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SUPPLEMENTING BOTH MUSCLES AND THE BRAIN: A LITERATURE REVIEW ON THE POTENTIAL OF CREATINE SUPPLEMENTATION IN COGNITIVE PERFORMANCE IN SELECTED DEMOGRAPHIC SUBGROUPS

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ABSTRACT

Creatin is one of the most common supplements for athletes and has been well-studied for its safety and efficiency. It has a documented impact on enhanced performance and recovery among sportsmen. Considering, many researchers have decided to study its impact on cognitive performance in different patient demographics. The positive impact of creatin on cognition observed in studies on athletes sparked interest in its usefulness in different demographic groups. Its favorable price and nearly adverse effect-free profile would make it a great nutraceutical for large-scale use. This study aimed to review the currently published clinical trials on the effect of creatin on cognitive performance in specific subgroups, i.e. healthy adult participants, healthy elderly participants as well as patients suffering from certain psychiatric conditions. The analysis of the published trials showed weak to moderate evidence on creatin's role in cognitive performance improvement. More large-scale randomized studies are warranted to establish the therapeutic value of creatin supplementation on mental processes.

KEYWORDS

Creatine Supplementation, Cognitive Functioning, Healthy Participants, Elderly Individuals, Psychiatric Disorders

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Introduction.

Creatin – structure and function in the human body

Creatin is an amino acid that is commonly found in the skeletal muscle and in much smaller quantities in the testes and the brain (Buford et al., 2007). Up to 2% of skeletal creatine is degraded and excreted by kidneys and the form of creatinine, thus the body needs to replenish 1-3 g of creatine to sustain its normal levels (Balsom et al., 1994; Harris et al., 1992; Hultman et al., 1996). Half of those needs are satisfied by diet, with red meat and fish being the major dietary source of creatin, while the other half is synthesized by the liver and kidneys from two endogenous amino acids: alanine and glycine (Bertin et al., 2007; Brosnan & Brosnan, 2016; Paddon-Jones et al., 2004; Sahlin & Harris, 2011). Certain population groups have a lower creatin content in the skeletal muscles (mostly vegetarians and vegans, less commonly people with inborn creatin kinase deficiencies), while professional athletes have greater creatin demands due to increased requirements for sources of available energy during strenuous exercise (Burke et al., 2003; Green et al., 1996).

The main role of creatin in the human body is providing such energy availability. Creatin kinase transfers a phosphoryl group from ATP, the pivotal energy source, to creatin, leading to formation of phosphocreatine and ADP. This newly formed phosphate bond in phosphocreatine has a much higher free energy of hydrolysis compared to ATP (Wyss & Kaddurah-Daouk, 2000). It is also a much more effective as an energy source than ATP, due to its smaller size and faster diffusion to places of high demand for energy. Moreover, at a cellular level, phosphocreatine can easily move between the places of ATP production – glycolysis in the cytosol and oxidative phosphorylation in the mitochondria – with places that need ATP as a substrate – that is, ATPases, all while maintaining a proper of ATP/ADP and ATP consumption (Hu & Yacoub, 2012; Lygate, 2024). Altogether, it helps mitigate the production of reactive oxygen species (ROS), compounds that, when at excessive amounts, are known to cause oxidative stress and cellular damage (Forrester et al., 2018). These cell-level reactions are known to cause not only impairment in physical exercise performance but also play a role in accelerating brain aging and the development of various neurological disorders. (Dringen et al., 2000; MohanKumar et al., 2023).

The use of creatin supplementation in sports

Although discovered in 1832 by a French scientist Chevreul, creatin has gained a wider interest as a nutraceutical in the 1990s, when Harris et al. showed that creatin supplementation can increase the skeletal creatin concentration by up to 50% (Harris et al., 1992). Followed by other studies, it has been concluded that a daily dose of 20-30 g of creatin supplementation a day does lead to an elevation of creatin concentration in the body with nearly no severe side effects (Becque et al., 2000; Greenhaff et al., 1994; Kurosawa et al., 2003; McKenna et al., 1999; Smith et al., 1999; Stout et al., 2000). Since its role as an energy source has been previously elucidated, researchers began to study the effect of creatin supplementation on physical performance among athletes. They found greater gains in strength and muscle mass coupled with increased performance in both high-intensity training as well as acute bouts of exercise. Moreover, they observed better adaptability to exercise in high temperatures, enhanced recovery time, lower rates of injury and prompt rehabilitation (Kreider et al., 2017). These results have been consistently replicated throughout the years by different scientists who examined various age groups and different types of sports.

