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SCIENTIFIC OPINION

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Creatine and improvement in cognitive function: Evaluation of a health claim pursuant to article 13(5) of regulation (EC) No 1924/2006

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The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch

Abstract

Following an application from Alzchem Trostberg GmbH, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Austria, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to creatine and improvement in cognitive function. The Panel considers that the food constituent, creatine, is sufficiently characterised. An improvement in cognitive function in one or more of its domains is a beneficial physiological effect. The applicant identified 21 human intervention studies on creatine supplementation and measures of cognitive function through a literature search. Two additional studies published after the search was conducted were identified through the reference list of a meta-analysis. In weighing the evidence, the Panel took into account that the acute effect of creatine on working memory, observed in two studies at 20 g/day for 5–7 days, was not seen at lower doses (2.2–14 g/day), or with continuous consumption (5 g/day for 6 weeks following a 5-day loading phase). Furthermore, the effect on response inhibition at 20 g/day for 7 days was an isolated finding among 10 intervention studies in healthy individuals, with no effects observed on other cognitive domains. The Panel also considered that the three intervention studies conducted in diseased individuals do not support an effect of creatine supplementation on cognition, and that the available evidence for a mechanism by which creatine could exert the claimed effect is weak. The Panel concludes that a cause-and-effect relationship has not been established between creatine supplementation and an improvement in cognitive function in one or more of its domains.

KEYWORDS

cognition, cognitive function, Creatine, health claim

CONTENTS

1 | INTRODUCTION

1.1 | Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006 harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health), which are based on newly developed scientific evidence or include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3). According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

1.2 | Interpretation of the Terms of Reference

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to creatine and improvement in cognitive function.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of creatine, a positive assessment of its safety, nor a decision on whether creatine is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

2 | DATA AND METHODOLOGIES

2.1 | Data

Information provided by the applicant

See also the section Steps taken by EFSA at the end of this opinion.

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is '*Creatine (CAS-No. 57-00-1). The most common traded form of creatine is creatine monohydrate (CAS-No. 6020-87-7).*'

Health relationship as claimed by the applicant

According to the applicant, the health effect relates to the improvement in cognitive function.

'Creatine supplementation was demonstrated to positively impact specific cognitive domains such as memory, attention, inhibitory control, and certain executive functions. While its effects may vary among different populations, cognitive tasks, and conditions such as sleep deprivation or hypoxia, it holds promise as a supplement for targeted cognitive enhancement, especially in situations demanding immediate cognitive processing, attention, and memory tasks'.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

The applicant claims that the effect *'derives from creatine and phosphocreatine present in the brain, but the precise molecular mechanism(s), on which the effect is based, is or are unknown. […] creatine is able to cross the blood brain barrier and therefore it is speculated that systemic creatine supplementation can increase brain creatine concentration, and creatine might exert the claimed effect by increasing the energy supply of neurons by means of different molecular mechanisms. Events of increased energy requirements of the brain (e.g., for the performance of mental tasks) go along with increased synthesis of adenosine triphosphate (ATP). Creatine is involved in the re-synthesis of ATP when its concentration falls in neurons with increased adenosine diphosphate (ADP) concentrations activating the creatine kinase reaction towards ATP synthesis, which in turn results in a decrease of the concentration of phosphocreatine. Creatine phosphate is very efficient to resynthesize ATP, it acts 12 times faster than it occurs via oxidative phosphorylation, and more than 70 times quicker than it occurs via de novo pathways. In addition, significant reduction in task-evoked cerebral oxygenated hemoglobin suggests increased oxygen utilization in the brain.'*

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim *'Daily creatine supplementation can contribute to improved cognitive function'*.

Specific conditions of use as proposed by the applicant

According to the applicant, the target population for the intended health claim is *'the general population, i.e. healthy individuals of both sexes over 18 years of age'*. The recommended dose of creatine proposed by the applicant to achieve the claimed effect is *'3 g/day'*.

Data provided by the applicant

The health claim application on creatine pursuant to Article 13(5) of Regulation (EC) No 1924/2006 was presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of a health claim application (EFSA NDA Panel, 2021b).

As outlined in the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2021a), it is the responsibility of the applicant to provide the totality of the available evidence.

The applicant has submitted a confidential and a non-confidential version of a dossier following the 'General scientific guidance for stakeholders on health claim applications' (EFSA NDA Panel, 2021a) and the 'Scientific and technical guidance for the preparation and presentation of a health claim application' (EFSA NDA Panel, 2021b).

The application contains personal data claimed as confidential by the applicant: names, addresses, signatures, email and telephone of natural persons. No confidential data from the application were used in this assessment.

The application does not contain data claimed as proprietary.

In accordance with Art. 38 of Regulation (EC) No 178/2002[1] and taking into account the protection of confidential information and of personal data in accordance with Articles 39 to 39e of the same Regulation, and of the Decision of EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,[2] the non-confidential version of the dossier has been published in the OpenEFSA portal.[3]

2.2 | Methodologies

The approach used by the NDA Panel for the evaluation of health claims is explained in the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2021a). In assessing each specific food/health relationship, which forms the basis of a health claim, the NDA Panel considers the following key criteria:

(i) the food/constituent is defined and characterised;
(ii) the claimed effect is based on the essentiality of a nutrient; OR the claimed effect is defined and is a beneficial physiological effect for the target population and can be measured in vivo in humans;
(iii) a cause-and-effect relationship is established between the consumption of the food/constituent and the claimed effect (for the target group under the proposed conditions of use).

Each of these three criteria needs to be assessed by the NDA Panel with a favourable outcome for a claim to be substantiated. In addition, an unfavourable outcome of the assessment of criterion (i) and/or (ii) precludes the scientific assessment of criterion (iii).

The scientific requirements for health claims related to functions of the nervous system, including psychological functions, are outlined in a specific EFSA guidance (EFSA NDA Panel, 2012).

2.3 | Public consultation

According to Art. 32c(2) of Regulation (EC) No 178/2002 and to the Decision of EFSA's Executive Director laying down the practical arrangements on pre-submission phase and public consultations, EFSA carried out a Public Consultation on the non-confidential version of the application from 26 July 2024 to 16 August 2024 (PC-1063). The outcome of the public consultation is described in Appendix A to this Scientific Opinion.

[1]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–48.

[2]Decision available at: https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/210111-PAs-pre-submission-phase-and-public-consultations.pdf.

[3]https://open.efsa.europa.eu/questions/EFSA-Q-2022-00411.

3 | ASSESSMENT

3.1 | Characterisation of the food/constituent

The food constituent proposed by the applicant as the subject of the health claim is creatine.

Creatine is a non-essential nitrogen-containing organic compound naturally found in foods, particularly meat and fish, which can also be synthesised in the human body from the amino acids glycine, L-arginine and L-methionine. Approximately 95% of the creatine pool in the body is located in skeletal muscle. The content of creatine in foods can be measured by established methods.

The Panel considers that the food constituent, creatine, which is the subject of the health claim, is sufficiently characterised.

3.2 | Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is an improvement in cognitive function. The proposed target population is 'the general adult population, i.e. healthy individuals of both sexes over 18 years of age'.

Cognitive function encompasses several domains, including memory, attention (concentration), alertness, learning, intelligence, language and problem-solving, which are well defined psychological constructs (EFSA NDA Panel, 2012).

The Panel considers that an improvement in cognitive function in one or more of its domains is a beneficial physiological effect.

