Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Creatine

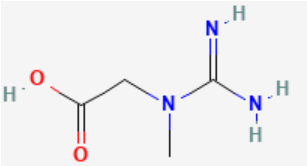
Evidence Summary

Adequate dietary intake is associated with better health outcomes. The benefits of additional supplementation vary but are most prominent with very mild impairments. It has a strong safety record.

Neuroprotective Benefit: Creatine may help promote brain bioenergetics, but potential neuroprotective effects appear to be limited to very early/preclinical stages of disease and may show a sex bias.

Aging and related health concerns: Creatine may facilitate increases in muscle size and strength in combination with resistance training, which may help protect against frailty. It doesn't protect against bone loss, and benefits to chronic fatigue appear minor.

Safety: Creatine has an excellent safety record, with the most common events, such as gastrointestinal events, occurring at similar rates as control groups. Water retention may occur in men. Case reports of kidney issues cannot be clearly tied to creatine.

Availability: OTC, typically as a powdered oral formulation.	**Dose**: The standard oral dose used for muscle involves a loading phase of 0.03 g/kg/day (~20 g/day or 5 g 4x/day) for 5-7 days followed by a maintenance phase of 3-5 g/day.	**Chemical formula:** $C_4H_9N_3O_2$ **MW**: 131.13 g/mol  Source: PubChem
Half-life: ~ 3 hours	**BBB**: Modestly penetrant	
Clinical trials: Creatine has been tested in hundreds of clinical trials, though most have been small, primarily related to exercise performance/strength. It has also been tested in neurodegenerative diseases including Parkinson's disease, Huntington's disease, and ALS.	**Observational studies**: Low dietary intake of creatine has been associated with higher risk for depression, liver dysfunction, and heart disease.	

What is it?

Creatine is an amino acid derivative [1]. It can be obtained from the diet or produced endogenously through a two-step process. In the first step, the amino acids glycine and arginine are converted to the intermediate product guanidinoacetate (GAA) by the enzyme arginine:glycine amidinotransferase (AGAT). In the second step, GAA is methylated by the enzyme guanidinoacetate N-methyltransferase (GAMT) using S-adenosyl methionine (SAM) as a donor, which is itself a derivative of the amino acid methionine, to produce creatine. Creatine is primarily used as part of an energy reserve system. ATP is the form of energy produced by aerobic and anaerobic respiration that is utilized by cells. Creatine provides a form of storage for excess ATP which helps cells better meet their real-time energy needs. Under conditions of high ATP, the high-energy phosphate is transferred to creatine to form phosphocreatine, and under conditions of high demand, the phosphocreatine is converted back to creatine, regenerating ATP in the process. These reactions are catalyzed by the enzyme creatine kinase. The direction of the reaction depends on the local energy conditions of the cell and cellular compartment. Mitochondrial localized isoforms of creatine kinase generally convert excess ATP to phosphocreatine, while cytosolic isoforms are more likely to regenerate ATP for cellular use. This energy reserve is particularly useful because a (muscle) cell can store ten-fold more energy in the form of phosphocreatine relative to ATP, and it can regenerate that ATP 10-40 times faster than using anaerobic

or aerobic respiration [2]. This system is used most extensively in the skeletal muscles, which is home to 95% of the body's creatine stores [3]. The remaining 5% is primarily in other high-energy tissues such as the heart and brain. Increasing the tissue reserves of creatine is a mechanism to increase the energy reserves of the tissue, which should allow it to work at maximum capacity for longer periods of time. As a result, the potential benefits from creatine supplementation are tied to how well it can increase creatine stores in a given tissue.

Since skeletal muscle is the largest sink of creatine, creatine supplementation has primarily been used for the purpose of boosting intramuscular stores to facilitate exercise. In the context of a typical omnivore diet including 1-2 grams of dietary creatine per day, intramuscular creatine stores are generally around 60-80% full [1]. As a result, increases in intramuscular creatine levels of around 20% have been routinely reported with creatine supplementation, though there is wide variation across individuals due to a number of factors. Creatine, generally in the form of creatine monohydrate, has been extensively tested and used as an ergogenic aid by athletes and exercise enthusiasts [1].

Creatine monohydrate has also been clinically tested for a variety of other indications. These studies have generally been small, and have not consistently shown beneficial effects. A large number of these studies have been for neurological conditions, with the goal of boosting brain creatine stores and improving brain bioenergetics [4]. The lack of benefits may stem from the resistance of brain creatine stores to supplementation relative to muscle stores. Additionally, disease processes may negatively affect the creatine reserve system in a manner that makes it less reliable.

Neuroprotective Benefit: Creatine may help promote brain bioenergetics, but potential neuroprotective effects appear to be limited to very early/preclinical stages of disease and may show a sex bias.

Types of evidence:

- 2 meta-analyses or systematic reviews of clinical trials assessing cognition in healthy adults
- 3 observational studies for dietary creatine and cognition
- 1 observational study for dietary creatine and depression
- 1 review of trials testing creatine in depression
- 3 clinical trials in Parkinson's disease
- 3 clinical trials in Huntington's disease
- 2 clinical trials in amyotrophic lateral sclerosis (ALS)
- 1 clinical trial in pediatric traumatic brain injury
- 1 clinical trial in stroke survivors

- 5 neuroimaging studies for brain creatine/phosphocreatine levels
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

A variety of clinical and observational studies have examined the relationship between creatine intake and cognitive function [5]. Although there are mixed results across studies, there is a general trend in which adequate dietary intake of creatine facilitates optimal cognitive performance, and the potential impact of additional creatine supplementation depends on baseline brain metabolic status and cognitive task complexity. High levels of brain creatine may help the brain weather periods of heightened energy demand without inducing metabolic stress.

