SOBIŃSKI, Adam, CZERWONKA, Matylda, KOŚCIUSZKO, Zuzanna, KURZA, Katarzyna, CIRAOLO, Silvia, PODOLEC, Julianna, KULCZYCKA-ROWICKA, Agnieszka, LESICZKA-FEDORYJ, Katarzyna, WOJDA, Joanna, and WALCZAK, Anna. The Impact of Creatine Supplementation on Physical Performance, Cognitive Functions, and Safety – A Literature Review. Quality in Sport. 2025;38:58256. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.38.58256
https://apcz.umk.pl/QS/article/view/58256

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 26.01.2025. Revised: 5.02.2025. Accepted: 11.02.2025 Published: 11.02.2025.

The Impact of Creatine Supplementation on Physical Performance, Cognitive Functions, and Safety – A Literature Review

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ABSTRACT

Purpose of Research: The study evaluates the effects of creatine supplementation on physical performance, cognitive function, and safety. It examines its mechanism of action, impact on muscle mass and strength, and role in brain health. Additionally, it reviews the safety profile of creatine in diverse populations, including athletes, older adults, and individuals with chronic conditions.

Research Materials and Methods: The study is based on clinical trials, meta-analyses, and systematic reviews from the past decade. Data were collected from studies on creatine supplementation at various doses, including loading and maintenance phases, and its effects on physical and cognitive outcomes, as well as kidney and liver function.

Basic Results Creatine supplementation significantly improved lean body mass (mean difference = 1.32 kg; $p < 0.000001$) and muscle strength, with greater effects in men. It also showed potential benefits for memory, particularly in older adults, with moderate improvements in non-stress conditions. Safety evaluations indicated no adverse effects on kidney or liver function, even with long-term high-dose use.

Conclusions: Creatine supplementation is a safe, effective strategy for enhancing physical performance, especially with resistance training. It also supports cognitive functions, particularly in populations with higher energy demands or age-related decline. These findings support creatine as a versatile, well-tolerated dietary supplement for sports and health applications.
Keywords: Creatine, Supplementation, strength training, brain health, memory

Introduction

Creatine is one of the most used dietary supplements, particularly among athletes and individuals engaged in high-intensity physical activities. Its popularity is rooted in its unique role in energy metabolism, primarily through the phosphocreatine system, which facilitates rapid ATP regeneration during short bursts of intense effort. This mechanism not only supports muscle performance but also aids in recovery and adaptation to physical training.

Beyond its well-documented benefits for muscle function, creatine has recently drawn significant attention for its potential impact on brain health and cognitive performance. Emerging research suggests that creatine supplementation may enhance memory, concentration, and various cognitive processes, particularly under conditions of increased energy demand, such as aging. These findings highlight its potential applications not only in the athletic population but also in the general public, including older adults who may experience age-related declines in cognitive function.

The objective of this study is to provide a comprehensive review of the latest literature on the effects of creatine supplementation on physical performance, cognitive functions, and safety. This includes an in-depth analysis of meta-analyses, systematic reviews, and clinical trials conducted in recent years, with a focus on identifying the mechanisms of action, efficacy in diverse populations, and the safety profile of creatine across various contexts. By synthesizing current evidence, this review aims to offer a nuanced understanding of the multifaceted benefits and potential limitations of creatine supplementation.

Methodology

The study employed a systematic literature review methodology, utilizing databases such as PubMed, Scopus, and Google Scholar. Inclusion criteria focused on clinical trials, meta-analyses, and systematic reviews examining creatine supplementation and its effects on physical performance, cognitive functions, and safety. The review considered studies conducted in general populations, athletes, and older adults. The analysis encompassed various dosages of supplementation, intervention durations, and populations differing in age, sex, and health status. The findings were interpreted in terms of their clinical significance and potential practical applications.

Characteristics and Mechanism of Action

Creatine, known as β-methylguanidinoacetic acid, is an organic compound composed of guanidine and acetic acid elements. In animals, it is produced through metabolic processes and is primarily stored in skeletal muscles and tendons, where it plays a crucial role in maintaining energy homeostasis (1).

