The Role Of Creatine Supplementation In Enhanching Cognitive Function In The General Population: A Literature Review

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ABSTRACT

Background: Creatine is a vital compound in cellular energy homeostasis, playing a key role in regenerating adenosine triphosphate (ATP) in tissues with high energy demands, such as the brain. Due to its importance in cerebral bioenergetics, creatine supplementation has been investigated as a potential cognitive enhancer. This literature review aims to synthesize and evaluate the current evidence on the effects of creatine supplementation on cognitive function in the healthy general population. **Methods**: A systematic search was conducted on PubMed and Google Scholar for articles published between 2015 and 2025. The search strategy utilized the PICO framework (Population: healthy adults; Intervention: oral creatine monohydrate; Comparison: placebo; Outcome: cognitive function) and specific keywords, including "creatine supplement," "cognitive function," and "adult." The review included only full-text, peer-reviewed randomized controlled trials (RCTs) conducted on healthy human populations. **Results**: The analysis of five selected RCTs revealed that the impact of creatine on cognition is highly context-dependent. In healthy adults under normal conditions, supplementation showed minimal to no significant improvement in major cognitive domains; for instance, working memory tasks showed only borderline improvement ($p = 0.064$). However, evidence indicates a beneficial effect under conditions of significant metabolic stress. Studies demonstrated that creatine can mitigate cognitive decline associated with sleep deprivation and hypoxia, particularly improving accuracy ($p = 0.026$), processing speed, and attention. The efficacy appears linked to higher doses or acute loading protocols used in response to these stressors. **Conclusion**: Creatine supplementation does not appear to be a general cognitive enhancer for healthy individuals in normal states. Its primary benefit seems to be as a neuroprotective agent that supports cognitive function during periods of high cerebral energy demand. Future research should focus on larger, more diverse cohorts, standardized dosing protocols, and the inclusion of neuroimaging measures to correlate biological changes with cognitive outcomes, thereby

clarifying the specific conditions under which creatine may be beneficial.

Keywords: Creatine; cognitive function; Literature Review

Introduction

Creatine is a nitrogenous organic acid that plays a key role in brain energy metabolism[1,2]. It is synthesized endogenously from the amino acids arginine, glycine, and methionine and obtained via dietary intake (primarily red meat and seafood)[1,3]. Once taken up into cells (via the SLC6A8 transporter), creatine is reversibly converted into phosphocreatine (PCr) by creatine kinase[1,4]. This PCr system provides rapid phosphate transfer to regenerate adenosine triphosphate (ATP) during periods of high demand[1,2]. In other words, creatine acts as a spatial and temporal energy buffer that supports ATP homeostasis under acute stress, supplementing slower processes like oxidative phosphorylation[1,5]. Notably, though most creatine is stored in skeletal muscle, the brain – which consumes roughly 20% of the body's energy – also contains a pool of creatine with a brain-specific creatine kinase isoform (BB-CK), underscoring the importance of creatine in cerebral energetics[2].

Humans obtain creatine both through endogenous synthesis and diet. Endogenous production is a two-step process occurring mainly in liver, kidney and within the brain itself[1,2]. Dietary creatine comes almost exclusively from animal products, such as meat, poultry, fish, are the richest sources, with dairy containing only small amounts[1]. In fact, young omnivorous adults lose about 1.7% of their total creatine pool per day (~14.6 mmol/day in a 70 kg male) to nonenzymatic conversion to creatinine[1]. Roughly half of this daily loss can be replaced through diet in omnivores, but vegetarians – who consume virtually no exogenous creatine – must rely almost entirely on internal synthesis[1,5]. Maintaining total body creatine (approximately 120 g in a 70 kg man) therefore imposes a substantial metabolic burden: creatine biosynthesis consumes about 40% of labile methyl groups from S-adenosylmethionine and ~20–30% of arginine's amidino groups. The brain's creatine homeostasis is similarly dual-sourced: the nervous system contains the full enzymatic machinery for creatine synthesis, and creatine is transported across the blood–brain barrier and between neurons and astrocytes. Habitual dietary intake has surprisingly little effect on baseline brain phosphocreatine levels: vegetarians and omnivores show comparable brain PCr content in neuroimaging studies[2,5]. Nonetheless, dietary creatine can augment brain creatine when intrinsic synthesis is limited (e.g. in genetic disorders of creatine biosynthesis)[2].