Creatine is used as part of a reserve energy system to allow for the rapid regeneration of ATP during times of peak demand [2]. The enzyme creatine kinase catalyzes the interconversion between creatine and phosphocreatine. The direction of the reaction depends on local energy conditions. In regions of high ATP production, such as within the mitochondria, one of the high energy phosphates is transferred from ATP to free creatine to form phosphocreatine plus ADP. The ADP returns to the mitochondrial matrix to stimulate further energy production via oxidative phosphorylation. The phosphocreatine exits the mitochondria into the cytosol to serve as a store of energy. During times of increased energy demand creatine kinase can convert the phosphocreatine back into free creatine, regenerating ATP in the process, which can go on to fuel the energy needs of the cell. This system allows for the temporal and spatial buffering of ATP. At a given time, typically about two-thirds is in the form of phosphocreatine and one-third is free creatine, at least based on estimates in muscle cells [3]. Significant alterations in the balance between creatine and phosphocreatine may be indicative of altered tissue bioenergetics.

Observational studies: Data from the National Health and Nutrition Examination Survey (NHANES) from 2001-2002 including 1,340 adults over age 60 was used to examine the relationship between dietary intake of creatine and cognitive function, based on the WAIS III Digit Symbol Substitution (DSS) test [6]. A significant positive correlation was found between dietary creatine intake and DSS scores. Participants consuming more than 0.95 g of creatine per day had higher scores on the cognitive test. An observational study in 42 older adults over age 60 found that higher dietary creatine intake was associated with better performance on a visuospatial short-term memory test [7]. Similarly, a study

including 27 overweight women over age 60 found that higher dietary creatine intake was associated with better performance on a response inhibition test, particularly with respect to reaction time [8].

In the NHANES cohort, the average creatine intake across all participants was 1.13 ± 1.00 g per day (95% confidence interval [CI] from 1.07 to 1.18) [6]. This is in line with general recommendations for dietary creatine intake of 1-2 grams per day to make up for the daily excretion of around 2 grams of creatine per day in the form of creatinine. As such, 1-3 grams of creatine per day is typically needed to maintain intramuscular creatine stores, which can come from either dietary sources or *de novo* synthesis. The level needed to reliably impact brain stores has been less clear.

Approximately 5% of the body's creatine stores are located outside of the skeletal muscles, primarily in the brain and heart [9]. Creatine is synthesized from the amino acids, glycine, arginine, and methionine, in a two-step enzymatic process, which is the predominant source of CNS creatine. It can also be transported into the CNS via the creatine transporter. Due to slow and limited uptake across the blood-brain-barrier (BBB), the relative impact of dietary creatine on brain stores appears to be less consistent relative to the impact of dietary creatine on intramuscular stores. However, intellectual disability is a core component of the developmental disorders associated with deficiency in either of the creatine biosynthesis enzymes (GAMT and AGAT) or in the X-linked creatine transporter gene (SLC6A8), suggesting that both dietary sources and *de novo* synthesis of creatine are important, at least during brain development [10]. It is thought that the brain primarily relies on endogenous synthesis, but during times of stress or increased energy demand, it also taps into creatine from peripheral/dietary sources [4].

It has been demonstrated in ***neuroimaging studies*** that oral creatine supplementation can potentially lead to increases in brain creatine levels. Imaging studies typically assess phosphocreatine or total creatine levels. In healthy young adults, supplementation with 20 grams of creatine per day (5 g 4x/day) for four weeks led to an increase of total brain creatine levels by 8.7% based on magnetic resonance spectroscopy (MRS) imaging when averaged across brain regions and participants [11]. However, there was considerable variation across individuals (3.5-13.3%) and across brain regions. The largest increases were observed in the thalamus (14.6%). Another study found that brain levels of phosphocreatine could be increased within seven days of supplementing with 20 g/day creatine in healthy adults [12]. Heterogeneity across individuals and brain regions was also observed. Those (individuals and brain regions) with the lowest basal levels of phosphocreatine (and ATP) increased levels with supplementation, while levels remained constant or declined in brain regions with high basal

phosphocreatine. The apparent decline in phosphocreatine may stem from more efficient coupling between mitochondrial production and energy consumption. These studies suggest that creatine supplementation at levels that can impact brain stores may help improve brain bioenergetics, though there is still debate over what that level may be.
The major reason for the uncertainty regarding the identification of a potentially cognitively beneficial dose of creatine stems from the general lack of studies that use both neuroimaging outcomes to measure the impact of creatine supplementation on brain levels, and cognitive outcomes. As a result, for the majority of studies, it is unclear whether a lack of benefit is related to a failure to raise brain creatine levels. The neuroimaging studies suggest that brain creatine levels may be largely resistant to changes through supplementation unless the individual has low baseline levels and/or large doses of creatine are used.

Clinical trials support the notion that creatine supplementation offers the most utility in individuals who may have lower baseline creatine stores or are experiencing a slight impairment in brain energy utilization, such as in the context of sleep deprivation [4]. Studies in healthy young populations tend not to show clear benefits with creatine supplementation, whereas studies utilizing older or cognitively stressed populations are more likely to show benefits. Furthermore, the ability to detect an effect can depend on the nature of the cognitive task assessed in the study. Since the utility of phosphocreatine stores is to rapidly replenish ATP levels, performance on fast paced tasks with little recovery time is most impacted by these stores. As a result, speed of processing related tasks are most likely to show positive effects with creatine supplementation.

A systematic review of six RCTs including 281 healthy individuals assessing the impact of creatine supplementation on cognition found that there was a high degree of variability across studies, but benefits were most apparent on measures of short-term memory [13]. A more recent meta-analysis of eight RCTs including 225 healthy individuals found that creatine supplementation was associated with improved measures of memory compared with placebo (standard mean difference [SMD]: 0.29, 95% CI 0.04 to 0.53) [14]. The effect was driven by trials assessing older adults (aged 66–76 years).