3.3 | Scientific substantiation of the claimed effect

The applicant performed a literature search on 14 February 2023 in the databases Chemical Abstracts and Medline to retrieve human studies published in English and German from 1990 onwards using keywords in relation to the food constituent (creatine monohydrate [6020-87-7] OR creatine [57–00-1] AND supplementation OR treatment OR intake) and keywords related to the claimed effect (cognition OR cognitive function OR behaviour OR mental OR brain function OR memory OR mental fatigue OR psychological OR psychomotor OR perceptual OR attention OR learning OR intelligence OR attention OR mood OR affect OR depression OR anxiety OR sleep). The full search strategy with keywords was provided by the applicant.

The applicant identified 21 human intervention studies investigating the effect of creatine supplementation on measures of cognitive function, either as pertinent for the scientific substantiation of the claim or as supportive evidence. However, the Panel notes that several studies had important methodological limitations or did not assess the effect of creatine per se on one or more measures of cognitive function.

One study (Cook et al., 2022) assessed a repeated rugby passing skill test, which is a test of perceptual-motor skill and not a cognitive test. Another study (Smolarek et al., 2020) investigated the combined effect of creatine supplementation and resistance training on muscle strength and cognition, which does not allow for the isolated effects of creatine to be determined. Two studies, including a single-arm intervention study (Bender et al., 2005) and a case report of two individuals (Bianchi et al., 2000), lacked a control group, limiting the validity of the results. A letter to the editor (Borchio et al., 2020) provided insufficient information on the methods, statistical analyses and results; despite the additional information provided by the applicant in response to the additional data request (ADR), the available information is inadequate for a scientific assessment. Furthermore, three studies (McMorris et al., 2006; McMorris, Mielcarz, et al., 2007; Rae et al., 2003) were previously evaluated by EFSA in a health claim opinion regarding creatine and memory (EFSA NDA Panel, 2011). These studies had several methodological limitations, including lack of information on randomisation procedures, inadequate adjustment for baseline differences, multiple uncorrected pairwise comparisons or an inappropriate significance level and insufficient details on the statistical models employed to allow a scientific assessment.

The Panel considers that no conclusions can be drawn from the aforementioned studies for the scientific substantiation of the claim.

Additionally, in response to an additional data request (ADR), the applicant submitted a systematic review and meta-analysis of 16 RCTs investigating the effect of creatine monohydrate on overall cognitive function, memory, executive function, attention and processing speed (Xu et al., 2024). The Panel notes that the meta-analysis conducted in the context of that systematic review pools the results of multiple related cognitive tests from the same studies, which are not independent from each other, to calculate a single effect estimate, leading to double-counting of participants in evidence synthesis and inflated sample sizes. The Panel considers that no conclusions can be drawn from this meta-analysis for the scientific substantiation of the claim.

The Panel notes that nine out of the 16 RCTs included in the systematic review were already identified by the applicant through the literature search. Two additional studies (Moriarty et al., 2023; Sandkühler et al., 2023) published after the search was conducted were deemed pertinent for the current application and will be discussed below alongside the remaining studies submitted by the applicant.

Human intervention studies in healthy individuals conducted under normal conditions

Nine intervention studies investigated the effect of creatine on various cognitive domains in healthy individuals (Alves, Merege Filho, et al., 2013; Benton & Donohoe, 2010; Hammett et al., 2010; Merege-Filho et al., 2017; Moriarty et al., 2023; Rawson et al., 2008; Sandkühler et al., 2023; Van Cutsem et al., 2020; Watanabe et al., 2002). These studies predominantly involved adult participants, except for Merege-Filho et al. (2017), which included only children aged 10–12 years. The participants' mean age ranged from 12 to 67 years across studies, with total sample sizes ranging from 14 to 123 individuals. A detailed description of the main characteristics and results of each study can be found in Table B.1, Appendix B.

Out of the nine studies, eight were conducted with daily creatine doses from 1.7 to 6.7 times the daily dose proposed in the CoU (3 g/day) for the claim. Two studies administered a daily dose of 20 g of creatine for 5–7 days (Benton & Donohoe, 2010; Van Cutsem et al., 2020), while two other studies used a loading dose of 20 g/day for the first 5 days, followed by 5 g/day for either 2 days (Hammett et al., 2010) or 24 weeks (Alves, Merege Filho, et al., 2013). One study provided 0.3 g/kg body weight/day (approximately 14 g/day) for 7 days (Merege-Filho et al., 2017) and another study 8 g/day for 5 days (Watanabe et al., 2002). Finally, two studies were conducted with supplemental creatine at doses of 5 g/day (Sandkühler et al., 2023) and 10 or 20 g/day (Moriarty et al., 2023) for 6 weeks. Cognitive domains assessed in these studies included different facets of memory (episodic, short-term, working, visual), attention, alertness, processing speed, executive function, inhibitory control and general cognitive ability (Table B.1, Appendix B).

Four intervention studies assessed the effect of high doses of creatine (between 8 and 20 g/day) given for short periods of time (5–7 days) on cognitive performance (Benton & Donohoe, 2010; Merege-Filho et al., 2017; Van Cutsem et al., 2020; Watanabe et al., 2002).

In the study by Benton and Donohoe (2010), young adult female meat-eaters ($n = 51$) or non-meat eaters (vegetarians or vegans; $n = 70$) were randomly assigned to consume either 20 g/day of creatine or a placebo for 5 days under a double-blind procedure. A three-way repeated measures ANOVA indicated a significant interaction between supplement type (creatine vs. placebo), diet (meat-eaters vs. non-meat eaters) and time (baseline vs. post-supplementation) for the memory word recall test ($p < 0.01$). Only the results for the effect of creatine as compared to baseline in meat-eaters vs. non-meat eaters were provided. The effect of creatine supplementation vs. placebo on memory for either all participants combined, meat-eaters or non-meat eaters was not reported. For the reaction time procedure task, which measures alertness and speed of processing, neither decision times nor movement times were significantly affected by creatine supplementation, regardless of dietary group. Although variability in the speed of response showed a significant interaction between supplement type (creatine vs. placebo), the number of lamps monitored and time ($p < 0.05$), no direct comparisons between intervention groups (creatine vs. placebo) were reported. Creatine supplementation did not affect vigilance (i.e. the ability to sustain attention) or word fluency. The Panel considers that this study does not show an effect of creatine consumed at a dose of 20 g/day for 5 days on any of the cognitive domains assessed (i.e. memory, alertness, speed of processing, attention, executive function and verbal ability).

In a counterbalanced cross-over design study of 14 young adults (Van Cutsem et al., 2020), a modified mentally fatiguing 90-min Stroop task, the Flanker task and a sport-specific visuomotor task were completed by participants as measures of cognitive performance before and after 7 days of creatine supplementation (20 g/day) or placebo. Creatine improved accuracy on colour stimuli (a measure of response inhibition) during the 90-min Stroop task compared to the placebo (main effect of the condition, $p = 0.025$), with no effect of time and no significant treatment × time interaction. Within the same task, no significant effects of creatine on reaction time on the colour stimuli, neither on accuracy nor on reaction time on the meaning stimuli (as measures of task-switching ability), were observed. Creatine supplementation did not affect cognitive performance on the Flanker task, a test of executive function, selective attention and inhibitory control, nor did it impact performance on a sport-specific visuomotor task, which measures psychomotor abilities including selective attention, inhibitory control and motor speed. Additionally, creatine did not mitigate the impairment in performance associated with mental fatigue on these tasks. The Panel notes that the study primarily focused on cognitive performance, and assessed a substantial number of endpoints related to this outcome. However, the specific cognitive test variable used to determine the sample size for the power calculation was not disclosed. The Panel considers that this study shows an effect of creatine at a dose of 20 g/day consumed for 7 days on the accuracy on colour stimuli in a modified version of the 90-min Stroop task and no effect of creatine on other measures of cognitive performance (task-switching ability, executive function, selective attention, motor speed and inhibitory control), nor on cognitive performance decline owing to mental fatigue.