Due to the integral role of creatine in ATP buffering, it has been hypothesized to influence cognitive processes[2]. Neurons are energy-hungry cells, and tasks like neurotransmission and synaptic plasticity require rapid ATP turnover[1,2]. By increasing the brain's PCr reservoir, creatine supplementation can accelerate ATP replenishment during cognitively demanding activities[2]. Moreover, creatine has indirect antioxidant effects: it can facilitate mitochondrial ATP coupling and scavenge reactive oxygen species, potentially reducing oxidative stress in neural tissue[2].

In humans, the link between creatine and cognition is highlighted by creatine-deficiency syndromes (mutations in *AGAT*, *GAMT*, or *SLC6A8*) that cause intellectual disability and developmental delays; importantly, supplementing these patients with creatine partially reverses their neurological symptoms (except in the transporter-deficiency, where uptake is impaired)[2,5]. Furthermore, higher resting brain creatine levels (achieved through mental training or otherwise) correlate with better performance on tasks like recognition memory[2,5]. Collectively, these mechanistic data suggest that elevating brain creatine could enhance cognitive function by bolstering energy reserves, neurotransmitter synthesis, synaptic plasticity, and neuroprotection[2,5].

The established role of creatine in brain energy metabolism, combined with the profound neurological effects seen in deficiency syndromes, provides a strong theoretical and clinical foundation for its potential as a cognitive enhancer. Yet, translating this potential into clear benefits for healthy adults has proven complex. The current body of evidence is suggestive but not yet definitive, marked by studies with small samples and inconsistent methodologies that make broad conclusions difficult. Critical gaps persist in the current understanding of optimal dosing and target populations. As highlighted by Xu et al. (2024), the growing challenge of age-related cognitive decline makes the systematic assessment of safe, non-pharmacological interventions like creatine a priority[6]. To address these gaps, the present review aims to synthesize the existing literature on creatine supplementation and cognitive function in healthy adults. The objective of this study is to clarify how creatine affects various cognitive domains, thereby providing an evidence-based rationale for its potential use as a cognitive enhancer.

Material and Methods

A systematic literature search was conducted to identify articles investigating the effects of creatine supplementation on cognitive function in adults. The search strategy was constructed using a combination of keywords and Boolean operators (AND/OR), structured as follows: ("creatine" OR "creatine supplementation" OR "creatine monohydrate") AND ("cognitive function" OR "cognition" OR "brain function" OR "memory" OR "executive function") AND ("adults" OR "healthy subjects").

The PICO (Population, Intervention, Comparison, Outcome) framework was utilized to structure the search for relevant literature. PICO is a framework commonly used in evidence-based practice to systematically formulate and answer clinical or research questions. The acronym represents P (Patient/Population), which describes the group of interest; I (Intervention), the treatment or exposure being studied; C (Comparison), the control or alternative; and O (Outcome), the result being measured. For this review, the PICO framework was defined as follows:

- P (Population): Healthy general population, including young adults, the elderly, vegetarians, and omnivores
- I (Intervention): Oral supplementation with creatine monohydrate
- C (Comparison): A control group receiving a placebo

- O (Outcome): Changes or improvements in domains of cognitive function (e.g., memory, processing speed, executive function, intelligence).