It is hypothesized that creatine supplementation may be particularly beneficial for ***older adults*** to help protect against age-related cognitive decline by enhancing brain bioenergetics [4]. However, the literature is unclear regarding whether there is a decline in brain creatine stores with age, similar to what is seen in muscle. One study assessed the impact of creatine supplementation on muscle and brain phosphocreatine levels in children, adults, and elderly participants [15]. The study used a standard

'loading protocol' designed for muscle gains of 0.3 g/kg for 7 days, which for the average adult would be around 20 g/day. While muscle phosphocreatine was most responsive to creatine supplementation in the elderly, brain levels were not appreciably impacted in any of the age groups. A separate MRS study found that brain creatine levels were reduced in ApoE4 carriers, and these levels further decreased in association with age and impaired cognitive status, based on the Mini-Mental State Examination (MMSE). In contrast, creatine levels were not associated with age or cognitive function in non-ApoE4 carriers [16].

Another group that has been hypothesized to preferentially benefit from creatine supplementation is ***vegetarians***. Since creatine is obtained primarily through meat and fish products, vegetarians tend to have very low or no dietary intake of creatine. One study including 45 young adult vegetarians found that 5 g/day of creatine supplementation for six weeks led to an improvement in performance on the Raven's Advanced Progressive Matrices (RAPM) and on the Backward Digit Span (BDS), which are tasks that involve speed of processing [17]. A separate study including 128 young adult women, found that 20 g/day of creatine for five days improved memory in vegetarians, but not in omnivores, while enhancing performance on a choice reaction-time task in both groups [18]. A more recent study including 123 young adults, half of which were vegetarians, tried to replicate the findings of the Rae et al., study [19]. Bayesian evidence supported a small beneficial effect of creatine, but there was no differential impact when comparing vegetarians and omnivores. Furthermore, neuroimaging studies suggest that brain creatine levels are comparable between vegetarians and omnivores. In the study assessing the impact of creatine supplementation (0.3 g/kg) on muscle and brain stores described earlier, supplementation preferentially boosted muscle phosphocreatine stores in vegetarians, but had no impact on brain stores in vegetarians or omnivores [15], further suggesting that brain stores are primarily a function of *de novo* synthesis.

One clinical trial in mutation carriers with prodromal Huntington's disease found that creatine supplementation (5 g b.i.d.) was associated with the slowing of cortical thinning over the course of six to 18 months, but did not significantly impact cognitive outcomes over this period [20]. It has not yet been established whether creatine supplementation during preclinical stages could slow neurodegenerative processes or facilitate the preservation of cognition in the context of other dementias.

Human research to suggest benefits to patients with dementia:

Due to its roles in promoting energy utilization, creatine has been hypothesized to benefit dementia patients experiencing brain hypometabolism [21]. The degree of potential benefit may be related to disease severity such that a slight enhancement in brain energy stores may allow for a detectable improvement in cognitive processing in those with very early/prodromal stages of disease, but on its own may be insufficient to noticeably impact cognition in those with more severe levels of impairment. Overall, the studies to date suggest the creatine supplementation has more potential to improve brain bioenergetics during a preclinical/prodromal disease stage as part of a secondary prevention strategy, and likely offers limited benefit in those with symptomatic dementia.

To date, the impact of creatine supplementation has not been determined in Alzheimer's disease (AD) patients, but there is an ongoing single arm trial testing the impact of 20 g of creatine monohydrate per day (10 g b.i.d.) for eight weeks on changes to peripheral and central creatine levels, cognition, and muscle strength in 20 AD patients (NCT05383833). The study is estimated to be completed in 2025.

Creatine supplementation has been largely unsuccessful in protecting against decline in patients with neurodegenerative diseases with prominent motor components, such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis [5]. The study with the most promising result was a combination trial in patients with Parkinson's plus mild cognitive impairment (MCI). Parkinson's MCI patients (n=75) taking creatine monohydrate (5 g b.i.d.) and CoQ10 (100 mg t.i.d.) for 18 months experienced less decline on the Montreal Cognitive Assessment (MoCA) relative to placebo-treated patients, though both groups experienced cognitive decline, and there was no difference in motor disease progression based on the unified Parkinson's disease rating scale (UPDRS III) [22]. A five-year study (NCT00449865) assessing creatine monohydrate (5 g b.i.d.) alone in patients with early Parkinson's disease (n=955) was terminated for futility stemming from a lack of benefit on a global clinical assessment including measures related to motor function, cognition, and activities of daily living [23]. This suggests that in a disease population, creatine alone may be insufficient, but may offer modest benefit when used in combination with other metabolic/mitochondrial function enhancing agents.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease: POTENTIAL MINOR BENEFIT EARLY STAGES (Preclinical)
Creatine supplementation has not yet been tested as a preventative or therapeutic strategy for AD, but there is evidence from preclinical studies and biomarker studies to suggest that it may help promote energy utilization in the AD brain [21]. Glucose hypometabolism is a prominent feature of the AD brain, and creatine stores may help provide a buffer to meet energy demands. These types of compensatory changes to the creatine system have been detected in the AD brain, suggesting that boosting this buffering capacity may offer additional benefit. However, there may be a limit to how well this system can compensate depending on the overall degree of pathology.

The levels of free creatine relative to phosphocreatine can vary depending on the local energy conditions [2]. Alterations to the creatine-phosphocreatine energy shuttle system have been detected in the AD brain, and likely serve as an indication of impaired mitochondrial function and altered bioenergetics. They are generally coupled with changes to the activity of creatine kinase. High levels of phosphocreatine could indicate an impaired ability to regenerate ATP from this energy reserve, while high levels of cytosolic forms of creatine kinase could indicate a cellular metabolic shift from oxidative phosphorylation (in the mitochondria) to glycolysis (in the cytosol).

An MRS imaging study comparing high energy phosphates in 31 mild AD patients relative to 31 controls found that levels of phosphocreatine were elevated in early affected brain regions, but not in later affected regions, suggesting the change may be part of a metabolic response in areas with AD pathology [24]. Alterations in expression of creatine kinase, the enzyme responsible for catalyzing the interchange between creatine and phosphocreatine, have also been detected in AD patients. In an analysis of biomarkers from 1,607 participants in the ADNI database, there was an association between lower levels of peripheral creatine kinase with cognitive impairment [25]. Levels of creatine kinase were reduced in the order of middle-aged to elderly to MCI to AD participants. Aβ and tau positive individuals had lower levels of creatine kinase, relative to those without these AD biomarkers. These decreases may be indicative of systemic metabolic dysfunction.
Some studies have found that higher levels of creatine kinase in disease affected areas may help protect against functional declines. In ALS patients, patients with higher levels of the creatine kinase isozyme primarily found in the myocardium and skeletal muscles (CK-MB) was found to be associated with less functional decline, and higher levels of creatine kinase have been associated with longer survival in this population [26]. In postmortem hippocampal and frontal cortex brain tissue, brain type creatine kinase (CK-B) was found to be elevated in AD patients relative to controls, which is thought to be related to a protective compensatory response [27].