In the intervention study which administered 14 g/day of creatine or placebo for 7 days to 67 children aged 10–12 years (Merege-Filho et al., 2017), no significant effects of creatine were found on any of the cognitive function domains tested, including working memory, short-term memory, long-term memory, selective attention, inhibitory control or executive function.

No direct comparisons between the creatine (8 g/day) and placebo groups were performed in the 5-day study by Watanabe et al. (2002). The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

Two studies investigated daily doses of creatine between 5 and 20 g/day given for longer periods of time (6 weeks). One randomised, double-blind, placebo-controlled study in 30 healthy young adults found no effect of supplemental creatine at doses of 10 or 20 g/day on measures of cognitive performance, including processing speed, episodic memory and executive function (Moriarty et al., 2023). The second study was a randomised, double-blind, placebo-controlled, crossover intervention in 123 healthy adults which included vegetarians and omnivores (Sandkühler et al., 2023). No significant effect

of creatine (5 g/day) was observed on the primary endpoints (the Raven's Advanced Progressive Matrices, a test of abstract reasoning and general cognitive ability and the Backward Digit Span, a test of working memory) or any of the eight other exploratory cognitive tasks, covering domains such as attention, verbal fluency, task switching and memory.

Two studies had an initial loading phase of 20 g/day of creatine for 5 days, followed by 5 g/day for either 2 days in healthy young volunteers ($n = 11$ per group; Hammett et al., 2010) or 24 weeks in older women ($n = 14$ per group; Alves, Merege Filho, et al., 2013). A significant improvement in working memory, as measured by the Backwards Digit Span test, was observed only in the study of shorter duration (Hammett et al., 2010) ($p_{group\ x\ time} = 0.008$), whereas no such effect was found in the study with a longer maintenance phase using the same working memory test (Alves, Merege Filho, et al., 2013). Hammett et al. (2010) found no significant effect of creatine supplementation on general cognitive ability or fluid intelligence, as measured by the Raven's Advanced Progressive Matrices test. Likewise, Alves, Merege Filho, et al. (2013) observed no effect of creatine on various cognitive functions, including visual and short-term memory, attention (visual, sustained and selective), inhibitory control and executive function. The Panel notes that the Hammett et al. (2010) study was not randomised, which limits the validity of its findings, especially in light of the longer, randomised and more methodologically rigorous study by Alves, Merege Filho, et al. (2013), which did not show a significant effect of creatine on working memory. The Panel considers that these studies do not show an effect of creatine at a dose of 5 g/day, following a loading dose of 20 g/day for 5 days, on working memory. Furthermore, no effect of creatine was observed in both studies on other domains of cognitive function, including general cognitive ability and fluid intelligence, visual and short-term memory, attention (visual, sustained and selective), inhibitory control and executive function.

Lastly, one randomised, double-blind, parallel, placebo-controlled intervention study conducted in 22 young adults used a creatine dose within the specified CoU for the claim (up to 3 g/day) (Rawson et al., 2008). A battery of tests was used to assess the effect of 0.03 g/kg body weight per day (approximately 2.2 g/day) of creatine on various aspects of memory, including running, short-term and working memory, as well as alertness and logical reasoning over a 6-week period. No significant differences were observed between the creatine and placebo groups in any of these endpoints.

The Panel considers that, among the eight intervention studies conducted in healthy individuals under normal conditions from which conclusions could be drawn, one study (Van Cutsem et al., 2020) showed an effect of creatine (20 g/day for 7 days) on one measure of response inhibition and one non-randomised study (Hammett et al., 2010) showed an effect of creatine (5 g/day for 2 days after a 5-day loading phase with 20 g/day) on working memory. The latter effect could not be replicated in a more methodologically rigorous study (Alves, Merege Filho, et al., 2013) with a similar design, where the maintenance phase (5 g/day) lasted 24 weeks, nor in another study which provided 5 g/day supplemental creatine for 6 weeks (Sandkühler et al., 2023). No significant effects of creatine were observed on other cognitive domains in these studies, nor in any cognitive domain in other studies using creatine at doses of 20 g/day (Benton & Donohoe, 2010) or 14 g/day (Merege-Filho et al., 2017) for 7 days, 10 or 20 g/day for 6 weeks (Moriarty et al., 2023) or 2.2 g/day for 6 weeks (Rawson et al., 2008).

Human intervention studies in healthy individuals conducted under stress-induced conditions

Three intervention studies investigated the effect of creatine supplementation on various cognitive domains under conditions of induced stress (McMorris, Harris, et al., 2007; Pires et al., 2020; Turner et al., 2015) (see Table B.2, Appendix B). Cognitive domains assessed in these studies included memory (episodic, short-term and working memory), attention, alertness, executive function, inhibitory control, information processing speed and cognitive flexibility. Two studies administered 20 g/day for 7 days (McMorris, Harris, et al., 2007; Turner et al., 2015), while Pires et al. (2020) provided 3 g/day for 4 weeks. The participants' mean ages ranged from 21 to 31 years, with total sample size ranging from 15 to 26 individuals. A detailed description of the main characteristics and results of each study can be found in Table B.2, Appendix B.

The two studies using 20 g/day of creatine for 7 days assessed measures of cognitive function in young adults under conditions of sleep deprivation (McMorris, Harris, et al., 2007) or acute oxygen deprivation (Turner et al., 2015).

In a placebo-controlled, parallel intervention study (McMorris, Harris, et al., 2007), among male sports science majors (mean (SD) age = 21.1 years (1.85)), participants were divided into a creatine and a placebo group with the same number of individuals ($n = 10$). It is unclear on which basis this assignment was done. While the study was purportedly double-blind, specific details regarding the blinding methods for both participants and investigators were not reported. Cognitive function was assessed following a 7-day supplementation with 20 g/day creatine or placebo at baseline (time 0) and after 18, 24 and 36 h of sleep deprivation, combined with intermittent moderate-intensity exercise occurring between testing sessions. An improvement in central executive working memory performance as measured by the random number generation task was reported after 36 h of sleep deprivation ($p_{group\ x\ time} < 0.05$). No effect of creatine was observed on this variable at other time points or on other cognitive functions assessed, including verbal and short-term memory, alertness and speed of processing. The Panel notes the lack of information regarding the assignment of participants to treatment groups and the measures taken to double-blind the study. The Panel also notes that no primary outcome was identified and that correction for the multiple endpoints tested was not applied. The Panel considers that this study with methodological limitations shows an effect of creatine supplementation (20 g/day for 7 days) on working memory after 36 h of sleep deprivation in combination with moderate-intensity exercise, and no effect on verbal and short-term memory, alertness and speed of processing under similar conditions.