To ensure alignment with the objectives of this review, the collected literature was screened based on specific inclusion and exclusion criteria. The inclusion criteria required studies to be: (1) full-text articles published in English-language, peer-reviewed journals; (2) published between January 1, 2015 and October 22, 2025; (3) conducted on healthy human subjects, ranging from young adults to the elderly and including both vegetarian and omnivore subpopulations; (4) randomized controlled trials (RCTs); and (5) investigating oral supplementation with creatine monohydrate using a clearly defined dosage and duration. Conversely, studies were excluded if they were: (1) animal studies, case reports, or other non-RCT designs such as observational studies; (2) utilizing multi-component supplements where the specific effects of creatine could not be isolated; and (3) failing to report quantitative data on cognitive function.

Based on these search strategies and selection criteria, a total of 282 research records were identified, distributed as follows: 153 from PubMed and 129 from Google Scholar. After removing 12 duplicate records, 270 documents proceeded to the initial screening phase. During this phase, titles and abstracts were reviewed, resulting in the exclusion of 252 records that were not relevant to the research topic. Consequently, 18 reports were sought for retrieval; however, one report could not be retrieved, resulting in 17 records deemed eligible for full-text review. During the full-text review process, 12 studies were excluded for not meeting the predefined inclusion criteria. The specific reasons for exclusion were: inappropriate populations (n=9), inappropriate research design (n=1), and incomplete data (n=1). After rigorous screening, 5 studies met the established inclusion criteria and were included in the final analysis. The detailed process of literature search and screening is illustrated in Figure 1.

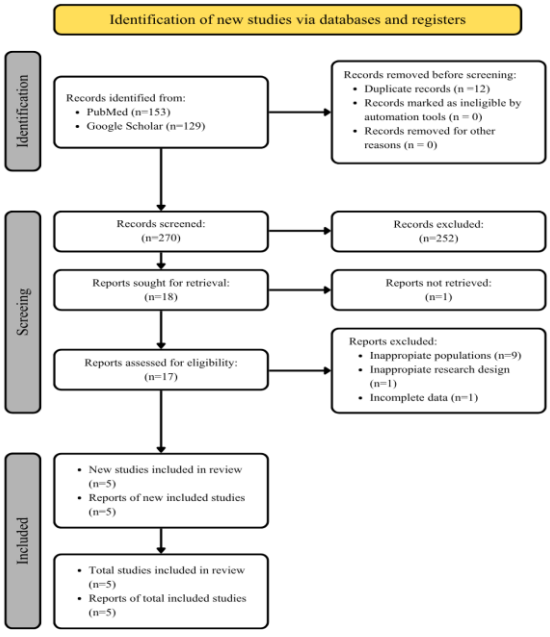

Figure 1. PRISMA diagram of searching and screening process

Discussion

Table 1. Reviewed Literature

Author (Year)	Methods / Design	N (Sample)	Participant Age	Male/Female (M / F)	Duration	Creatine Type / Dose	Outcomes
Sandkühler et al. (2023)	Randomized, double-blind, placebo-controlled, cross-over; primary tasks: RAPM & BDS; 8 exploratory tests.	123	Adults ≥18 years	Mixed (not specified)	6 weeks	Creatine monohydrate (CreaPure®) 5 g/day	**Small beneficial effect**; borderline improvement on BDS (p=0.064); no significant change in RAPM; side effects more frequent with creatine.
Moriarty et al. (2023)	Randomized, double-blind, repeated-measures; fNIRS on prefrontal cortex; 3 groups (CR10, CR20, placebo).	30	Mean 21 years (19–33)	11 M / 19 F	6 weeks	Creatine monohydrate 10 g/day (CR10) or 20 g/day (CR20)	**No significant effect** on attention, episodic memory, or processing speed; trend toward lower PFC O_2Hb in CR10 (p=0.06).
Van Cutsem et al. (2020)	Randomized, double-blind, crossover; 90-min Stroop mental-fatigue protocol + visuomotor & Flanker tasks.	14	24 ± 3 years	10 M / 4 F	7 days (loading phase)	Creatine monohydrate 20 g/day	**Improved Stroop accuracy** and strength endurance; no protection against fatigue-related decline on visuomotor/Flanker tasks.
Gordji-Nejad et al. (2024)	Randomized, double-blind, cross-over; single high-dose (0.35 g/kg) during partial sleep deprivation; MRS + cognitive battery.	15	23 ± 2 years (20–28)	7 M / 8 F	Single acute dose (~7–9 h post-dose)	Creatine monohydrate 0.35 g/kg single oral dose	Increased brain PCr/Pi and tCr/tNAA; prevented pH drop; **improved reaction time and cognition during sleep deprivation.**
Turner et al. (2015)	Randomized, double-blind, placebo-controlled, cross-over; 7-day loading (20 g/day) + 90-min hypoxia exposure; MRS + TMS + cognitive tests.	15	Mean 31 years (21–55)	10 M / 5 F	7 days (loading), 5-week washout	Creatine monohydrate 20 g/day for 7 days	**Increased brain creatine (~9%); preserved attention/executive function during hypoxia**; neuroprotective under energy stress.