There are several preclinical studies testing creatine supplementation in AD models, however, the translatability of these findings is unclear due to the differential ability of dietary creatine to alter brain levels in rodents relative to humans. While neuroimaging studies in humans suggest that the potential boost to brain creatine stores is generally under 10%, brain stores of creatine have been shown to increase by 30 to 50% in some animal models [28].

In seven-month-old 3xTg AD mice fed a diet containing 3% creatine for eight weeks, females showed modestly enhanced performance on the Morris water maze, whereas males performed slightly worse [29]. The differences may be related to sex differences in the model, as mitochondrial enhancements were seen with creatine supplementation in both sexes. In the female AD mice, creatine supplementation was associated with increased expression of learning and memory related molecules, such as CREB, CaMKII, and PSD-95, as well as increased levels of the NF-κB suppressor, IκB. Actin dynamics and p-tau levels were not affected. In a rat model of intrahippocampal Aβ42, supplementation with a 2% creatine-enriched diet for six weeks had no significant effect on performance on the Morris water maze or levels of neuronal degeneration [30]. These studies suggest that in impaired animals, the potential impact of creatine alone is likely to be very modest, and that early intervention during preclinical stages may be needed for meaningful benefit.

Another potential avenue to increase the access of creatine to the brain is via intranasal administration. In male rats, intranasal creatine was administered with an initial loading phase of 0.075 g/kg/d of creatine hydrochloride, followed by a maintenance phase of 0.0375 g/kg/d of creatine for the remainder of the 14-day study [9]. This intranasal administration protocol led to significant increases in creatine levels in the olfactory bulbs, medial prefrontal cortices, and hippocampi of these mice, while oral administration did not significantly increase creatine levels in these brain regions. The increase in hippocampal creatine was associated with increased performance on the Barnes maze, a hippocampal-dependent spatial learning and memory task.

Parkinson's disease: NO CLEAR BENEFIT

Creatine supplementation has not been associated with the slowing of disease progression in patients with Parkinson's disease (PD) [4]. Creatine was tested as part of Neuroprotective Exploratory Trials in Parkinson Disease, Futility Study 1. Two hundred patients with early PD were treated with either creatine (10 g/day), minocycline, or placebo for 18 months [31]. Symptomatic PD treatment was required in approximately 60% of patients from each arm by the end of the study. As a follow-up, creatine (5 g b.i.d.) was tested as part of the NINDS Exploratory Trials in Parkinson Disease program (NCT00449865). This study enrolled 1,741 patients with early PD, within five years of diagnosis, to be

followed from five to eight years [23]. The trial was terminated for futility following the second interim analysis including 955 patients who had been enrolled for at least five years. Clinical decline was based on five outcome measures, including the Modified Rankin Scale, Symbol Digit Modalities Test, PDQ-39 Summary Index, Schwab and England Activities of Daily Living scale, and ambulatory capacity. In this scoring system, higher summed ranks indicate worse outcomes. At this interim analysis, mean of the summed ranks for placebo was 2,360 (95% CI 2,249 to 2,470), while it was 2,414 (95% CI 2,304 to 2,524) for creatine, indicating that creatine did not offer any advantage over placebo.
An MRS imaging study found that levels of total creatine along with the metabolite N-acetyl aspartate (NAA) were reduced in PD patients with MCI relative to PD patients without MCI, suggesting that this population may be more amenable to benefit from creatine supplementation [32]. Creatine (5 g b.i.d.) was tested in combination with CoQ10 (100 mg t.i.d.) in patients with PD with MCI (n=75) for 18 months [22]. Participants in the combination group showed less decline from baseline on the MoCA at 12 (by 2.67 points) and 18 months (by 4.7 points) relative to participants in the placebo group. Combination treated patients' MoCA scores declined from 20.15±3.11 to 19.52±2.74 at 12 months, and to 18.55±4.11 at 18 months, while placebo patients declined from 19.63±4.12 to 16.33±3.37 at 12 months and to 13.33±3.58 at 18 months. There was no difference in the rate of PD progression as measured by the UPDRS III. Similar to creatine, CoQ10 is an endogenous nutrient with antioxidant properties that promotes the production of ATP. Since they are complementary agents in promoting mitochondrial function and energy production, the combination may have greater utility than either agent alone. Additionally, there is evidence from preclinical studies to suggest that creatine may also have antioxidant effects [33]. No combination therapies involving creatine have been clinically validated to date.

Huntington's disease: NO CLEAR BENEFIT IN SYMPTOMATIC/ POTENTIAL MINOR BENFIT IN PRODROMAL STAGES
Clinical trials testing creatine supplementation in Huntington's disease (HD) patients have indicated a lack of benefit on disease-related metrics, but one study indicated that creatine may promote a modest slowing of brain atrophy in presymptomatic mutation carriers. Serum levels of the oxidative stress marker 8-hydroxy-2'-deoxyguanosine (8OH2'dG) were reduced in HD patients following 16 weeks of creatine [34]. Patients received a dose of 8 g/day, which was sufficient to raise both serum and brain levels of creatine in this population. The Phase 3 placebo-controlled CREST-E trial (NCT00712426) testing creatine at doses up to 40 g/day up to 48 weeks in patients with stage I and II HD (n=553) was halted for futility following the first interim analysis [35]. The primary outcome was the rate of change in total functional capacity, which showed a difference of 0.12 points per year (nominal 95% confidence limits

(CI) −0.11 to 0.35), favoring placebo. There was a significant sex effect such that women taking creatine exhibited an accelerated decline of 0.42 points per year relative to placebo, while men were more likely to benefit from creatine, as demonstrated by a non-significant slowing of the rate of decline (0.25 points/year) relative to placebo. There were no differences in any of the other disease related or quality of life outcome measures between the creatine and placebo groups.

