limb muscle groups: quadriceps ($n = 60$), hamstrings ($n = 5$), calves ($n = 0$), and foot dorsiflexors ($n = 2$) (Fig. 2). We also included articles reporting changes in performance. Thus, three other studies [46–48] were added and some results relating to changes in performance in two studies already included in the review were taken into account [22, 49].

3.8 Meta-Analysis at T0

The effects of creatine supplementation and placebo at T0 are available online in the Electronic Supplementary Material (ESM). The meta-analysis conducted on stratification for squat (ESM Fig. S1), leg press (ESM Fig. S2), quadriceps (ESM Fig. S3), and lower limb (ESM Fig. S4) did not show any between-group differences. The only ES that was significantly greater than zero at baseline was the leg press following stratification for quadriceps (ES = 0.216, 95 % CI 0.029–0.404, $p = 0.024$).

3.9 Meta-analysis at T1

Results from the first level of stratification showed that ES of creatine supplementation on maximal weight lifted (kg) in squat and total weight lifted (kg) at leg press were, respectively, 0.336 (95 % CI 0.047–0.625, $p = 0.023$) (Fig. 3) and 0.297 (95 % CI 0.098–0.496, $p = 0.003$) (Fig. 4). The effects of creatine supplementation for laminated analysis on quadriceps are presented in ESM Fig. S5. ES were also significant for leg press [0.346 (95 % CI 0.157–0.535, $p < 0.0001$)], squat [0.324 (95 % CI 0.047–0.602, $p = 0.022$)], and jump [0.307 (95 % CI 0.067–0.546, $p = 0.012$)]. No significant results were reported for leg extension and isokinetic tests. The overall ES remained significantly greater than zero: 0.266 (95 % CI 0.150–0.381, $p < 0.0001$). As shown in ESM Fig. S6, the overall ES for lower limb was significant [0.235 (95 % CI 0.125–0.346, $p < 0.0001$)]. The only isolated muscle performance with an ES greater than zero was quadriceps [0.233 (95 % CI 0.113–0.353, $p < 0.0001$)]. Funnel plots from this meta-analysis verified the absence of publications bias (ESM Fig. S7).

3.10 Meta-Analysis on the Change Between T1 and T0

Results from the first level of stratification showed that the ES for strength performance changes following creatine supplementation compared with controls for maximal weight lifted (kg) in squat was 0.390 (95 % CI 0.099–0.682, $p = 0.009$) (ESM Fig. S8) and was non-significant for total weight lifted (kg) from leg press (ESM Fig. S9). Results from the second level of stratification showed that the ES for strength performance changes following creatine supplementation compared with controls for quadriceps was 0.251 (95 % CI 0.082–0.420, $p = 0.004$) (ESM Fig. S10). For laminated analysis on quadriceps, performance following creatine supplementation compared with controls increased for squat (ES = 0.319, 95 % CI 0.041–0.597, $p = 0.025$) and jump (ES = 0.455, 95 % CI 0.146–0.765, $p = 0.004$) (ESM Fig. S10). No significant results were reported for leg press, leg extension, and isokinetic tests (ESM Fig. S10). The overall ES for non-specified lower-limb performance was 0.184