Another interesting property of creatine is neuroprotection in the brain and spinal cord. Such findings have firstly been reported in rats and mice. The animals were given supplemental creatin and then were inflicted: traumatic brain injury (TBI) or cerebral ischemia (CI) or spinal cord injury (SCI) in a controlled manner. Results showed a much lesser degree of brain cortex damage in TBI, reduced scar tissue size in CI and alleviated gray matter loss after SCI. Furthermore, the CI models showed greater survival of neuronal cells and improved memory and learning following the ingestion of creatin. Such outcomes may be attributed to improved mitochondrial energy mechanics when sources of energy are plentiful and available in the form of phosphocreatine.(Adcock et al., 2002; Allah Yar et al., 2015; Prass et al., 2007; Rabchevsky et al., 2003; Sullivan et al., 2000; Zhu et al., 2004)

Could creatin supplementation aid cognition?

Encouraged by the positive results of creatin supplementation on muscle mass and function as well as incentives regarding creatin's neuroprotective potential in animal models, more researchers have realized the need to study the effect of creating on the most energy-consuming organ in the body, i.e. the brain. Its need for fuel is constant, yet may increase dramatically following a mentally challenging task (Bruckmaier et al., 2020). In such moments, thanks to its preferential properties as an energy source, creatin may rapidly donate its phosphoryl group and thus maintain stable ATP levels (Aujla et al., 2025). As stated before, creatin is indeed naturally present in the brain. It has been hypothesized that brain creatin concentration might also be increased by supplementation, and that such increase could have beneficial effects on the cognition (Candow et al., 2022).

Unfortunately, the effect of supplementation on brain creatin content is not as straightforward. The uptake of both exogenous and endogenous (liver-produced) creatin is regulated by the blood brain barrier and its constituent, creatin transporter 1 (CT1), which is a membrane protein crucial for creatin influx to the brain cells. Also, although it has previously been stated that it is liver and kidneys that produce creatin from alanine and guanine, this feat is also accomplished by the brain, though to a much smaller extent. One problem is a small concentration of CT1 in blood brain barrier vessels, which vastly limits the amount of dietary creatin that may be utilized by the brain (Béard & Braissant, 2010; Braissant, 2012). Another problem is the mechanism of negative feedback loop of exerted on the L-arginine:glycine amidinotransferase (LAGA), an enzyme that produce creatin in the brain – the more dietary creatin, the more halt in the activity of those enzymes (Jia & Zhu, 2023). It might be the reason why studies on brain creatin content measured by H1 magnetic resonance imaging in both rats and human showed no significant increase after creatin supplementation (Horn et al., 1998; Merege-Filho et al., 2017), and a study on vegetarians showed brain creatin concentrations no different to those found among meat-eaters (Yazigi Solis et al., 2014). Some evidence shows that this lowered expression of CT1 and the downregulation of LAGA might be partially overcome by increasing creatin dose beyond the recommended 20 g/day, but the long term effects are still undetermined (Dechent et al., 1999). Another solution is the use of guanidinoacetic acid (GAA), a precursor of creatin that may pass through the blood brain barrier much easier thanks to less specific transport mechanisms (Tachikawa & Hosoya, 2011). The supplementation of GAA for 8 weeks has shown to influence the brain creatin content in a nonuniform way, that is increasing in the cerebellum, and white and gray matter, while actually decreasing in the thalamus (Ostojic et al., 2017). The mechanism behind such varying distribution of creatin in different regions of the brain remains to be discovered.

Notwithstanding, some researchers still decided to examine whether providing an additional supply of creatin could positively affect cognition in humans. There are various studies with different regimens, some of which

include a combination of creatin and different nutraceuticals (i.e. caffeine or guarana complex), while others couple the effect of creatin and sleep deprivation or physical activity on cognitive performance measured by specific tasks. After careful analysis of available research, we have selected a few appropriate studies. The reasoning behind our choice is included in the following paragraph (methodology) and partially in the discussion.