In contrast, a slowing of cortical thinning was observed in the PRECREST secondary prevention trial (NCT00592995) testing creatine supplementation at a dose of 5 g b.i.d. in 47 prodromal HD mutation carriers [20]. The placebo-controlled trial lasted for six months, followed by an open-label period of 12 months. Based on neuroimaging measures, there was a significant slowing of cortical thinning in several cortical regions, including parts of the precentral, superior and middle temporal, superior and middle frontal, precuneus, posterior parietal, and occipital regions at the end of the RCT. A similar benefit was seen in cross-over participants during the open-label phase. Additionally, creatine-treated participants did not exhibit a significant change in basal ganglia volume, whereas participants in the placebo group experienced progressive atrophy in the caudate and putamen. A trend toward a reduction in 8OH2dG levels was also observed with creatine. Despite the impacts on brain atrophy, there was no significant effect of creatine on measures of cognitive performance, which remained below that of healthy controls in both groups.

Together these studies suggest that creatine may help ease bioenergetic stress during early stages of disease, but the optimal time of intervention and dosing strategy has not been established.

Amyotrophic lateral sclerosis: NO CLEAR BENEFIT

Creatine supplementation has not shown benefits in clinical trials in ALS patients [4]. Creatine was tested as an intervention for ALS by the NEALS consortium. A multicenter placebo-controlled RCT including 104 ALS patients testing 5 grams of creatine per day for six months found that there was no evidence of benefit on its primary outcome of maximum voluntary isometric contraction of eight upper extremity muscles or on the secondary outcomes of grip strength, ALS Functional Rating Scale-Revised (ALSFRS-R), or motor unit number estimates [36]. It was thought that the dose of 5 g/day may be too low to benefit this population. Creatine was subsequently tested at a higher dose as part of a phase-II trial using a ranking and selection paradigm (n=60) [37]. The trial tested creatine at a dose of 30 g/day, compared to tamoxifen at a dose of 40 or 80 mg/day (NCT01257581). In this study, ALS patients taking creatine experienced a higher rate of adverse events and less benefit on the primary outcome of the ALSFRS-R, relative to those taking tamoxifen. As a result, tamoxifen and not creatine was chosen for the next stage of the selection trial. The lack of benefit may also be related to the relatively advanced level of disease progression in these patients [4].

Brain injury: POTENTIAL MINOR BENEFIT PARTICULARLY WITH PROPHYLACTIC USE

Although clinical evidence is limited, the potential benefit of creatine in relation to facilitating recovery from brain injury appears to be greater than what has been observed in the context of neurodegenerative disease [5]. This may stem from the different etiologies for acute and chronic deficits in brain bioenergetics. The brain enters a state of hypermetabolism immediately following injury, but is generally unable to meet and sustain the excess energy demand, and thus transitions into a state of hypometabolism. Brain creatine levels have been shown to decrease with injury [4], thus boosting levels of the phosphocreatine energy reserve could potentially help meet this acutely increased need for demand, and mitigate long-term impairments.

To date, there has only been one open-label pilot randomized clinical trial testing creatine (0.4 g/kg/day in an oral suspension for six months) in children and adolescents with severe traumatic brain injury (TBI) (n=39) [5]. Relative to controls, creatine supplementation was associated with a shorter duration of post-traumatic amnesia, intubation and hospital stay. Additionally, improvements in neurophysical, cognitive, personality/behavior and social function were observed within three months, and improved self-care was seen at six months. Further follow-up indicated a reduction in post-traumatic headaches, dizziness and fatigue in this population.

Preclinical studies suggest that creatine supplementation prior to brain injury may be most beneficial by allowing for the rapid regeneration of ATP without further stressing the cell [5]. Phosphocreatine can regenerate ATP 40x faster than oxidative phosphorylation and 10x faster than glycolysis [2]. Furthermore, since the utilization of this energy reserve does not involve a proton pump, it can generate high levels of ATP without the risk of cellular acidosis or the induction of reactive oxidative species. As a result, the utilization of phosphocreatine during times of peak demand not only preserves cellular bioenergetics, but also helps prevent additional tissue damage.

Creatine may also help facilitate recovery as part of rehabilitation programs, but the evidence is limited to date. A randomized, double-blind, placebo-controlled trial (NCT03941678) tested the impact of creatine administered at a loading dose of 0.3 g/kg/day (0.075 g/kg 4x/day) for seven days followed by a maintenance dose of 0.1 g/kg/day for the reminder of the ten-week study in combination with progressive resistance training in stroke survivors (n=8) [38]. While there was no difference in the volume of training between the groups, participants supplemented with creatine exhibited a significant increase in distance traveled on the 6-minute walk test (Δ 39.2 ± 12.7 m), which is within the range considered clinically meaningful. Improvements in cognitive measures were observed with resistance exercise in both the creatine and placebo groups.

Depression: POTENTIAL BENEFIT FOR WOMEN
Symptoms of depression have been associated with low levels of creatine [39]. A variety of clinical trials suggest that creatine supplementation may be beneficial for mitigating depressive symptoms in women. Cerebral hypometabolism has been observed in depressive patients, suggesting that impaired brain bioenergetics may play a role in symptoms.
The association between dietary creatine intake and depressive symptoms, as measured by the Patient Health Questionnaire (PHQ-9), was examined using data from 16,816 participants from the NHANES 2005 to 2012, 1,455 of which were screened positive for major depressive disorder [39]. This observational study found an inverse association between dietary creatine intake and depression (adjusted Odds Ratio [OR]: 0.68, 95% CI 0.52 to 0.88). The association was strongest in women, particularly those aged 20-39, not taking antidepressant medication. In women, each gram of creatine consumed was associated with 18% lower odds of depression.
Neuroimaging studies have observed a reduction in creatine levels within the prefrontal cortex in individuals with depressive symptoms, suggesting that they may be responsive to supplementation [4]. Similar to other indications, the results regarding the effect of creatine on depressive symptoms in clinical trials have been mixed [5]. This may be a feature of the studies using different dosing strategies and including a small number of subjects. Many studies have also assessed the ability of creatine to augment the effects of antidepressant medication, and the use of different medications may be an additional source of variability. In general, the studies suggest that there may be a preferential benefit of increasing dietary creatine consumption in women with depressive symptoms [4].
In addition to potentially boosting brain bioenergetics, there is some evidence to suggest that creatine may also function as a neurotransmitter, and potentially influence mood regulation in this manner [4].