A review of the five selected literature indicates that the impact of creatine supplementation on cognitive function varies significantly depending on the specific context of each study. In healthy adult populations under normal, non-stressful conditions, most small-scale studies report no significant improvements in major cognitive domains. For instance, Sandkühler et al. (2023) and Moriarty et al. (2023) both 6-week cross-over randomized controlled trials (RCTs) demonstrated only a marginal improvement in working memory, as measured by the Backward Digit Span test (p=0.064), with no discernible effect on reasoning (Raven's APM) or other cognitive tasks[7,8]. This aligns with their conclusions that the effect of creatine on cognition in healthy adults is likely minimal to non-existent.

Conversely, the benefits of creatine become more pronounced under conditions of high metabolic or cognitive demand. Two studies highlighted creatine's protective effect against stress-induced cognitive decline. Gordji-Nejad et al. (2024) found that a single dose of 0.35 g/kg of creatine improved processing speed and cognitive performance during sleep deprivation[9]. Similarly, Turner et al. (2015) reported that 7-day supplementation with creatine (20 g/day) prevented a decline in attention during severe hypoxia. Van Cutsem et al. (2020) employed a mentally fatiguing Stroop task protocol and found that the creatine group exhibited higher accuracy (p=0.026) compared to the placebo group, although visuomotor and Flanker task performance still deteriorated due to fatigue[10,11]. In other words, creatine appears to enhance executive function/inhibition (Stroop) and maintain focus during acute fatigue, but it does not completely shield against all adverse effects of cognitive exhaustion.

Regarding intervention design, all five studies generally adopted double-blind, placebo controlled RCT methodologies. This contributes to their relatively strong internal validity. The primary variability identified among the studies lies in the dosage and duration of creatine

administration. Sandkühler et al. (2023) and Moriarty et al. (2023) utilized conventional doses of 5–10 g/day for 6 weeks[7]. In contrast, Gordji-Nejad et al. (2024), Van Cutsem et al. (2020), and Turner et al. (2015) employed higher doses (up to 20 g/day or a single 0.35 g/kg dose) over shorter periods (7 days or a single administration) to induce a rapid increase in bodily creatine levels.

The results suggest that higher doses or "energy crisis" scenarios, such as sleep deprivation and hypoxia, tend to yield measurable positive effects, whereas standard long-term dosing in healthy individuals produces minimal impact[9–11]. This context-dependent efficacy can be explained through a physiological perspective linking neural metabolism to the creatine kinase system. Creatine supplementation elevates brain PCr stores, which function as a rapid temporal energy buffer to regenerate adenosine ATP from ADP. Under normal resting conditions, slower oxidative phosphorylation is sufficient to meet neuronal energy needs, rendering the additional PCr reserve redundant. However, during acute metabolic stress where neuronal ATP turnover outpaces synthesis the enhanced PCr pool becomes critical for sustaining synaptic function. This mechanism clarifies why creatine acts less as a general enhancer and more as a neuroprotective buffer against energy deficits.