Turner et al. (2015) conducted a randomised, placebo-controlled, crossover study in which 15 participants received 20 g/day creatine and placebo for 7 days each with a 5-week washout period in between. Participants underwent a battery of seven cognitive function tests under conditions of normoxia and then under acute oxygen deprivation induced by a

hypoxic gas mixture (10% oxygen), at run-in (habituation phase) and after each intervention period. A significant effect of creatine was observed in the continuous performance (commission of errors) test assessing vigilance/sustained attention (paired-samples *t*-test; $p < 0.05$), whereas no effect was reported on other tests performed under the 'complex attention' domain, including the continuous performance (omission of errors) test, the test of shifting attention (cognitive flexibility) and the Stroop test (reaction time/information processing speed), or on other cognitive functions assessed, including memory, processing speed, executive function, psychomotor speed, reaction time and cognitive flexibility. The Panel notes that a significant effect of creatine was observed only in one out of the 17 endpoints tested related to cognition, that the primary outcome was not identified and that corrections for multiple pairwise comparisons to account for a chance finding were not applied. The Panel notes the exploratory nature of this study and considers that no conclusions can be drawn for the scientific substantiation of the claim.

In the third study (Pires et al., 2020), 26 female Muay Thai (a martial art) athletes who had undergone 4 weeks of creatine supplementation (3 g/day; $n = 13$) or placebo ($n = 13$) completed a series of cognitive tests following exhaustive exercise (10-min warm-up, followed by 40 min of technical training and 30 min of intensive fighting). No significant between-group differences in any of the cognitive outcomes assessed, including measures of short-term memory and working memory, alertness, processing speed, selective attention, executive function and inhibitory control were found in the main analyses using repeated measures ANOVA. No conclusions can be drawn from the reported 'forced' post hoc analyses assessing changes within each supplementation group over time for the scientific substantiation of the claim. The Panel considers that this study does not show an effect of creatine at a dose of 3 g/day for 4 weeks on any measure of cognition.

The Panel considers that two intervention studies conducted in healthy individuals under stress conditions allow conclusions to be drawn for the scientific substantiation of the claim. One study with methodological limitations showed an effect of creatine on working memory after 36 h of sleep deprivation combined with moderate-intensity exercise at a dose 6.7 times higher (20 g/day for 7 days) than that proposed in the CoU (3 g/day). No effect was observed on verbal or short-term memory, alertness or processing speed under similar conditions (McMorris, Harris, et al., 2007). In the second study, no effect of creatine at doses in line with the proposed CoU consumed for a longer period (4 weeks) was observed on short-term or working memory, alertness, processing speed, selective attention, executive function or inhibitory control following exhaustive exercise (Pires et al., 2020).

Human intervention studies in diseased individuals

Three studies examined the effects of creatine on measures of cognitive function in patients with primary fibromyalgia (Alves, Santiago, et al., 2013), bipolar depression (Toniolo et al., 2017) or symptomatic Huntington's disease (Verbessem et al., 2003). A detailed description of the main characteristics and results of each study can be found in Table B.3, Appendix B.

Alves, Santiago, et al. (2013) investigated the effects of creatine supplementation in 28 women with primary fibromyalgia. The RCT supplementation protocol involved an initial loading phase of 20 g/day for the first 5 days, followed by a maintenance dose of 5 g/day for the remaining 16 weeks ($n = 13$), compared with a placebo ($n = 15$). The assessment of cognitive function covered a range of domains, including memory (short-term and working memory, immediate and delayed recall), attention, inhibitory control and executive function. No significant between-group differences were observed for any of these endpoints.

The RCT by Toniolo et al. (2017) investigated the effect of 6 g/day creatine supplementation compared to a placebo over a period of 6 weeks in 18 adult patients diagnosed with bipolar disorder type I or II, all of whom were experiencing moderate or severe depression at the time of recruitment. A comprehensive battery of neuropsychological tests was administered at baseline and at the end of the intervention period to assess various cognitive domains, including short-term memory and working memory, selective attention, executive function and verbal fluency. A statistically significant improvement was observed in the creatine group compared to the placebo group in verbal fluency test scores. No significant differences were observed between the two groups in any other neuropsychological test.

The RCT by Verbessem et al. (2003) investigated the effect of creatine supplementation (5 g/day) vs. placebo on cognition over 1 year in 41 patients with Huntington's disease. The test battery consisted of the Unified Huntington's Disease Rating Scale, which includes measures of several cognitive domains such as selective attention, inhibitory control, executive function and verbal fluency. No significant differences between the creatine and placebo groups were observed in any of the cognitive endpoints assessed.

The Panel notes that the daily creatine dose administered in these studies is between 1.7 and 6.7 times the daily dose proposed in the CoU for the claim. The Panel considers that these studies in patients do not support an effect of creatine supplementation on cognitive function.

Overall conclusions from human intervention studies

The Panel considers that, overall, the 10 human intervention studies from which conclusions could be drawn, all conducted in healthy individuals under normal conditions (Alves, Merege Filho, et al., 2013; Benton & Donohoe, 2010; Hammett et al., 2010; Merege-Filho et al., 2017; Moriarty et al., 2023; Rawson et al., 2008; Sandkühler et al., 2023; Van Cutsem et al., 2020) or stress-induced conditions (McMorris, Harris, et al., 2007; Pires et al., 2020) do not show a consistent effect of creatine supplementation on cognitive function. The Panel notes that the acute effect of creatine on working memory reported in some studies at doses of 20 g/day given for 5–7 days under normal conditions (Hammett et al., 2010) or under sleep deprivation (McMorris, Harris,

et al., 2007) was not observed at lower creatine doses, ranging from 2.2 to 14 g/day (Merege-Filho et al., 2017; Pires et al., 2020; Rawson et al., 2008; Sandkühler et al., 2023), or with continuous consumption of creatine (5 g/day for 6 weeks after the 5-day loading phase with 20 g/day) (Alves, Merege Filho, et al., 2013). The Panel also notes that the effect of creatine (20 g/day for 7 days) on one measure of response inhibition reported in one study (Van Cutsem et al., 2020) is an isolated finding across the body of evidence, where no effect of creatine supplementation was observed on other cognitive domains, including different facets of memory (episodic, short-term, visual), verbal fluency, attention, alertness, processing speed, psychomotor speed, executive function and general cognitive ability/flexibility and fluid intelligence. Finally, the Panel notes that the three intervention studies conducted in diseased individuals (Alves, Santiago, et al., 2013; Toniolo et al., 2017; Verbessem et al., 2003) do not support an effect of creatine supplementation on cognition.

Mechanism of action

The applicant acknowledges that the precise molecular mechanism(s) by which creatine supplementation could improve cognitive function is/are unknown. It is speculated that, as creatine can cross the blood brain barrier, creatine supplementation could increase brain creatine phosphate concentration and its availability for fast ATP re-synthesis in neurons during high energy-demanding mental tasks, thereby decreasing mental fatigue and improving cognitive performance.

In support of this mechanism, the applicant provided one case report of an infant with guanidinoacetate methyltransferase (GAMT) deficiency, an inborn error of metabolism. (Stöckler et al., 1994; Stöckler et al., 1996). This enzyme (GAMT) is needed for the endogenous synthesis of creatine. Very low plasma and urine creatine concentrations were accompanied by a generalised depletion of brain creatine and creatine phosphate and a severe extrapyramidal disorder. Creatine supplementation (4–8 g/day) for 25 months normalised plasma, urine and brain creatine concentrations, as well as clinical symptoms. It is unclear whether the neurological symptoms in this patient resulted from creatine depletion in the brain or from direct neurotoxicity of the intermediate metabolite guanidinoacetate, which also normalised after supplementation with creatine. The Panel notes that this case report provides no information about a mechanism by which creatine supplementation could improve cognitive function or cognitive performance in healthy individuals.