APOE4 interactions: The effect of ApoE4 on the efficacy of creatine supplementation has not yet been clinically tested, however, there is evidence to suggest that ApoE4 carriers may preferentially benefit from creatine supplementation, particularly at preclinical stages. ApoE4 carriers are more likely to exhibit brain hypometabolism, and a neuroimaging study found that brain creatine stores were lower in ApoE4, particularly in those experiencing cognitive decline [16].

Aging and related health concerns: Creatine may facilitate increases in muscle size and strength in combination with resistance training, which may help protect against frailty. It doesn't protect against bone loss, and benefits to chronic fatigue appear minor.

Types of evidence:

- 3 meta-analyses or systematic reviews on athletic performance
- 7 meta-analyses or systematic reviews on muscle/body mass
- 2 clinical trials on postmenopausal bone loss
- 3 pilot clinical trials in fatigue disorders
- Numerous laboratory studies

Strength/Athletic performance: POTENTIAL BENEFIT

Creatine supplementation has been most extensively studied as an ergogenic agent, particularly with respect to resistance strength training. The International Society of Sports Nutrition (ISSN) has concluded that creatine monohydrate is currently the most effective ergogenic nutrition supplement available to increase high-intensity exercise capacity and lean body mass during training [1].

The muscles hold 95% of the body's creatine stores. Creatine is converted into phosphocreatine to serve as an additional source of ATP during periods of high demand. This reserve source of high-energy phosphate allows for a delay in the time to muscle fatigue/failure, and thus is most beneficial for the type II fast twitch muscles used for strength and sprints. In the context of resistance training, delaying the time to fatigue allows for longer, more intense workouts, which in turn can lead to increased muscle gains.

Although the potential for performance gains has been mixed across studies, a number of variables go into whether a meaningful difference can be detected, such as the type of exercise being performed, and the degree to which all of the participants are exerting themselves to the point of muscle failure.

Creatine may also benefit performance in professions which involve strength and athleticism. An RCT in 30 male firefighters found that supplementation with 5 g/day of creatine for 21-26 days improved occupational performance on some tasks, including the time to rescue [40].

A systematic review and meta-analysis of 14 studies including 267 young athletes (mean age <30), predominantly (95%) men, assessed the impact of short-term creatine supplementation (20 g/day for 3-7 days) on repeated sprint ability [41]. The analysis found that creatine was associated with an increase in mean power output in sprint cycling, but no significant effects were detected on peak power, fatigue, or post-test blood lactate levels. The results with respect to the impact of creatine on endurance performance have been more variable, with most studies showing no benefit or even a slight detriment, which is thought to be related to the propensity for a slight weight gain due to increased water retention. A meta-analysis of 13 studies found that creatine supplementation was not significantly associated with endurance performance in a trained population [42].

Similar to the studies assessing the impact of creatine on cognition, the interpretation of studies assessing creatine for athletic performance are hindered by a lack of pre and post assessments of muscle creatine levels in study participants [41]. Studies show that creatine supplementation can potentially increase muscle creatine content by 20%. The degree to which creatine supplementation can increase muscle creatine stores depends on a variety of factors, including regularity of use, amount of type II muscle fibers, baseline muscle creatine content, and possibly age. Exercise can enhance the uptake of creatine into the muscle, particularly when consumed in close proximity to the session of physical activity. As a result of all of these variables, the degree of creatine store augmentation can vary highly across individuals, and contribute to the heterogeneity across studies.
Most of the studies have been conducted in young healthy men, so there is less evidence to support the use of creatine as an ergogenic aid in women. It has been hypothesized that women may be less responsive to creatine supplementation as an ergogenic aid relative to men because resting intramuscular creatine stores are around 10% higher in women [43]. This may stem from women having lower total creatine stores as an extension of having lower overall muscle mass. The studies conducted to date show a similar level of heterogeneity in outcomes in females relative to males, and generally support the notion that creatine supplementation can also improve anaerobic and aerobic exercise capacity in young women [43]. Part of the variability in outcomes amongst women may be related to the fluctuations in creatine kinase activity over the course of the menstrual cycle, which may impact creatine metabolism [43]. Although it has not been systematically studied to date, this suggests that responsiveness to creatine supplementation may vary depending on the phase of the menstrual cycle.

Muscle gains: POTENTIAL BENEFIT
A systematic review and meta-analysis of 10 RCTs assessing the impact of creatine on enhancing metabolic performance found that creatine supplementation was associated with increased muscle performance with an odds ratio of 5.98 (95% CI 2.64 to 13.54) [3]. Since the majority of studies were conducted in young adults in their 20s and 30s, the data generally supports that creatine can promote muscle growth in this population when used in combination with strength training. A separate systematic review and meta-analysis of 10 studies assessing the longitudinal effects of creatine supplementation in combination with resistance training found a small positive effect on regional changes in muscle mass (pooled mean estimate: 0.11, 95% CI −0.02 to 0.25), with considerable heterogeneity depending on the body region [44]. The effect was more prominent in younger adults relative to older adults. Similarly, a review of 16 RCTs assessed the effect of creatine supplementation on improving muscle growth in various populations and found that trained young adults were most

likely to experience significant muscle gains, but this could also be a feature of the training regimens used [45].