The sample populations in these studies were predominantly healthy young adults. The composition of the samples varied by gender, including both male and female participants. None of the studies specifically focused on older adults or clinical populations. One study even reported a broad age range of 21–55 years, reflecting the general adult population. Dietary habits (vegetarian and omnivore) were examined by Sandkühler et al., but no significant differences in outcomes were found. Therefore, these findings can be interpreted as applicable to the general healthy adult population, although caution is warranted when generalizing to older age groups or individuals with pathological conditions[7].

Cognitive evaluation in these studies, corresponding to the "Outcome" component of PICO, encompassed the domains of memory, processing speed, executive function, and intelligence. Researchers utilized various specific instruments, such as the Backward Digit Span and Raven's APM (Sandkühler et al.) to measure working memory and reasoning; episodic memory and reaction speed tests (Moriarty et al.); and the Stroop and Flanker tests (Van Cutsem et al.) to assess executive function and attention[7,8,11]. The results showed no consistent improvements in memory or abstract intelligence under resting conditions. Conversely, enhancements were identified in aspects of executive function, focus, and processing speed, particularly when individuals were under stress. This indicates that the efficacy of creatine is conditional and dependent on cerebral energy requirements. Creatine appears to be more beneficial for tasks demanding rapid processing or sustained vigilance, yet less influential in enhancing general intelligence or semantic memory in populations without a pre-existing deficit.

Critically, although the double-blind RCT design is a methodological strength, these studies possess significant limitations. Most involved small participant numbers (N=14–30), with the

exception of Sandkühler et al. (N=123)[7]. Small sample sizes reduce the statistical power to detect what may be small effects of creatine. The treatment durations also varied and were sometimes relatively short (7–42 days), whereas increases in brain creatine levels typically become apparent only after prolonged supplementation. The use of different cognitive tests across studies complicates direct comparisons. Furthermore, some studies did not measure brain creatine concentrations, making it difficult to substantiate the proposed mechanism for cognitive enhancement. The transition from in-person to online testing in the study by Sandkühler et al. due to the COVID-19 pandemic introduced additional data variability. The potential for unblinding due to creatine's characteristic gastrointestinal side effects and different powder textures could also compromise the double-blind design. For example, Sandkühler et al. noted that approximately 59% of participants correctly guessed their treatment sequence, a result that was borderline statistically significant. All these factors must be considered as limitations of the study designs[7].

On the other hand, several strengths can be identified. All studies utilized placebo controls and robust cross-over or parallel RCT designs. Cognitive assessments were conducted using standardized and validated instruments (e.g., Raven's, Stroop, PVT) under controlled conditions. Several studies also incorporated physiological measurements (e.g., fNIRS, MRS, TMS), which enhances the understanding of the underlying mechanisms. The studies by Sandkühler et al. and Turner et al., for instance, confirmed that creatine supplementation did increase brain creatine stores, albeit modestly. The consistency in certain design aspects, such as the use of a 20 g/day dose by both Van Cutsem et al. and Turner et al., facilitates comparison between specific studies[10,11].

Conclusion

Based on the reviewed literature, creatine supplementation does not appear to serve as a general cognitive enhancer for healthy individuals in normal states. Instead, its primary benefit emerges as a neuroprotective agent that supports cognitive function specifically during periods of high cerebral energy demand. Consequently, clinical implications are most relevant for populations routinely exposed to metabolic stress or cognitive fatigue, such as shift workers requiring sustained vigilance or older adults experiencing age-related decline in cerebral bioenergetics.

Given that these effects appear to be conditional and subtle, future investigations must move beyond current limitations by prioritizing larger, more heterogeneous samples—including individuals with mild cognitive deficits—to enhance generalizability. Crucially, research protocols must establish standardized dosing and supplementation durations while incorporating advanced neuroimaging techniques, such as Magnetic Resonance Spectroscopy (MRS), to directly correlate changes in cerebral creatine levels with cognitive outcomes. Considering creatine’s established safety profile and low cost, executing strategically designed trials with sufficient statistical power to definitively confirm or refute these benefits remains a high-priority direction for future research.

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