The applicant also provided some evidence that creatine supplementation at a dose of 20 g/day consumed for periods of 7–28 days increases creatine concentration (Dechent et al., 1999; Turner et al., 2015) and the phosphocreatine/ATP ratio (Pan & Takahashi, 2007) in certain areas of the brain in adults. The Panel notes that this effect was not observed in children aged 10–12 years using 13.5 g/day creatine for 7 days (Merege-Filho et al., 2017). Finally, the applicant also suggested that creatine may induce changes in haemoglobin oxygenation in the brain, but the evidence available at present is weak and indirect (Hammett et al., 2010; Watanabe et al., 2002).

Overall, the Panel considers that evidence provided for a mechanism by which continuous consumption of creatine could improve cognitive performance/function in healthy adults, either under normal or under stress conditions, is weak.

Weighing of the evidence

In weighing the evidence, the Panel took into account that the acute effect of creatine on working memory reported in some studies at doses of 20 g/day given for 5–7 days under normal conditions (Hammett et al., 2010) or under sleep deprivation (McMorris, Harris, et al., 2007) was not observed at lower creatine doses, ranging from 2.2 to 14 g/day (Merege-Filho et al., 2017; Pires et al., 2020; Rawson et al., 2008; Sandkühler et al., 2023), or with continuous consumption of creatine (5 g/day for 6 weeks after the 5-day loading phase with 20 g/day) (Alves, Merege Filho, et al., 2013). Furthermore, the effect of creatine (20 g/day for 7 days) on one measure of response inhibition reported in one study (Van Cutsem et al., 2020) is an isolated finding across the body of evidence (i.e. 10 intervention studies in healthy individuals), where no effect of creatine supplementation was observed on other cognitive domains, including different facets of memory (episodic, short-term, visual), verbal fluency, attention, alertness, processing speed, psychomotor speed, executive function and general cognitive ability/flexibility and fluid intelligence. The Panel also took into account that the three intervention studies conducted in diseased individuals do not support an effect of creatine supplementation on cognition, and that the available evidence for a mechanism by which creatine could exert the claimed effect is weak.

The Panel concludes that a cause-and-effect relationship has not been established between creatine supplementation and an improvement in cognitive function in one or more of its domains.

4 | CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food/constituent, creatine, is sufficiently characterised.
- The claimed effect proposed by the applicant is an improvement in cognitive function. The target population proposed by the applicant is 'the general population, i.e. healthy individuals of both sexes over 18 years of age'. An improvement in cognitive function in one or more of its domains is a beneficial physiological effect.
- A cause-and-effect relationship has not been established between the consumption of creatine and an improvement in cognitive function in one or more of its domains.

DOCUMENTATION AS PROVIDED TO EFSA

Health claim application on creatine and improvement in cognitive function pursuant to Article 13.5 of Regulation (EC) No 1924/2006 (Appian number: HC-2023-19,270). Submitted by Alzchem Trostberg GmbH.

STEPS TAKEN BY EFSA

1. This application was received by EFSA on 20/02/2024. The application was validated on 07/05/2024 and the scientific evaluation started.
2. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
3. The Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. EFSA sent a first Additional Data Request (ADR1) letter to the Applicant on 10/07/2024. The clock was stopped on 10/07/2024. The clock restarted on 25/07/2024. A second ADR letter (ADR2) was sent to the Applicant on 16/09/2024, and the clock stopped on 16/09/2024 and restarted on 19/09/2024.
4. During its meeting on 30/10/2024, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to creatine and improvement in cognitive function*: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006*.

ABBREVIATIONS

ADP	Adenosine diphosphate
ADR	Additional Data Request
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
CAS	Chemical Abstract Service
CoU	Conditions of use
GAMT	Guanidinoacetate methyltransferase
NDA Panel	Panel on Nutrition, Novel Foods and Food Allergens
PC	Public consultation
RCT	Randomised controlled trial

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REQUESTOR

Competent Authority of Austria following an application by Alzchem Trostberg GmbH

QUESTION NUMBER

EFSA-Q-2024-00106

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APPENDIX A

Outcome of the public consultation on the Application on Creatine and improvement in cognitive function (HC-2023-19270)

One comment was submitted by one contributor from the UK. The comment is published on the EFSA web page as received (https://open.efsa.europa.eu/consultations/a0cTk000004hDMLIA2?search=creatine).

General comments

Contributor/organisation	Comment and reply
Office for Health Improvement and Disparities (OHID), Department of Health and Social Care (DHSC)/Public Authority outside the EU (The United Kingdom)	**Comment**: UKNHCC Scientific Opinion on creatine supplementation and improved cognitive function - https://www.gov.uk/government/publications/uknhcc-scientific-opinion-creatine-supplementation-and-improved-cognitive-function Attachment contains the UKNHCC Scientific Opinion on creatine supplementation and improved cognitive function **Reply**: EFSA acknowledges the UK Authority's assessment.

APPENDIX B

Evidence tables of studies submitted for the scientific substantiation of the claimed effect

TABLE B.1 Human intervention studies in healthy individuals.

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Alves, Merege Filho, et al. (2013) Brazil	RCT, double-blind, placebo-controlled, parallel Population sampled: older females Inclusion criteria: aged 60–80 years, not engaged in any regular physical fitness program for at least 1 year prior to the study and not supplemented with creatine for at least 6 months. Exclusion criteria: (i) cardiovascular involvement (e.g. arrhythmias, arterial hypertension, heart failure, myocarditis, and pericarditis); (ii) current tobacco usage; (iii) previous creatine supplements usage; and (iv) other chronic diseases (e.g. diabetes mellitus, rheumatoid arthritis, chronic kidney disease, hepatic diseases or psychiatric comorbidity, including clinically diagnosed depression). Age (years): 66.8 Sex: females *N* = |*n* = G1: 14|12 G2: 14|13 G3: 14|10 G4: 14|12	Duration: 24 weeks Doses G1: Placebo G2: Cr 5 g/days G3: Placebo + ST G4: Cr 5 g/days + ST *G2 and G4 received 20 g of Cr (4 × 5 g/days) for first 5 days followed by 5 g/days as a single dose throughout the trial* Compliance: 100% self-reported adherence to supplementation protocol.	**Memory** Delayed Recall Test of the Brief Cognitive Screening Battery (BBCS): Immediate and delated recall memory. Digit Span Test: Short-term memory and working memory. **Attention** Stroop test (Victoria version): Selective attention, inhibitory control and executive function Trail Making Test: executive function, attention, working memory, visual search and planning.	Mixed model assuming 'pre values' as a covariate. Approximate inference about fixed effects was used in mixed linear models (i.e. Kenward-Roger correction) to deal with the unbalanced design. Tukey pos-hoc was used for multi-comparison purposes	**Delay recall of BBCS** **Δ (95% CI)** G1: −0.4 (−1.2 to 0.4) G2: 0.6 (−0.2 to 1.4) G3: 0.6 (−0.4 to 1.6) G4: 0.9 (0.2–1.6) *p* = 0.07 **Digit Spain Test** **Δ (95% CI)** Forward order (0–7) G1: −0.3 (−1.2 to 0.6) G2: 0.3 (−0.5 to 1.1) G3: −0.2 (−1.1 to 0.7) G4: 0.7 (−0.2 to 1.6) *p* = 0.99 Backward order (0–7) G1: 0.2 (−0.5 to 0.9) G2: 0.3 (−0.5 to 1.1) G3: 0.0 (−0.7 to 0.7) G4: 0.2 (−0.8 to 0.2) *p* = 0.90 **Stroop conditions** **Δ (95% CI)** Colour (s) G1: −1.9 (−5.1 to 1.3) G2: 0.7 (−2.5 to 3.9) G3: −1.6 (−5.0 to 1.8) 1 G4: −1.2 (−5.0 to 2.6) *p* = 0.68 Non-colour word (s) G1: −1.4 (−7.2 to 4.4) G2: −1.3 (−7.7 to 5.1) G3: −4.6 (−10.1 to 0.9) G4: −1.2 (−5.8 to 3.4) *p* = 0.16