Although not to the same degree as in young adults, the evidence suggests that in combination with resistance training, creatine can also promote muscle growth and strength in older adults [46]. A meta-analysis of 22 studies with a mean age of 57–70 years old including 721 participants found that the combination of creatine with resistance training was associated with a mean increase in lean body mass of 1.37 kg (95% CI 0.97 to 1.76), as well as increases in chest press strength (standardized mean difference [SMD]: 0.35, 95% CI 0.16 to 0.53), and leg press strength (SMD: 0.24, 95% CI 0.05 to 0.43) [47].

The combination of creatine with resistance training was also found to reduce fat percentage to a small, but statistically significant degree. A meta-analysis of 12 studies including 266 participants under the age of 50 found that creatine plus resistance training was associated with a reduction in body fat percentage by −1.19% (95% CI −2.03 to −0.34%) [48]. This was similar to the reduction in body fat percentage of −0.55% (95% CI −1.08 to −0.03) seen in a meta-analysis of 19 studies including 609 participants ≥50 years of age [49]. Though, creatine was not associated with a significant reduction in absolute fat mass in either of these analyses.

A systematic review and meta-analysis of 35 RCTs including 1,192 participants found that creatine supplementation in combination with resistance training was associated with a mean increase in lean body mass of 1.10 kg (95% CI 0.56 to 1.65), but creatine without exercise had no effect on lean body mass [50]. Additionally, the increase in lean body mass was significant in men, but only showed a non-significant trend in women.

Although the gains in lean body mass tend to be less robust in women and older adults, the research suggests that supplementation with creatine may still promote gains in muscle mass and strength when paired with resistance training in postmenopausal women [43].

Postmenopausal bone loss: NO BENEFIT

In vitro studies suggested that creatine may promote the activity of bone forming cells (osteoblasts) and inhibit the activity of bone reabsorbing cells (osteoclasts) [51]. However, clinical trials examining the impact of creatine supplementation on bone loss in postmenopausal women have failed to find meaningful effects [43].

Creatine monohydrate at a dose of 3 g/day for two years did not significantly impact measures of bone mineral density or bone microarchitecture in a trial of 200 postmenopausal women with osteopenia (NCT01472393) [52]. Similarly, a trial (NCT02047864) testing the combination of creatine (0.14 g/kg/day), resistance training, and walking in postmenopausal women (n=237) for two years did not find

evidence for an effect of creatine on the primary outcome of femoral neck bone mineral density, though there were some improvements in bone geometric properties at the proximal femur [51]. Both studies showed a slight increase in lean body mass with creatine, which did not appear to stem from preservation of bone mass. The lack of impact to bone density does not appear to be restricted to postmenopausal women, as a small (n=38) trial in older men (aged 49–69) found that creatine (0.1 g/kg/day) in combination with whole body resistance training for 12 months had no significant impact on bone mineral density or bone geometric properties [53].

Chronic fatigue: POTENTIAL MINOR BENEFIT

There is evidence to suggest that creatine metabolism may be perturbed in the context of some types of chronic fatigue syndromes [54]. There have been a few small pilot clinical trials assessing the efficacy of creatine supplementation in different types of fatigue-related disorders. The observed benefits to date have been modest.

In patients with fibromyalgia (n=28), supplementation with creatine using a loading dose of 20 g/day for five days followed by 5 g/day for the remainer of the 16-week study, reliably increased muscle phosphocreatine content (+80.3% vs -2.7%), and isometric muscle strength (+6.4% vs -3.2%), relative to the placebo group [55]. However, there were no significant differences with respect to pain, cognitive function, quality of sleep, or quality of life measures.

In patients with chronic obstructive pulmonary disease (COPD) (n=23), supplementation with creatine using a loading dose of 0.3 g/kg/day for seven days, followed by 0.07 g/k/day for the remainer of the eight week study in conjunction with a rehabilitation exercise program increased walking time on the Endurance Shuttle Walking Test by 61% relative to baseline, however, the effect was not significant relative to the placebo group, which showed a 48% increase [56]. Further, there were no significant differences on measures of health-related quality of life, lung function, artery blood gases, grip strength, or knee extensor strength/fatigue.

The most promising results appear to be in a pilot trial in 12 patients with post covid-19 fatigue syndrome treated with 4 g creatine/day for six months [57]. Supplementation significantly increased creatine levels in the muscles as well as in particular brain regions, including the left frontal white matter, and right parietal white matter. Notably, there was a significant reduction in general fatigue at three months, and in post-COVID-19 fatigue syndrome-related symptoms at six months. Cohen's d effect sizes ≥0.8 are generally considered large effects. In this study, the Cohen's effect sizes at six months were 1.02 for decreasing mental fatigue, 1.25 for breathing difficulties, 0.99 for lung pain, 3.03 for body aches, 1.26 for headache, and 2.46 for difficulties concentrating.

Creatine supplementation is currently being tested in a clinical trial in patients with chronic fatigue syndrome (NCT02374112). The trial was initiated in 2016 and was estimated to be completed in 2023, though no results have yet been made available.

Safety: Creatine has an excellent safety record, with the most common events, such as gastrointestinal, occurring at similar rates as control groups. Water retention may occur in men. Case reports of kidney issues cannot be clearly tied to creatine.

Types of evidence:

- 1 meta-analysis or systematic review on creatine safety in females
- 1 meta-analysis of clinical studies assessing renal safety
- 2 reviews on the safety and efficacy of creatine
- 3 observational studies on dietary creatine and adverse health events
- Numerous laboratory studies

Creatine derived from meat and fish is regularly consumed as part of a typical omnivorous diet. Intake in the general population is around 1 g/day [6]. Observational studies linking dietary patterns with health outcomes, largely derived from the National Health and Nutrition Examination Surveys (NHANES) in the United States, have found that low creatine consumption is associated with worse health outcomes than high creatine consumption. In these studies, low consumption was generally defined as <1 g/day, while high intake was ≥2 g/day. In adults ≥ 65 years of age, low intake of creatine was associated with increased risk for angina pectoris (ischemic heart disease-related traits) (adjusted OR: 2.62, 95% CI 1.14 to 6.01) and liver conditions (adjusted OR: 2.59, 95% CI from 1.23 to 5.48), relative to those with medium to high dietary intake of creatine [58]. Relative to low intake, high intake of creatine was not associated with increased risk for liver fibrosis (OR: 0.92, 95% CI 0.70 to 1.21), cirrhosis (OR: 0.94, 95% CI 0.53 to 1.65), hepatic steatosis (OR: 0.77, 95% CI 0.59 to 1.02), or kidney failure (OR: 0.74, 95% CI 0.39 to 1.38) [59; 60].