Creatine is endogenously synthesized in the body from arginine and glycine through the action of arginine glycine amidinotransferase (AGAT), which converts these substrates into guanidinoacetate (GAA). GAA is subsequently methylated by guanidinoacetate N-methyltransferase (GAMT) with the involvement of S-adenosylmethionine (SAM), resulting in the production of creatine (2,3). These processes occur mainly in the kidneys and liver, although AGAT is also found in the pancreas and certain regions of the brain (4,5). Endogenous creatine synthesis covers approximately half of the daily creatine requirement (4), while the remaining amount is derived from dietary sources, such as red meat and fish (6) or dietary supplements (7). In the body, creatine exists in two forms: as free creatine (Cr) and as phosphorylated creatine, or phosphocreatine (PCr) (8). The primary storage site for creatine (PCr + Cr) is skeletal muscle, which accounts for approximately 95% of the body's creatine stores in both forms (9). The remaining 5% is found in other tissues, including the brain, testes, heart muscle, and smooth muscles (10).

Creatine plays a critical role in supplying energy to cells. During intense physical activity, phosphocreatine is broken down, releasing creatine and a phosphate group. This phosphate is then utilized to convert ADP into ATP (adenosine triphosphate), which serves as the primary energy source for cellular processes. The generated ATP is subsequently used to initiate and sustain muscle contraction (9).

Effects on Physical Performance

Lean mass effect

In a meta - analysis conducted by Forbes et al. (11) which included 16 randomized clinical trials (RCTs) with 18 therapeutic groups and a total of 509 participants, it was demonstrated that resistance training combined with creatine supplementation significantly increased lean body mass compared to the placebo group that engaged in resistance training alone. The mean difference in lean mass gain was 1.32 kg [95% CI: 0.93–1.72], with a highly significant p-value of < 0.000001 (11).

The analysis further revealed that higher doses of creatine, both with and without a loading phase, contributed significantly to an increase in lean body mass compared to placebo. The mean difference observed was 1.16 kg [95% CI: 0.49–1.82], with a p-value of 0.0006 (11). Interestingly, even lower doses of creatine supplementation were shown to be more effective than placebo, with similar improvements in lean mass (11).

Creatine supplementation, regardless of the dose or the use of a loading phase, consistently demonstrated effectiveness in enhancing lean body mass when combined with resistance training. The benefits were apparent across different dosing strategies, with both high and low doses providing significant advantages compared to placebo. This indicates that creatine supplementation can be an effective strategy for increasing lean mass, independent of specific dosing protocols, making it a versatile option for individuals aiming to improve their body composition in conjunction with resistance training.

The findings underscore the robust efficacy of creatine in improving lean mass, highlighting its potential as a valuable supplement in both athletic and general populations. Furthermore, the consistency of the results across different dosing regimens provides flexibility in its application, catering to various user preferences and needs while still delivering significant benefits.

Effects on strength

A meta-analysis conducted by Wang et al. (12) encompassing 23 studies, including 20 with male participants ($n = 447$), 2 with female participants ($n = 40$), and 1 with both genders (13 men and 9 women), confirmed that creatine supplementation combined with resistance training significantly increased upper-body strength compared to placebo. The improvement was highly significant, with a weighted mean difference (WMD) of 4.43 kg [95% CI: 3.12–5.75, $p < 0.001$] (12). Male participants using creatine experienced a greater increase in upper-body strength compared to the placebo group (WMD = 4.95 kg [95% CI: 3.52–6.38], $p < 0.001$). However, the difference was not statistically significant in women (WMD = 1.54 kg [95% CI: −1.81–4.89], $p = 0.368$), indicating a trend where men derive greater benefits from creatine supplementation than women ($p = 0.067$, $Q = 3.366$) (12).

Interestingly, the improvement in upper-body strength due to creatine supplementation was not influenced by the dosage (≤5 g/day vs. >5 g/day), duration, frequency of supplementation, or participants' training experience (12).