Methodology

An electronic literature search was conducted using PubMed up to July 2025. Keywords included 'creatin', 'cognition', 'healthy adults', 'elderly' and 'psychiatric disorders'. Studies were selected based on relevance to the role of creatin supplementation in cognitive performance. Included were randomized clinical trials published in English, focusing on healthy adults, healthy elderly and patients suffering from psychiatric disorders. Studies on children and adolescents, animal studies, studies involving sleep deprivation, studies without an available DOI and non-full-text articles were excluded. The information on the study design was summarized in tables, while the results from those studies were synthesized narratively.

Creatin supplementation on cognition in healthy individuals

Cognition plays a vital role in everyday life; thus, its enhancement is highly desirable. As previously mentioned, it has been hypothesized that an increased supply of energy donors for the brain, i.e. creatin, could provide beneficial effects in that aspect. Studies conducted on healthy individuals to study the relationship between creatin supplementation and cognition are very variable, since they use different population subgroups (e.g. vegetarians, omnivores, women), employ different creatin dosage regimens and use various types of cognitive tests to measure a difference (or lack thereof) in the mental performance. What is more, some studies also evaluated whether creatin combined with strength training could yield superior results, since exercise has been largely documented for its role in cognitive enhancement (Boa Sorte Silva et al., 2024). In this review, we included randomized controlled trials performed on humans. Due to the small number of such studies, we allowed for the inclusion of one study that supplemented both creatin and guanidinoacetic acid, a natural precursor of creatin, and we also included a study that had 4 subject groups examining the effect of creatin supplementation or placebo with or without strength training.

The information on the type of study design, creatin dosage and different measurements used to assess the effect of creatin supplementation is summarized in Table 1.

Table 1. Comparison of the studies examining the effects of creatine supplementation on cognitive functions in healthy individuals. Abbreviations: g/d: grams per day, BDS: Backward Digits Span, RAPM: Raven Advanced Progressive Matrices, TCOWAT: The Controlled Oral Word Association Test, GAA: guanidinoacetic acid, SpO_2: oxygen saturation, tHb: total hemoglobin, REST: rest phase, MED: meditation that focused on mindful breathing phase, TASK: during a three-component cognitive task phase, REC: post-task recovery phase, fNIRS: functional near-infrared spectroscopy, fMRI: functional magnetic resonance imaging, BOLD: Blood Oxygenation Level Dependent signal

Study	Study design	Treatment duration	Number of participants	Creatin dose	Cognitive tests used (?)
Sandkühler et al., 2023	parallel arm	6 weeks	123	5g/d	• BDS • RAPM • exploratory tests*
Rae et al., 2003	crossover	6 weeks	45	5g/d	• BDS • RAPM
Benton et al., 2011	parallel arm	5 days	121	20g/d	• memory-word recall • reaction times • vigilance-rapid information processing task • verbal fluency (via TCOWAT)
Zanini et al., 2024	crossover	7 days	19	2g/d creatin + 2g/d GAA	• SpO_2 and tHb in the prefrontal cortex during REST, MED, TASK, REC

Van Cutsen J et al., 2020	crossover	7 days	14	20g/d	• 7 min sport-specific visuomotor task • dynamic handgrip strength endurance task • 3 min Flanker test • 90 min Stroop task
Moriarty et al., 2023	parallel arm	6 weeks	30	10g/d or 20g/d*	• oxyhemoglobin in the prefrontal cortex (via fNIRS) • processing speed • episodic memory • attention
Hammett et al., 2010	parallel arm	7 days	22	20g/d for 5 days, 5g/d for 2 days	• BDS • RAPM • BOLD signal in primary visual cortex (via fMRI)
Ling et al., 2009	parallel arm	2 weeks	34	5g/d***	• RAPM • Memory Scanning • Number-Pair Matching • Sustained Attention • Flanker test

*exploratory tests: focused on attention, verbal fluency, task switching and memory

**two study groups in Moriarty study

***the substance used in this study was creatin ethyl ester, while all the other trials used creatin monohydrate

Sandkühler et al., Rae et al., Hammett et al. and Ling et al. used a shorter, standardized 10-min version of Raven Advances Progressive Matrices (RAPM) to evaluate abstract reasoning. The test consists of a series of geometric forms, among which one is missing. The participant must choose the most suitable out of eight alternatives. While Rae et al. and Ling et al. showed significant difference in the results following a period of creatin supplementation, Sandkühler et al. failed to replicate them, documenting only weak to moderate evidence for small benefit, similarly to Hammet et al., who only reported a non-significant increase in RAPM score in the creatin group. The study by Sandkühler et al. also showed no effect on the exploratory tests (listed in notes under Table 1), which could partially be explained by the fact that those tests were too easy for the participants, so no significant difference could be observed.(Hammett et al., 2010; Ling et al., 2009; Rae et al., 2003; Sandkühler et al., 2023)