(Continues)

TABLE B.1 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
					Colour word (s) G1: −5.8 (−13.5 to 1.9) G2: 0.1 (−8.8 to 9.0) G3: −6.7 (−13.0 to −0.4) G4: −0.2 (−11.6 to 11.2) $p = 0.88$ **Trail Making Test** **Δ (95% CI)** G1: 8 (−13 to 29) G2: −4 (−24 to 16) G3: −12 (−31 to 7) G4: −2 (−12 to 8) $p = 0.52$
Benton and Donohoe (2010) United Kingdom	RCT, double-blind, placebo-controlled, parallel Population sampled: Non-meat eaters (vegan, vegetarian) and meat-eaters undergraduate volunteers Inclusion criteria: NR Exclusion criteria: NR Age (years): 20.3 (SE 2.1) Sex: females *N* = | *n* = G1: 60 | NR G2: 61 | NR 51 meat-eaters 70 non-meat eaters All participants completed the trial	Duration: 5 days Doses G1: Placebo G2: Cr 20 g/days Compliance: Subjects were asked to return any tablets that had not been consumed which established that compliance did not appear to be a problem	**Memory** World recall test: episodic memory **Alertness** Reaction time procedure: Reaction time **Attention** Rapid information processing task: vigilance Controlled Oral Word Association Test: verbal fluency/verbal ability, executive function and semantic memory	Three-way ANOVA: supplement (placebo/ creatine) × diet (non-meat eater/meat eater) × time (before/ after supplement), with the last factor as a repeated measure Where a significant interaction resulted, it was examined by calculating simple and simple–simple main effects.	World recall test: Interaction supplement × diet × time reached significance ($p < 0.01$) Meat-eaters had lower memory scores compared to baseline after consuming the creatine supplement ($p < 0.001$). Reaction time procedures Neither decision times (tablet × before/after NS) nor movement times (NS) were influenced by the supplementation of creatine or by the dietary style. Variability in the speed of response (the standard deviations of the decision times): the interaction supplement × number of lamps monitored × time reached statistical significance ($p < 0.05$). Placebo group showed greater variability after supplementation in the most demanding condition, compared to the creatine group which showed no change (indicating better performance). This effect occurred irrespective of dietary style.

TABLE B.1 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
					Rapid information processing task Supplementation did not influence the ability to sustain attention. Neither the number of correct (supplement × diet × time; NS) nor the number of incorrect responses (supplement × diet × time; NS) reached statistical significance. Controlled oral word association test Supplementation did not influence word fluency, with the interaction supplement × diet × time being non-significant (NS)
Hammett et al. (2010) United Kingdom	Non-randomised, placebo-controlled, pre–/post-intervention trial Population sampled: healthy human volunteers Inclusion criteria: NR Exclusion criteria: NR Age (years): G1: 30.18 (SD 8.37) G2: 25 (SD 4.82) Sex: NR *N* = |*n* = G1: 11|11 G2: 11|11	Duration: 7 days Doses G1: Cr 20 g/days × 5 days + Cr 5 g/days × 2 days G2: Placebo *The final dose was administered at least 1h before the testing session began* Compliance: All subjects reported compliance with the dosing regimen.	**Memory** Backwards Digit Span: working memory span **Fluid intelligence/general cognitive ability** Raven's Advanced Progressive Matrices: active reasoning and problem solving	Repeated measures two-way ANOVA: Group × Time (week) Paired *t*-tests to compare pre- and post-intervention scores within group.	Backwards Digit Span Within-group (% change) G1: 26.9% ($p = 0.0069$) G2: NR ($p = 0.6761$) Between-group: Significant interaction between week and compound ($F(1, 20) = 8.58$, $p = 0.008$, two-tailed). Raven's Advanced Progressive Matrices: Within-group (% change) G1: 9.6% ($p = 0.0745$) G2: −4.5% ($p = 0.4572$) NS interaction effect (*p* value NR)

(Continues)

TABLE B.1 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Merege-Filho et al. (2017) Brazil	RCT, double-blind, placebo-controlled, parallel Population sampled: Healthy children aged 10 to 12 years Inclusion criteria: NR Exclusion criteria: (i) diagnosed cognitive disorders (e.g. attention deficit hyperactivity disorder, depression, post-traumatic stress disorder); (ii) posttraumatic brain injury; (iii) any diagnosed infectious or chronic diseases; (iv) previous use of any dietary supplements; (v) vegetarian diet; and (vi) ocular diseases that could compromise the visual acuity in the cognitive tests. Age (years): G1: 11.5 ± 0.8 G2: 11.6 ± 0.9 Sex (M/F): G1: 19/16 G2: 19/13 *N* = |*n* = G1: 44|35 G2: 44|32	Duration: 7 days Doses G1: 0.3 g/kg bw/days [~14 g/day] G2: Placebo Compliance: NR	**Memory** Rey Auditory Verbal Learning Test (RAVLT): Episodic memory, including measures of immediate recall, short-term memory and long-term memory **Attention** Stroop test (Victoria version): Selective attention, inhibitory control and executive function Trail Making Test (TMT): executive function, attention, working memory, visual search and planning. **Fluid intelligence/general cognitive ability** Raven's Advanced Progressive Matrices (RMP): active reasoning and problem solving Participants underwent one session of habituation at 7 days before the baseline assessment.	Stroop and TMT scores were analysed by a mixed-model analysis (group × time) RPM and RAVLT scores were compared between groups by Kruskal–Wallis *t* tests	There were no significant differences within or between groups for any of the tests scores ($p > 0.05$). Stroop test Colour (s) G1: −0.4 (−1.9 to 1.1) G2: −1.9 (−2.9 to −0.8) Non-colour word (s) G1: −0.8 (−1.8 to 0.1) G2: −2.6 (−3.8 to −1.5) Colour word (s) G1: −2.5 (−4.1 to −0.9) G2: −3.6 (−4.8 to −2.5) Rey auditory verbal learning test Learning (0–48) G1: 3.5 (2.3–4.7) G2: 3.5 (1.9–5.0) Short-term memory (0–12) G1: 0.7 (0.2–1.2) G2: 0.8 (0.1–1.4) Long-term memory (0–12) G1: 0.6 (0.1–1.1) G2: 0.4 (−0.4 to 1.4) Raven Progressive Matrices Total score (0–36) G1: 0.5 (−0.5 to 1.5) G2: 1.3 (0.3–2.3) Trail making test Part A (s) G1: −1.8 (−3.4 to −0.3) G2: −0.6 (−2.1 to −0.9) Part B (s) G1: −5.5 (−8.0 to −2.0) G2: −4.5 (−7.2 to 1.7)