Lower-body strength gains were also significantly higher with creatine supplementation compared to placebo (WMD = 11.35 kg [95% CI: 8.44–14.25], $p < 0.001$). When considering gender differences, men showed a markedly greater increase in lower-body strength compared to placebo (WMD = 11.68 kg [95% CI: 8.60–14.76], $p < 0.001$), whereas the difference in women was not statistically significant (WMD = 8.03 kg [95% CI: −0.83–16.90], $p = 0.076$) (12).

Additionally, higher doses of creatine (>5 g/day) were associated with a trend toward greater lower-body strength gains compared to lower doses (≤5 g/day) ($p = 0.068$, $Q = 3.341$). However, the training status, duration, or frequency of resistance training did not significantly impact strength differences between creatine and placebo groups (12).

The findings of Wang et al. (12) which demonstrate increases of 4.43 kg in upper-body strength and 11.35 kg in lower-body strength, align with previous meta-analyses by dos Santos et al. (13) and Forbes et al. (14), These studies also highlighted the effectiveness of creatine supplementation in improving muscle strength across both upper and lower body regions (12).

Effects on Cognitive Function and Brain Health

Effects on memory

In recent years, there has been a growing body of literature examining the effects of creatine supplementation on neurobehavioral and psychological aspects (15–20). While muscle creatine levels largely depend on both exogenous and endogenous creatine synthesis occurring in the kidneys, pancreas, and liver (21), the brain has the ability to synthesize creatine independently (22). Roschel et al. (22) suggest that brain creatine is not entirely dependent on internal synthesis from other organs or supplementation (23). his is supported by evidence indicating that essential enzymes for endogenous creatine synthesis are also present in the nervous system (22). his is supported by evidence indicating that essential enzymes for endogenous creatine synthesis are also present in the nervous system (24). demonstrating that brain creatine is not fully reliant on organ production or external supplementation (22). In some studies, creatine supplementation reduced the brain tissue's need for oxygen (25) and improved verbal, long-term, and spatial memory (26).

A meta-analysis by Prokopidis et al. (16) reviewed 10 systematic reviews and 8 meta-analyses, including studies on both younger and older adults, male and female participants, and various creatine supplementation doses (16). The findings revealed that creatine supplementation improved memory compared to placebo, although moderate heterogeneity was observed across the included randomized studies (16). Subgroup analyses highlighted differences in the effects based on dose, age of participants, supplementation duration, and test conditions (16). Regarding dosage, neither low doses (<5 g/day) nor high doses (>5 g/day) were associated with significant memory improvements (SMD = 0.24; 95% CI: −0.04 to 0.52; $I^2 = 38\%$; $p = 0.09$ and SMD = 0.33; 95% CI: −0.07 to 0.74; $I^2 = 78\%$; $p = 0.11$, respectively) (16). However, significant differences were observed when considering age; older adults (66–76 years) showed notable improvements in memory (SMD = 0.88; 95% CI: 0.22–1.55; $I^2 = 83\%$; $p = 0.009$), whereas younger participants (11–31 years) exhibited no significant changes (SMD = 0.03; 95% CI: −0.14 to 0.20; $I^2 = 0\%$; $p = 0.72$) (16). Gender-specific analyses indicated moderate improvements in women (SMD = 0.39; 95% CI: −0.07 to 0.86; $I^2 = 62\%$; $p = 0.10$), while no significant changes were observed in men (SMD = −0.12; 95% CI: −1.02 to 0.78; $p = 0.79$) (16) he form of creatine supplementation also appeared to matter; powdered creatine yielded better results (SMD = 0.35; 95% CI: 0.05–0.66; $I^2 = 73\%$; $p = 0.02$) compared to capsule forms, which showed no significant effects (SMD = 0.04; 95% CI: −0.30 to 0.39; $I^2 = 0\%$; $p = 0.80$) (16). These findings suggest that creatine supplementation may positively influence memory, particularly in older adults who use powdered forms. However, results in younger populations and across varying doses remain inconclusive, necessitating further research.