Sandkühler et al., Rae et al. and Hammett et al. also used Backward Digit Span (BDS), a test on working memory where the participant must listen to increasingly longer series of digits and then repeat them in the reverse order. Again, Sandkühler failed to replicate a significant score increase in BDS, which was indeed observed by both Rae et al. and Hammett et al.

The study by VAN Cutsen involved two physical tasks (visuomotor task and dynamic handgrip strength test) followed by two cognitive tests – Flanker test and Stroop task. After the supplementation period of 7 days, the tests were performed again, but in the opposite order, i.e. the cognitive tests took place before the physical tests. The results showed significant enhancement in accuracy in Stroop Task, a test where the participant is supposed to name the color of a word, rather than to say a word and a significant increase in handgrip strength (yet only in the nondominant hand) in the creatin group. Creatin supplementation failed to improve the scores on the visuomotor task nor the Flanker test – one that assesses attention and response inhibition by asking the participant to concentrate on a target stimulus such as an arrow whilst ignoring the other arrows moving in the target's vicinity (J et al., 2020). Another study by Benton et al. found a significant influence of creatin supplementation on memory-word recall and a slightly weaker effect on reaction times, while creatin had no influence on vigilance-rapid information processing task or verbal fluency scores (Benton & Donohoe, 2011). Meanwhile, Moriarty et al. failed to demonstrate any effect of creatin on any of the constituents of its cognitive test battery, i.e. processing speed, episodic memory and attention. Furthermore, this study used functional near-infrared spectroscopy (fNIRS) to measure the prefrontal cortex oxyhemoglobin level ($PFCO_2Hb$) during those cognitive tests and showed significantly lower levels of that parameter in the group ingesting 10 grams of creatine versus placebo during the processing speed test (Moriarty et al., 2023).

There were two more studies that used neuroimaging to evaluate the effect of creatin supplementation on certain oxygen and circulation-related parameters. Zanini et al. measured the levels of oxygen saturation and total hemoglobin levels in the prefrontal cortex during four phases: rest phase (REST), meditation that focused on mindful breathing phase (MED), during a three-component cognitive task phase (TASK) and during post-task recovery phase (REC). They found a significant increase in oxygen saturation levels (SpO_2) in the creatin group during the REST, MED and REC phases, yet not in the TASK phase (Dragana Zanini, 2024). While a decrease in oxygen levels is a natural phenomenon following a cognitive task and creatin would not be expected to counter that effect, perhaps the observed increase of SpO_2 during the phases associated with rest could provide an additional 'oxygen buffer' during the subsequent cognitive task.

Conversely, Hammett et al. used Blood Oxygenation Level Dependent (BOLD) signal in the primary visual cortex (V1) via functional Magnetic Resonance Imaging to measure brain activity. BOLD signal reflects deoxyhemoglobin level that rises following neural activity, which consumes large amounts of oxygen and thus depletes oxyhemoglobin levels. Although they observed a significant increase in BDS score in the creatin group, the rise in the BOLD response in the creatin group was nonsignificant (Hammett et al., 2010). This means that enhanced cognitive performance was not associated with increased brain activity. If this study included measurements from various brain regions, it would be easier to assess whether that phenomenon was limited to V1 or if it also included other structures responsible for higher brain functions.

In conclusion, the studies on healthy participants failed to show a consistent effect of creatin supplementation on cognitive functions. If even, the results were limited to very specific tasks, such as the BDS, which cannot account for the complexity of cognitive tasks necessary to perform by humans during their everyday lives. The dose regimens and treatment duration were also variable among studies, though some scientists explained that when it comes to increasing the creatine levels in the body, a higher loading dose of 20 grams per day (the dose used by athletes) over a few days can be just as effective as a lower dose of 5 grams per day ingested during a few weeks. Nevertheless, as of today, the evidence on the effectiveness of creatin on cognition among healthy individuals is rather weak and requires larger sample sizes. Undeniably, the safety and low prevalence of side effects (the most common one being slight weight gain) makes creatin a great candidate for such large-scale trials.