TABLE B.1 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Moriarty et al. (2023) Canada	RCT, double-blind, placebo-controlled, parallel Population sampled: Healthy young adults Inclusion criteria: NR Exclusion criteria: previously ingested creatine supplements within the previous 4 weeks; pre-existing kidney disease or liver abnormalities Age (years): G1: 21.8 ± 4.1 G2: 20.4 ± 0.7 G3: 20.8 ± 1.4 Sex (M/F): G1: 3/7 G2: 4/6 G3: 4/6 *N* = |*n* = G1: 10|10 G2: 10|10 G3: 10|10	Duration: 6 weeks Doses G1: Cr 10 g/days G2: Cr 20 g/days G3: Placebo Compliance: Measured but NR	Pattern comparison test: processing speed Picture sequence memory test: episodic memory Dimensional change card sort test: executive function Tests were selected from the NIH Toolbox Fluid Cognition Battery	3 (G1 vs. G2 vs. G3) × 2 (pre- and post-test time points) ANOVA with repeated measures	**Mean absolute change % (95% CI) from baseline to 6 weeks** Cognitive test 1 G1: 3.6 (−3.4, 10.6) G2: 19 (−0.19, 38.2) G3: 18.7 (3.9, 33.5) Interaction *p*-value = 0.17 Cognitive test 2 G1: 11.7 (−4.6, 27.9) G2: 8.8 (−7.6, 25.3) G3: 10 (−0.5, 20.5) Interaction *p*-value = 0.95 Cognitive test 3 G1: 8.2 (−4.2, 20.7) G2: 11.5 (3.8, 19.2) G3: 4.9 (−4.8, 14.7) Interaction *p*-value = 0.59 *Unclear which test specifically each test number refers to*
Rawson et al. (2008) USA	RCT, double-blind, placebo-controlled, parallel Population sampled: Young adults Inclusion criteria: Non-vegetarian Exclusion criteria: previously ingested creatine supplements within the previous 6 weeks Age (years): G1: 21.0 ± 2.1 G2: 20.6 ± 2.2 Sex (M|F): G1: 6/5 G2: 7/4 *N* = |*n* = G1: 11|11 G2: 11|11	Duration: 6 weeks Doses G1: 0.03 g/kg bw/days [~2.2 g/days] G2: Placebo Compliance: NR	**Memory** Running memory: concentration and sustained attention Memory search (Sternberg memory recall task): processing speed and ability to retrieve information from short-term memory Code substitution (immediate and delayed): attention, executive function, associative learning, as well as motor speed. **Alertness** Simple reaction time: alertness and speed of processing **Logical reasoning**	Repeated measures two-way (Group × Time) ANOVA	No effect of 6 weeks of creatine or placebo supplementation on cognitive processing (group × time $p > 0.05$) Running memory (ms) Pre-intervention G1: 501.0 ± 139.7 G2: 448.4 ± 59.5 Post-intervention G1: 479.7 ± 108.0 G2: 430.8 ± 57.4 Group × time *p* = 0.71 Memory recall (ms) Pre-intervention G1: 501.0 ± 140.0 G2: 448.4 ± 59.5 Post-intervention G1: 479.7 ± 108.0 G2: 430.7 ± 57.3

(Continues)

TABLE B.1 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
					Group × time $p = 0.62$ Code substitution (ms) Pre-intervention G1: 798.6 ± 145.7 G2: 817.7 ± 152.6 Post-intervention G1: 780.5 ± 114.1 G2: 770.4 ± 68.4 Group × time $p = 0.72$ Code substitution (delayed) (ms) Pre-intervention G1: 818.2 ± 161.3 G2: 858.3 ± 235.0 Post-intervention G1: 825.7 ± 145.9 G2: 828.8 ± 147.0 Group × time $p = 0.54$ Simple reaction time (ms) Pre-intervention G1: 226.2 ± 35.5 G2: 227.4 ± 43.7 Post-intervention G1: 231.5 ± 48.1 G2: 211.7 ± 17.1 Group × time $p = 0.18$ Logical reasoning (ms) Pre-intervention G1: 2036.9 ± 703.6 G2: 1814.9 ± 577.9 Post-intervention G1: 1920.9 ± 649.7 G2: 1650.2 ± 483.9 Group × time $p = 0.97$ Similar NS results observed for response speed of correct responses (milliseconds), and throughput (correct responses/minute) outcome variables for the specific tests.

TABLE B.1 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Sandkühler et al. (2023) Germany	RCT, double-blind, placebo-controlled, cross-over (no washout) Population sampled: Healthy adult volunteers Inclusion criteria: age of 18 and above, stable eating behaviour, i.e. being either omnivore or vegetarian/vegan for at least 6 months, ability to consent. Exclusion criteria: psychological or physical disorders or disabilities if they are likely to cause instabilities in test scores or interact with creatine, previously ingested creatine supplements in the last 6 months, alcohol consumption higher than 20 g (if female) or 40 g (if male) per day, consumption of recreational drugs more than once a week, more than 6 h of intense sports per week. Age (years): 30.6 ± 10.1 Sex (M/F): 54/71 *N* = 148|*n* = 123	Duration: 6 weeks Doses G1: Cr 5 g/days G2: Placebo Compliance: Days supplemented per week (M, SD) G1: 6.89 (0.26) G2: 6.87 (0.26)	*Primary outcomes* **Fluid intelligence/general cognitive ability** Raven's Advanced Progressive Matrices: abstract reasoning and problem solving **Memory** The Wechsler auditory Backward Digit Span (BDS): working memory. *Exploratory outcomes* • The D2 Test of Attention: sustained attention • The Trail-Making-Test A: visual attention • The Trail-Making-Test B: task switching • The Block-Tapping-Test: visuospatial working memory • The Auditory Verbal Learning Test: word-learning test including immediate recall, delayed recall and recognition • The Brief-Visuospatial-Memory Test—Revised: visuospatial memory • The Stroop test: inhibitory control • Regensburger Wortfüssigkeitstest: verbal fluency	Mixed ANOVA with test score after supplementation as the dependent variable, supplement (creatine vs. placebo) as the within-subjects factor and supplement order (creatine-first vs. placebo-first) as the between-subjects factor	**G1-G2 scores** **Marginal mean (SE) [95% CI]** Raven's Advanced Progressive Matrices: 0.23 (0.23) [−0.24; 0.70] Two-way ANOVA: *P* value = 0.327 The Wechsler auditory Backward Digit Span (BDS): 0.41 (0.22) [−0.24; 0.84] Two-way ANOVA: *P* value = 0.064 *No indication that creatine improved the performance of our exploratory cognitive tasks. The distribution of p-values was what one would expect if there was no effect.*

(Continues)