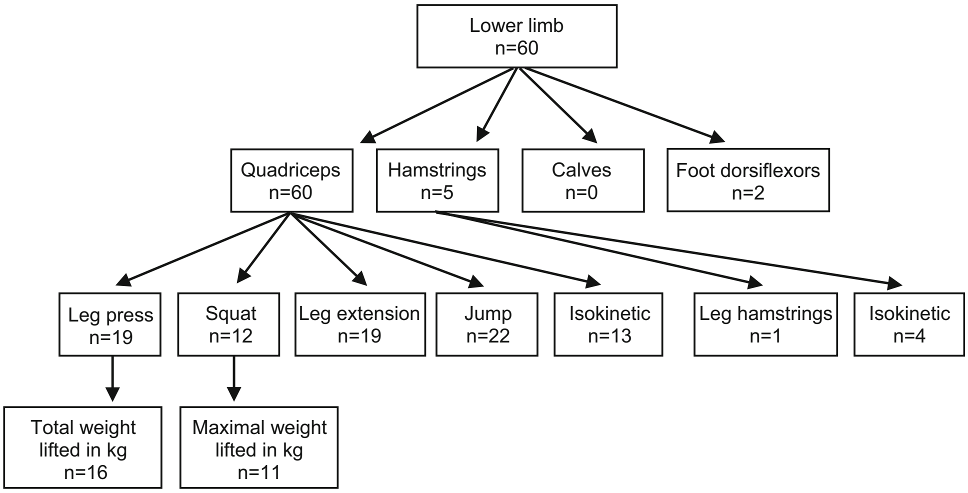

Fig. 2 Creatine supplementation and lower-limb type of exercises: general study design

Study	Population			Supplementation				Time T0-T1 (days)	Effect-size (95%CI)	Weight (%)
	Sex (%M)	Age mean ±SD (y)	Physical activity	Loading dose (g/d)	Total dose (g)	Duration (days)	Training			
Bemben et al. [47]	100	19±0	Competition	20	390	63	Strength	63	0.858 (-0.142, 1.859)	8.35
Izquierdo et al. [35]	100	21±5	Competition	20	100	5	Aerobic	7	0.410 (-0.501, 1.321)	10.07
Larson-Meyer et al. [15]	0	19±2	Competition	15	350	15	Mixed	60	0.179 (-0.972, 1.329)	6.32
Law et al. [37]	100	23±4	Recreation	20	100	5	Strength	6	0.083 (-0.870, 1.036)	9.21
Pearson et al. [125]	100	21±3	Recreation	0	350	70	Strength	-	0.545 (-0.455, 1.546)	8.35
Stone et al. [61]	100	18±3	Competition	0	700	35	Mixed	35	0.158 (-0.725, 1.040)	10.73
Vanderberghe et al. [16]	0	21±3	Sedentary	20	430	74	Strength	70	0.711 (-0.221, 1.643)	9.63
Volek et al. [118]	100	26±5	Recreation	25	560	84	Strength	84	0.262 (-0.643, 1.167)	10.21
Volek et al. [119]	100	21±6	Recreation	26	275	28	strength	28	0.438 (-0.528, 1.403)	8.97
Wilder et al. [121]	100	19±1	Competition	20	329	70	Mixed	73	-0.270 (-1.227, 0.687)	9.12
Wilder et al. [121]	100	19±1	Competition	0	210	70	Mixed	73	0.352 (-0.609, 1.313)	9.06
Overall (I-squared = 0.0%, p=0.949)									**0.336** (**0.047, 0.625**)	100.0

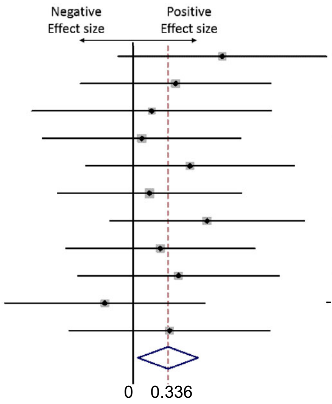

Fig. 3 Meta-analysis on maximal weight lifted (kg) in squat. *CI* confidence interval, *M* male, *SD* standard deviation, *T0* baseline, *T1* following supplementation