Creatin supplementation on cognition in the elderly

One of the most prevalent problems in the elderly demographic is osteosarcopenia, that is the loss of muscle mass and bone density. These phenomena greatly increase the probability of falls and premature deaths in this population. According to WHO, the number of people aged 60 years and over will increase from 1 billion in 2020 to 1.4 billion in 2030 and is expected to double by 2050 (2.1 billion). It poses a vital public health concern. Recently, Moreira-Velasco et al. published a meta-analysis examining the impact of creatine, β-hydroxy-β-methylbutyrate, prebiotics and probiotics in osteosarcopenia. They found that creatin may play a supportive role especially. They highlighted the importance of coupling creatin supplementation with physical exercise, and found that the combination of creatin with protein and vitamin D was superior to any other supplement combination (Moreira-Velasco, 2025).

Still, physical deterioration is not the only problem faced by the elderly. Currently, many people become partially or fully disabled due to cognitive impairments. According to WHO, 57 million people had dementia worldwide in 2021 and every year, around 10 million new cases are reported. The prevalence of dementia is positively correlated with age (Livingston et al., 2024). Considering the combined worldwide low natural increase and high medical costs associated with dementia, the current systems might prove unable to support all these patients with cognitive difficulties (Fox et al., 2025). Therefore, there is a huge interest in the development of new drugs combating these disorders, one of them being aducabumab and lecanemab, novel monoclonal antibodies targeted against beta-amyloid plaques, which are one of the proposed culprits of Alzheimer's disease (Zhang et al., 2023). Also, there is growing interest in identifying nutraceuticals, that is naturally occurring compounds present in food, that could aid cognitive processes in the elderly. Creatin is one of them, being chosen for its well-documented safety, tolerability and documented impact on cognition in healthy participants and athletes (Roschel et al., 2021). Indeed, if it proved to support not only osteosarcopenia but also cognitive function in the elderly, it would be a great supplement with an ability to "kill two birds with one stone", or rather two great geriatric problems that are constituents of the frailty syndrome.

A study by Ostojic et al. aimed to determine whether the diet-dependent creatin supply could affect cognitive function in the elderly. They collected a considerably large group of 1340 people with a mean age 71.4 ± 7.8 years and had them supply a detailed 24-h in person dietary interview to ensure accurate

measurements of daily creatin ingestion. They used the WAIS III Digit Symbol Substitution Test (DSS) to assess cognitive function. The individuals consuming over 0.95 g of creatine per day (3rd and 4th quartiles of creatine intake) had significantly higher performance on DSS test when compared to their peers with lower creatine intake (1st and 2nd quartiles) (Ostojic et al., 2021). Still, such study design demands very detailed calculations of the creatin intake and may be troublesome for the participants themselves, having to measure the portions of all the foods consumed throughout the day. Therefore, some studies established a well-defined creatin dosage to assess the impact of creatin on mental processes with more accuracy.

When searching for trials concerning the impact of creatin supplementation on cognition on elderly participants, we were only able to find three trails that met our criteria, i.e. were double-blind, placebo-controlled and did not involve the supplementation of any other compounds apart from creatin. Due to a small number of studies eligible for review, we only allowed one additional study concerning the supplementation of GAA, which as we stated before, is a natural precursor of creatin with superior availability in the brain tissue. Altogether, we included three trials. The information on the type of study design, creatin dosage and different measurements used to assess the effect of creatin supplementation is summarized in Table 2.

Table 2. Comparison of three trials that studied the effect of creatine supplementation on cognitive function in the elderly. Abbreviations: N/A: not acquired, SD: standard deviation, d: day, GAA:guanidinoacetic acid, MoCA: Montreal Cognitive Assessment, 1H-MRS – proton magnetic resonance spectroscopy

Study	Cohort	Mean age (SD), years	Study design	Treatment duration (weeks)	Creatin dose	Cognitive tests performed
Alves et al.	28	N/A	parallel arm	24	20g/d for 5 days, then 5g/d	• cognitive tests battery • Geriatric Depression Scale (GDS)
Seper et al.	21	69.6 (4.9)	crossover	8	2g/d creatin plus 2g/d GAA	• brain creatine content (via 1H-MRS) • MoCA
McMorris et al.	32	76.4 (8.5)	parallel arm	2	20g/d	• random number generation • forward and backward number and spatial recall • long-term memory tasks