Creatine has been safely used as a supplement for over 150 years [2]. The most widely used form is creatine monohydrate, whose effects have been studied in hundreds of clinical trials. The safety profile of creatine monohydrate in these studies has been excellent [61]. The most reported side effect is a small weight gain, which occurs most frequently during a high dose loading phase and is related to increased intramuscular water retention. The effect has also primarily been reported in men.

Gastrointestinal effects such as nausea or bloating are also commonly reported, but overall, the incidence rates in clinical studies do not significantly differ from those in control groups. A systematic review of 29 studies including 951 female participants concluded that creatine monohydrate supplementation was not associated with an increased risk for adverse events, and no serious adverse events or deaths have been reported [62]. A meta-analysis including 18 of these studies found that creatine supplementation in females was not associated with increased risks for total adverse events (Risk ratio [RR]: 1.24, 95% CI 0.51 to 2.98), gastrointestinal events, (RR: 1.09, 95% CI 0.53 to 2.24), or weight gain, (MD: from 1.24 kg, 95% CI −0.34 to 2.82 pre-intervention to 1.37 kg, 95% CI −0.50 to 3.23 post-intervention) [62].

Concerns regarding possible negative impacts to liver kidney function were derived from a few case reports, but these generally involved individuals with other underlying health conditions or most often young men taking very high doses of creatine as an ergogenic aid in combination with a variety of other supplements, such that the contribution of creatine cannot be clearly established [59]. The link with potential kidney dysfunction can be further complicated by the use of creatinine as a marker of kidney damage. Creatinine is the excreted metabolic waste product of creatine, and circulating levels can increase temporarily after exercise due to the release of creatine from muscle cells. Supplementation with creatine in combination with resistance exercise may further increase these levels, which could be flagged as abnormal [63]. However, this is a byproduct of increased creatine metabolism, and not a kidney issue, as it is not accompanied by abnormal readings on other kidney function-related measures. Clinical studies have found that when creatine supplementation raises creatinine levels, it typically remains within the normal range. A meta-analysis including six studies found that creatine supplementation did not significantly affect creatinine levels (SMD: 0.48, 95% CI 0.24 to 0.73) [64]. However, caution is still warranted in individuals with established kidney disease/impairment.

Creatine supplementation has been tested in a variety of clinical trials in individuals with neurodegenerative disease, elderly individuals, and populations with a higher degree of frailty [46]. Similar to healthy young populations, gastrointestinal side effects were the most common, but otherwise creatine has generally been well tolerated even at relatively high doses up to 20 g/day, and is not associated with serious adverse events.

Sex effect: Endogenous stores of creatine differ between men and women, and studies suggest that the responsiveness to supplementation may also differ in a sex-related manner [43]. Due to greater amounts of skeletal muscle and lower baseline intramuscular stores, men appear to be more responsive

to increasing intramuscular stores with creatine supplementation. Although the evidence to date is less robust, females appear to be more responsive to creatine supplementation with respect to the modulation of brain stores, or at least, are more impacted by reductions in brain levels. Some of the sex effects may be related to an interaction between creatine and estrogen.

Drug interactions: According to Drugs.com, there are five known drug interactions with creatine, which fall within the moderate to mild range. Creatine has moderate interactions with the antiviral entecavir and the chemotherapeutic pemetrexed, as creatine may increase blood levels of these drugs. There are also mild interactions with cimetidine (antacid), probenecid (gout medication), and trimethoprim (antibiotic). Additional possible interactions include with non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, and drugs that affect the kidneys. Taking creatine with caffeine may increase the risk for dehydration (Mount Sinai).

Sources and dosing:
Creatine monohydrate is the most widely tested form of creatine. It is used as an oral supplement, typically in the form of a powder, and is considered the best in terms of bioavailability, and established safety [61]. Traditional doses for creatine monohydrate for use as an ergogenic aid include a loading phase of 0.03 g/kg/day (~20 g/day or 5 g 4x/day) for 5-7 days followed by a maintenance phase of 5 g/day. There is currently no clinically established dose of creatine for optimizing brain stores or use in neurological disorders. Studies to date suggest that brain stores are less responsive to supplementation and may require higher doses (i.e. 20 g/day) and/or longer durations (several months).

Creatine can also be obtained through diet. Typical consumption is around 1-2 g/day, which is about the same level that is excreted on a daily basis. Since creatine is primarily contained in muscle, enriched dietary sources include red meat, poultry, and seafood. Foods that contain the amino acids arginine, glycine, and/or methionine, such as some beans and seeds, can promote the body's endogenous production of creatine.

Since creatine is derived from dietary sources and endogenous synthesis, high levels of supplementation can potentially downregulate endogenous production, such that the potential to benefit from supplementation may decrease over time [4].

Research underway:

According to Clinicaltrials.gov, there are currently 44 active clinical trials involving creatine. Creatine is being tested in concussion recovery, autism spectrum disorder, Alzheimer's disease, cancer, cardiac/vascular responses, voice performance in the elderly, chronic fatigue syndrome, depression, body composition, sperm quality, childhood myositis, sarcopenia, lowering S-adenosylhomocysteine, exercise, and athletic performance.

Search terms:

Pubmed, Google: Creatine

- Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, neurodegeneration, cognition, clinical trial, aging, frailty, meta-analysis, systematic review, safety

Websites visited for Creatine:

- Clinicaltrials.gov
- Examine.com
- DrugAge
- Geroprotectors
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Labdoor.com
- ConsumerLab.com

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