Study	Population			Supplementation				Time T0-T1 (days)	Effect-size (95%CI)	Weight (%)
	Sex (%M)	Age mean ±SD (y)	Physical activity	Loading dose (g/d)	Total dose (g)	Duration (days)	Training			
Brose et al. [21]	50	69±6	-	0	490	98	Strength	98	0.023 (-1.067, 1.114)	3.34
Brose et al. [21]	50	68±4	-	0	490	98	Strength	98	0.282 (-0.739, 1.302)	3.81
Camic et al. [26]	100	22±3	Sedentary	0	70	28	-	28	0.076 (-0.458, 0.610)	13.94
Camic et al. [26]	100	22±3	Sedentary	0	35	28	-	28	0.405 (-0.134, 0.944)	13.66
Chrusch et al. [85]	100	70±6	Sedentary	26	578	72	Strength	70	0.711 (-0.030, 1.452)	7.23
Ferguson and Syrotuik [13]	0	25±3	Recreation		266	70	Strength	70	-0.060 (-0.829, 0.709)	6.71
Gotshalk et al. [92]	100	65±5	-	25	178	7	None	7	0.152 (-0.779, 1.083)	4.58
Herda et al. [94]	100	21±2	Recreation	0	150	30	Mixed	30	0.022 (-0.721, 0.764)	7.20
Kilduff et al. [100]	100	20±3	Recreation	23	278	28	Strength	28	1.109 (0.135, 2.084)	4.18
Peeters et al. [126]	100	21±3	Recreation	20	393	42	Strength	42	0.305 (-0.489, 1.100)	6.29
Peeters et al. [126]	100	21±3	Recreation	20	393	42	Strength	42	-0.038 (-0.876, 0.799)	5.66
Pluim et al. [60]	100	23±5	Competition	22	194	34	Mixed	34	0.420 (-0.400, 1.241)	5.89
Syrotuik et al. [39]	100	23±2	Recreation	23	115	5	Strength	39	0.426 (-0.635, 1.488)	3.52
Syrotuik et al. [39]	100	23±2	Recreation	23	191	37	Strength	39	0.160 (-0.890, 1.209)	3.60
Syrotuik et al. [43]	55	23±3	Recreation	23	196	40	Strength	35	0.384 (-0.443, 1.210)	5.81
Vandenberghe et al. [16]	0	21±3	Sedentary	20	430	74	Strength	70	0.707 (-0.224, 1.638)	4.58
Overall (I-squared = 0.0%, p=0.924)									**0.297** (**0,098, 0,496**)	100.0

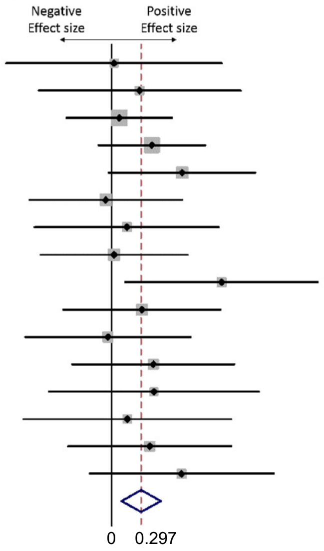

Fig. 4 Meta-analysis on total weight lifted (kg) at leg press. *CI* confidence interval, *M* male, *SD* standard deviation, *T0* baseline, *T1* following supplementation

(95 % CI 0.032–0.336, $p = 0.018$) (ESM Fig. S11). The only isolated muscle gain in performance was reported for quadriceps with an ES of 0.184 (95 % CI 0.026–0.342, $p = 0.023$) for quadriceps (ESM Fig. S11). Funnel plots from this meta-analysis verified the absence of publications bias (ESM Fig. S12).

3.11 Meta-Regression After Supplementation

The meta-regressions summarized in ESM Tables S1 and S2 demonstrated that results after supplementation depend on results at baseline for meta-analyses that were stratified for quadriceps performance and for the whole lower limb. There were insufficient data to allow meta-regression analyses on squat and leg press performance to be conducted.