Safety of Creatine Supplementation

In the review conducted by de Guingand et al. (27), which analyzed 29 studies involving 951 female participants of varying ages, hormonal statuses, and supplementation goals, no significant adverse effects were reported. The creatine doses varied across studies, ranging from 2–10 g/day for several weeks to 12 months as maintenance doses, and 20–30 g/day for 5–7 days during a loading phase (27). Gastrointestinal symptoms such as nausea, bloating, and abdominal discomfort occurred with similar frequency in both the creatine and placebo groups. No fatalities were reported in any of the studies. Furthermore, no significant differences were observed in kidney function biomarkers (e.g., eGFR) or liver enzyme levels between creatine and placebo groups. These findings suggest that creatine is a safe dietary supplement for women (27).

An earlier study by Lugaresi et al. (28) assessed the effects of long-term creatine supplementation on kidney function in a group of 26 young men engaged in regular resistance training and consuming high-protein diets (≥1.2 g/kg/day). Participants in the creatine group received 20 g/day for 5 days during a loading phase, followed by 5 g/day for 12 weeks as a maintenance dose (28). The results showed no significant differences in glomerular filtration rate (GFR) between the creatine and placebo groups (creatine group: pre-study 101.42 ± 13.11; post-study 108.78 ± 14.41 $mL/min/1.73m^2$; placebo group: pre-study 103.29 ± 17.64; post-study 106.68 ± 16.05 $mL/min/1.73m^2$; group x time interaction: $F = 0.21$; $p = 0.64$). Similarly, there were no significant changes in proteinuria, albuminuria, or electrolyte levels (e.g., sodium, potassium) between the groups (28). These findings confirm the safety of creatine use in healthy, physically active populations, even when combined with high-protein diets.

A review by Candow et al. (29), which examined studies involving older adults, postmenopausal women, individuals with Parkinson’s disease, and those with chronic conditions, highlighted that direct studies on creatine supplementation in such populations remain limited. However, available evidence suggests that creatine supplementation is safe (29). or instance, in frail older adults (n = 9, 70 ± 5 years), creatine supplementation (5 g/day) for 14 weeks, combined with a protein diet and resistance training, had no effect on levels of urea, creatinine, bilirubin, alkaline phosphatase, aminotransferases, or creatine kinase (29). Similarly, in postmenopausal women (n = 23, 57 ± 6 years) who supplemented with creatine (0.1 g/kg/day) for 12 months, no negative changes in liver or kidney function were observed. This was confirmed by a larger study involving postmenopausal women (n = 56) who consumed 1 g of creatine daily for a year, which also showed no effect on urinary albumin levels (29). In patients with type II diabetes, 12 weeks of creatine supplementation had no significant impact on renal parameters compared to placebo. Additionally, a two-year creatine supplementation regimen (2–20 g/day) in Parkinson’s disease patients (n = 40, 60 ± 9.4 years) did not show any evidence of cytotoxicity (29). Notably, the International Society for Sports Nutrition confirmed that creatine is a safe supplement for older adults (30).

Conclusion

Creatine supplementation is a well-established method for improving physical performance and supporting recovery, particularly when paired with resistance training. Research shows that it enhances muscle strength, increases lean body mass, and accelerates ATP resynthesis.

Additionally, creatine plays a key role in cognitive function, making it a promising supplement for neuroprotection and improving cognitive abilities, especially in older adults. Its positive effects on memory are most noticeable in populations with reduced endogenous creatine synthesis, such as the elderly. However, the results in younger individuals remain inconsistent, indicating the need for further research in this group.

Creatine is a versatile and well-tolerated supplement with broad applications in both athletic and health-related settings, which explains its growing popularity across various populations. Moreover, studies consistently demonstrate that creatine is safe to use, even in long-term supplementation. Research involving both healthy individuals and those with chronic conditions, like type II diabetes or Parkinson's disease, has found no negative impact on liver or kidney function. Any reported side effects, such as mild gastrointestinal discomfort, were comparable to those in placebo groups. This strong safety profile supports the use of creatine as a reliable and effective supplement for improving physical and cognitive performance.

Disclosure:

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All authors have read and agreed with the published version of the manuscript. Funding Statement: The study did not receive special funding. Conflict of Interest Statement: There is no conflict of interest.

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