Alves et al. used a battery of cognitive tests that assess memory, selective attention, and inhibitory control as well as the Geriatric Depression Scale (GDS) to evaluate whether creatin supplementation with or without strength training would show an enhancement in cognitive function and an improved mood when compared to placebo with or without training. Neither creatin nor strength training affected the scores on the cognitive tests, while strength training irrespective of creatin supplementation significantly improved mood among heathy elderly participants (Alves et al., 2013). Similarly, a study by Seper et al. also failed to show an increase in Montreal Cognitive Assessment Score, a common screening test for cognitive impairment following creatin and GAA supplementation, even despite elevating the brain creatine content in 6 brain regions (Seper et al., 2021). Once again, it shows that mere elevation of brain creatin content does not directly lead to significant cognitive enhancement. Only the study by McMorris et al. showed some effect of creatin, since there was a significant improvement in forward number recall, forward and backward spatial recall and long-term memory scores (McMorris et al., 2007). Still, this data can be considered very limited and larger randomized controlled studies are warranted. The elderly population should be treated with utmost caution when implementing any drugs, but thanks to creatin's promising results in the treatment and prophylaxis of osteosarcopenia, perhaps more researchers will include cognitive performance measurements in the studies that predominantly focused on the physical-related benefits of this supplement.

Creatin supplementation on cognition in patients with psychiatric conditions

Psychiatric disorders are commonly associated with deterioration of cognitive skills, which considerably influences the mortality rates among these patient groups (McGrath et al., 2023). The rising prevalence of psychiatric disorders has triggered a quest for remedies that could combat this big scale social problem. Some of the widely researched nutraceuticals are omega-3 fatty acids, folic acid, vitamin D and B12 and various antioxidants (Bozzatello et al., 2024). Creatin has also sparked interest as for whether it could positively impact the cognitive processes in patients suffering from psychiatric disorders, especially since some research showed the association of low prefrontal cortex creatin levels and with higher depression scores (Faulkner et al., 2021). Though many of these studies are observational, we have managed to find a few randomized controlled trials performed on patients with depression, bipolar disorder and schizophrenia to assess the effect of creatin supplementation on cognition. The information on the type of study design, creatin dosage and different measurements used in these studies is summarized in Table 3.

Table 3. Comparison of the studies examining the effect of creatine supplementation on cognitive functioning among patients with psychiatric disorders. Abbreviations: g/d: grams per day, mg/d: milligrams per day, 5-HTTP: 5-hydroxytryptophane, PHQ-9: Patient Health Questionnaire (nine-item), HDRS: Hamilton Depression Rating Scale), MADRS: Montgomery-Asberg Depression Rating Scale, CGIS: Clinical Global Impression scale, BAI: Beck Anxiety Inventory, C-SSRS: Columbia-Suicide Severity Rating Scale, YMRS: Young Mania Rating Scale, NAA: N-acetyl aspartate, 1H-MRS: Proton Nuclear Magnetic Resonance Spectroscopy, PANSS: Positive and Negative Syndrome Scale.

Study	Cohort	Psychiatric disorder	Study design	Treatment duration	Drugs and dose	Measurements (primary outcomes)
Sherpa et al.	60	mild to severe depression	parallel arm	8	5g/d creatin + biweekly individual CBT	Depressive symptom severity measured by PHQ-9
Kious et al.	12	Moderate to severe SSRI/SNRI resistant depression	no placebo control	8	5g/d creatin + 200mg/d 5-HTP	• HDRS • MADRS • CGI • BAI • C-SSRS • YMRS
Yoon et al.	27	Major depressive disorder	control group: 39 age-matched healthy women	8	creatin (week 1: 3g/d, weeks 2-8: 5g/d) + escitalopram (week 1: 10mg/d, weeks 2-8: up to 20mg/d	• HDRS • changes in prefrontal NAA levels and number of rich club connections (measured by H1-MRS)
Toniolo et al.	18	bipolar disorder	parallel arm	6	6g/d creatin	• MADRS • neuropsychological assessment
Kapstan et al.	10	schizophrenia	crossover	12	3-5g/d creatin	• PANSS • CGI • cognitive battery • assessment of side effects