3.12 Meta-Analyses with Only Double-Blind Studies

Results were similar when computing meta-analyses only with double-blind studies. ES for maximal weight lifted (kg) in squat and total weight lifted (kg) at leg press were, respectively, 0.402 (95 % CI 0.082–0.721, $p = 0.014$) and 0.291 (95 % CI 0.086–0.499, $p = 0.005$) at T1 and 0.456 (95 % CI 0.133–0.779, $p = 0.006$) and non-significant for changes from T0 to T1. For laminated analysis on quadriceps, ES were also significant at T1 for leg press [0.344 (95 % CI 0.150–0.538, $p = 0.001$)], squat [0.424 (95 % CI 0.120–0.728, $p = 0.006$)], and jump [0.317 (95 % CI 0.076–0.558, $p = 0.010$)], and were significant for changes from T0 to T1 for squat [0.364 (95 % CI 0.059–0.670, $p = 0.019$)] and jump [0.323 (95 % CI 0.046–0.599, $p = 0.022$)]. The overall quadriceps ES was 0.284 (95 % CI 0.170–0.398, $p < 0.0001$) at T1 and 0.224 (95 % CI 0.053–0.395, $p = 0.010$) for changes from T0 to T1. Eventually, the overall ES for lower limb was 0.245 (95 % CI 0.132–0.357, $p < 0.0001$) at T1 and 0.149 (95 % CI −0.001 to 0.300, $p = 0.052$) for changes T0–T1. The only isolated muscle performance with an ES greater than zero was quadriceps [0.244 (95 % CI 0.121–0.366, $p < 0.0001$)] at T1.

4 Discussion

Sixty-three studies met our inclusion criteria to assess creatine supplementation for lower-limb strength performance. The main finding was that creatine supplementation improved lower-limb strength performance, mainly at the site of the quadriceps. The maximal weight lifted during squats and total weight lifted at leg press increased by approximately 8 and 3 %, respectively, with creatine supplementation.

4.1 Overview of Studies Included

These meta-analyses include a large number of studies that are heterogeneous within both study design and reported results. These are the first meta-analyses with rigorous inclusion criteria and a large number of studies that has focused only on lower-limb strength performance without regard to endurance exercise.

4.2 Characteristics of Individuals

Creatine supplementation has been studied most extensively in young trained males. Responses to creatine supplementation did not differ between males and females [13–15], nor between sedentary [16, 19, 26, 50] and physically active populations. Results were also independent of age [19, 20]. More direct comparisons of the effect of creatine supplementation in males and females are needed to elucidate any sex differences in response to creatine. In our review, we included only two studies with this direct sex comparison [19, 21]. Creatine supplementation in combination with exercise has been shown to be more responsive in individuals with no training history; specifically, a 31 % increase in performances for untrained individuals versus 14 % for athletes [51]. However, it should be noted that our classification of training status was imperfect. For the purpose of these meta-analyses, populations described as “healthy” or “physically active” or “with less than three hours of physical activity per week, without competition” were classified as “recreationally” trained participants. To date, no study has specifically compared responses in populations of varying ages.

4.3 Characteristics of Intervention

Creatine supplementation regimens that included maintenance [21, 26, 27, 31, 44, 50, 52, 53] did not result in greater improvement from baseline in lower-limb performance compared with short-term loading regimens. Our meta-analyses were also unable to detect differences in performance based on the type of creatine used for supplementation. However, 97 % of studies used creatine monohydrate. What remains unknown is whether oral creatine supplementation is as effective as other substances such as caffeine [54], D-pinitol [55] or β-hydroxy-β-methylbutyrate [56] in improving performance. The effects of various combinations of performance-enhancing substances also remain unknown.

An interesting observation is the apparent lack of an effect of the design of the training regimen on performance improvement. That is, many studies conducted resistance training interventions, whereas others studies used mixed training regimens [15, 28, 31, 33, 44, 45, 53, 57–61]. Few studies evaluated aerobic training alone [14, 35, 42, 62]. Also, muscle strength gains seemed similarly responsive to supplementation whether single-leg or isolated-leg muscle group training occurred. No study to date has compared different modalities of training.

4.4 External Validity

Results were strongest when data were stratified for squat and leg press. Less precise information was obtained from quadriceps and global lower-limb meta-analyses because of the heterogeneity in tasks and units of measure.

4.5 Study Designs

These meta-analyses included only randomized placebo-controlled trials, which are considered to be among the highest level of quality [63]. Many studies failed to report sufficient results to be included in this review, such as studies with incomplete results for all timepoints [64, 65] or lack of reporting of dispersion around results [16].

4.6 Stratification

Although numerous reviews and four meta-analyses have supported the efficacy of creatine supplementation in improving performance in various muscle groups, these are the first meta-analyses to conduct stratified analyses on lower-limb muscles. One previous meta-analysis stratified results between the upper and lower body [4], whereas another stratified arm flexor strength for specific measurements [2].

The creatine ES is small according to Cohen's classification and is surrounded by considerable variance, explaining the fact that the efficacy of creatine is not consistent for all variables and populations studied. Our current meta-analyses lend additional support to the effectiveness of creatine for performance tasks in a range that is comparable with the three previous meta-analyses [2–4]. Creatine effect was reported to be more pronounced in upper (ES $= 0.42 \pm 0.07$) than lower (0.22 ± 0.02) body performance tasks [4].

4.7 Meta-Regression

In agreement with Branch [4], we failed to detect differences between the duration, training status, and sex involved in performances following supplementation. In contrast, Nissen and Sharp [3] showed that previously untrained participants gained more strength with resistance training than pre-trained participants. However, Nissen and Sharp included multiple dietary supplements with only 18 creatine studies [3]. Furthermore, Dempsey et al. [2] described that performances following creatine supplementation in combination with resistance training were more successful than with supplementation alone. We demonstrated that mixed training seemed to be a determining factor in performance after supplementation. Moreover, young males were more responsive to supplementation than older individuals and females [2]. However, more recently, the ergogenic effect of creatine among older women resulted in a 3.7 % increase for one repetition-maximum leg press within the creatine supplemented group [66].

Most performance variables included in our meta-analyses were measured in a laboratory with the exception of jumping, a field-based task. We observed that ES from laboratory testing were greater than those from field-based settings. This aspect was more pronounced in the meta-analysis of Branch [4]. We postulate that differences in reported ES may be related to greater internal validity and control of extraneous factors that could potentially alter performance. However, a major aim of dietary supplementation is increased competitive performance, which is frequently required in athletes. The gain of body mass could be responsible for the lower effect of creatine in some studies [67]. Further analyses are necessary to understand the effect of creatine supplementation on body composition.

Furthermore, high and low responders to creatine supplementation have been identified [68]. Different levels of responsiveness may contribute to a considerable variability in the changes in muscle strength and weightlifting performance following supplementation. The specific mechanisms may include variability in muscle creatine uptake and use [69]. Baseline muscle creatine content is also highly variable, ranging from 90 to 180 mmol/kg dry mass [51]. The elevated baseline level of muscle creatine content was also associated with low muscle creatine uptake [69, 70]. As such, high responders were associated with a low baseline level of muscle creatine content and/or a greater increase in muscle creatine following supplementation [69, 71, 72]. Furthermore, several factors may influence muscle creatine uptake, such as diet [18, 70] and status of training [69]. Although speculative, training may increase creatine uptake via the improvement of insulin sensitivity [69]. However, similar ES in strength performance have been observed between "responders" and "non-responders". This occurred despite stronger performances from individuals with a greater uptake of creatine [71].

4.8 Limitations

All meta-analyses have limitations [63]. Meta-analyses inherit the limitations of the individual studies of which they are composed. Despite our rigorous criteria for including studies in these meta-analyses, their quality varied. Multiple variations in study protocols and evaluation made combining results of different studies somewhat problematic. The scarcity of publications with negative findings may also generate some bias in reporting. However, according to funnel plots, no publications bias was observed. The mechanisms of creatine uptake and use might explain some variability. However, mechanistic literature was not the focus of our meta-analyses.

5 Conclusion

Creatine supplementation is effective in lower-limb strength performance for exercise with a duration of less than three minutes. Despite considerable variability in our meta-analyses, the gains in strength performances following creatine supplementation were similar to previous literature. Creatine supplementation was effective in the lower-limb strength performances, independent of population characteristic, training protocols, and supplementary doses and duration. However, a greater number of included studies may have strengthened the quality of understanding outlined in our meta-analyses.

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