The studies involving patients with depression all showed an improvement in depression symptom scores (measured via the nine-item Patient Health Questionnaire (PHQ-9), Hamilton Scale (HDRS) or Montgomery-Asberg Depression Rating Scale (MADRS)) all showed an improvement in mood impairment. Following creatin supplementation, Kious et al. observed a significant improvement in Clinical Global Impression (CGI) score, a 3-item scale used by psychiatrists to evaluate the severity of a patient's illness and

changes in their condition over time. Furthermore, there were patients who reached remission criteria according to HDRS and MADRS (7 and 8 patients, respectively) (Kious et al., 2017). Such results were not replicated in a study on patients with bipolar disorder, who demonstrated merely a nonsignificant decrease in MADRS, while the neuropsychological assessments resulted in a significant improvement only verbal fluency after creatin supplementation (Toniolo et al., 2018).

Yoon et al. additionally used H1-MRS on patients with major depressive disorder (MDD) and 39 healthy aged-matched participants to compare any changes in N-acetyl aspartate (NAA) in the prefrontal cortex and the number of rich club connections in the brain before and after an 8-week supplementation of creatin and escitalopram (the latter substance used only in the MDD group). NAA contributes to energy mitochondria and gives a strong signal in H1-MRS, thus its common use as a marker for neuronal activity (Saccaro et al., 2024). Rich clubs are regions of the brain that act as central hubs, rapidly integrating and transferring information. Such highly organized structures require large amounts of energy, and those high consumption rates might be observed as an elevated NAA level (Dennis et al., 2013; van den Heuvel & Sporns, 2011). In this study, both NAA levels and the number of rich club connections measured before creatin supplementation were much lower in patients with MDD compared to healthy participants, and the levels of these parameters were inversely correlated with the depressive symptoms. However, though NAA and rich club connections significantly increased after creatin supplementation, those changes did not correlate with an amelioration in depressive symptoms (Yoon et al., 2016). It further reinforces the results from studies involving neuroimaging among healthy adult and elderly participants – increasing the levels of certain substances in the brain (creatin, NAA) does not equate significant improvements in cognition or mood.

The one trial that investigated patients suffering from schizophrenia showed absolutely no effect of creatin on the prevalence and severity of symptoms (measured by PANSS: Positive and Negative Syndrome Scale), CGI score or performance in a battery of cognitive tests (Kaptsan et al., 2007).

The conflicting evidence does not allow us to draw definite conclusions about the role of creatin supplementation in the cognitive performance of patients suffering from mental disorders. The theory of replenishing the lowered brain creatin concentration in those patients seemed promising, but the results were inconsistent. It should still be noted that seven (58.3%) participants in the study by Kious et al. believed that creatin supplementation was beneficial and continued the treatment beyond the study period, despite the need to purchase the supplement themselves. Even if creatin is not a cure for depression, the relatively low cost and excellent safety profile make it an option in adjunct therapy, especially for patients who strongly believe in the efficiency of supplements.

Discussion and conclusions

In conclusion, the effect of creatin supplementation on cognitive performance in healthy adults and the elderly, as well as patients with psychiatric disorders, remains unknown. The results from randomized controlled trials show conflicting evidence. Improvements are observed in tests that involve very specific tasks, which often do not represent the typical daily cognitive tasks. This limitation is obvious, since studies need a specific measurement method – still, positive results in singular tasks should not lead to far-fetched interpretations. Our study is not perfect either – some of the trials included in the analysis used GAA, 5HTP or strength training in the addition to creatin, while the creatin supplementation between the studies was also variable. The reasoning behind that choice was partially explained in the paragraphs above, but the decision to include only clinical trials has also greatly reduced the number of studies eligible for analysis. Therefore, we consciously eased up our inclusion criteria while still ensuring proper study design to allow for reasonable comparison.

Unsurprisingly, more studies are warranted to adequately assess the role of creatin supplementation in cognition, including the definition of appropriate dosage regimens in different population subgroups. This need seems to be perceived – we found two randomized controlled trials (with no results posted yet) that aim to examine the effect of creatin supplementation on cognition in individuals suffering from Long COVID-19 and in elderly patients with Alzheimer's disease. (NCT06992414, NCT05383833). If proved to be effective, creatin could one day become a mainstay of adjunct therapy in various groups of patients, since irrespective of age and comorbidities, humans quest for cognitive enhancement.

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