TABLE B.1 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Van Cutsem et al. (2020) Belgium	RCT, double-blind, placebo-controlled, counterbalanced crossover with 5-week washout period Population sampled: Healthy adult volunteers Inclusion criteria: no known mental or somatic disorder, and low to moderately active according to the short form of the International Physical Activity Questionnaire Exclusion criteria: NR Age (years): 24 ± 3 Sex (M/F): 10/4 *N* = 16 | *n* = 14	Duration: 7 days Doses G1: Cr 20 g/days G2: Placebo Compliance: NR *A 60-min familiarisation trial took place to get to know the routine and to avoid learning effects. Participants completed all procedures as if it was an experimental trial except for the 90-min cognitive task*	**Attention** Modified Stroop test (to induce cognitive fatigue): Selective attention, inhibitory control and executive function Accuracy and reaction time measured Flanker test: Selective attention, inhibitory control and executive function	Repeated measures two-way (Group × Time) ANOVA 'If no significant interaction effects were observed, main effects of condition and time were immediately observed and further interpreted through pairwise comparisons with Bonferroni correction.'	Mentally fatiguing task (Stroop test) *Colour stimuli* The creatine group showed significantly greater accuracy across 8 trial blocks compared to the placebo group, indicating better resistance to mental fatigue ($P_{group} = 0.025$). Accuracy throughout the Stroop task on colour stimuli or reaction time on colour stimuli showed no interaction effect between condition and time ($P_{group\ x\ time}$ NR). Meaning stimuli Interactions group × time for reaction time and accuracy are not reported For the meaning stimuli, neither accuracy nor reaction time was different between Cr and placebo. Participants were however getting faster in time on the meaning stimuli (first task epoch = 727 ± 18 ms, eighth task epoch = 692 ± 15 ms; $P_{group} = 0.002$). Flanker test Interactions group × time for reaction time and accuracy not reported Reaction time did not differ in time or between conditions (CR = 379 ± 5 ms, PLAC = 378 ± 5 ms; *p*-value NR).

TABLE B.1 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Watanabe et al. (2002) Japan	RCT, double-blind, placebo-controlled, parallel Population sampled: Healthy adult volunteers Inclusion criteria: without any severe general medical diseases or neuropsychiatric diseases Exclusion criteria: NR Age (years): 24.3 ± 9.1 Sex (M/F): 19/5 *N* = |*n*= G1: 12|12 G2: 12|12	Duration: 5 days Doses G1: Cr 8 g/days G2: Placebo Compliance: NR	**Mental fatigue** Uchida-Kraepelin test (UKT)	Linear regression analysis and paired *t*-test	UKT Significant increase in test scores after administration of creatine ($p < 0.02$), but no significant change for the placebo group ($p > 0.05$). No between-group comparison of performances reported.

Note: Data are presented as mean ± standard deviation and 95% confidence interval (95% CI), unless when otherwise stated.

Abbreviations: ANOVA, analysis of variance; BBCS, Brief Cognitive Screening Battery; BDS, Backward Digit Span; bw, body weight; Cr, creatine; CPT, continuous performance test; F, female; FTT, finger tapping test; G, group; M, male; *N*, number randomised; *n*, number analysed; NIH, National Institutes of Health; NR, not reported; NS, non-significant; PLAC, placebo; RAVLT, Rey Auditory Verbal Learning Test; RCT, randomised controlled trial; RPM, Raven's Advanced Progressive Matrices; RVDLT, Rey Visual Design Learning Tests; SAT, test of shifting attention; SD, standard deviation; SDC, symbol digit coding; SE, standard error; ST, strength training; TMT, Trail Making Test; UKT, Uchida-Kraepelin test; USA, United States of America.

TABLE B.2 Human intervention studies conducted under stress-induced conditions.

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
McMorris, Harris, et al. (2007) United Kingdom	Non-randomised, placebo-controlled, double-blind, parallel trial Population sampled: Sport science majors Inclusion criteria: NR Exclusion criteria: NR Age (years): 21.11 (SD 1.85) Sex: Males *N* = |*n* = G1: 10|10 G2: 10|9	Duration: 7 days Doses G1: Cr 20 g/days G2: Placebo *Subjects did not take creatine or placebo on the day of the test*. Compliance: NR Subjects undertook six 6-h cycles of testing and exercise. Three types of exercise were undertaken: stair climbing and step-ups, each for 2 × 5 min with a 3-min rest interval, and 15-min continuous walking. Subjects were instructed to maintain 65% estimated maximum heart rate during exercise.	**Memory** Baddeley number recall test: short-term memory Random number generation task: working memory and executive function **Alertness** Classical four-choice visual reaction time test: Alertness and speed of processing Cognitive testing at baseline, 18, 24 and 36 h sleep deprivation	Group × Time analysis of covariance (ANCOVA), with baseline performance as the covariate. Post hoc planned comparisons for the main effect of time were conducted using Tukey's Honestly Significant Difference (HSD) tests. Where there were interaction effects, within-group effects were measured by HSD and between-group effects by the Tukey–Kramer variation of HSD for unequal sample sizes.	Random number generation task Significant group × time interaction effect ($p < 0.05$). Tukey's HSD showed that for the creatine group performance at 36 h was significantly ($p < 0.01$) better than at the other times. The Tukey–Kramer test showed that the only significant ($p < 0.05$) between-group effect was at 36 h with the creatine group performing the better Redundancy measure Non-significant interaction group × time (*p*-value not reported)

(Continues)

TABLE B.2 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
					The results for the measure of redundancy variable demonstrated a significant main effect for group ($p < 0.005$), with the creatine group being better than the placebo group. Mean (SD) scores Forward no. recall (Baddeley test) *Baseline* G1: 6.70 (1.57) G2: 7.00 (1.80) *18 h* G1: 6.90 (1.60) G2: 6.89 (1.17) *24 h* G1: 7.40 (1.17) G2: 7.67 (1.12) *36 h* G1: 6.90 (1.37) G2: 7.33 (0.87) Choice reaction time (ms) *Baseline* G1: 353 (29) G2: 350 (36) *18 h* G1: 346 (23) G2: 347 (36) *24 h* G1: 342 (35) G2: 342 (41) *36 h* G1: 337 (17) G2: 336 (36) No interaction effects nor any significant effects for number recall and reaction time.

TABLE B.2 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Pires et al. (2020) Brazil	RCT, double-blind, placebo-controlled, parallel Population sampled: Female Muay Thai athletes Inclusion criteria: NR Exclusion criteria: (i) were taking medications that could impact muscle or brain biology and function, (ii) had ingested creatine monohydrate within 4 weeks prior to the start of the study, (iii) were vegetarian or vegan or (iv) had pre-existing kidney or liver abnormalities Age (years): 25.9 ± 4.6 Sex: Females *N* = | *n* = G1: 14 | 13 G2: 13 | 13	Duration: 4 weeks Doses G1: Cr 3 g/days G2: Placebo Compliance: NR Participants completed a Muay Thai exhaustive training session which consisted of a 10 min warm-up, followed by 40 min of technical training and 30 min of intensive fighting. Immediately following the bout of exercise, participants completed a series of standardised cognitive performance tests	**Memory** Differentiation task test (DTT): Working memory Corsi Block Tapping test (CBT): Working memory Visual forward digit span: Short-term memory **Alertness** Visual reaction time test (VRT): reaction time **Attention** Eriksen flanker task (EFT): selective attention, executive function and inhibitory control GO/NO GO reaction time test: sustained attention, speed of processing and inhibitory control	Repeated measures two-way (Group × Time) ANOVA If a significant interaction was found an LSD post hoc analysis was performed. Absolute changes for each outcome variable (post mean – pre mean) were assessed using an independent samples *t*-test.	**Absolute changes (95% CI)** Visual Reaction Time G1: −15.5 (−25.6, −5.3) G2: −0.1 (−12.1, 11.9) $p = 0.068$ Go/No Go Visual Reaction Time G1: −20.1 (−36.7, −3.5) G2: −0.3 (−14.3, 13.6) $p = 0.087$ Auditory Reaction Time G1: −27.8 (−46.8, −8.7) G2: −7.5 (−32.1, 17.0) $p = 0.214$ Go/No Go Auditory Reaction Time G1: −11.8 (−32.1, 8.4) G2: −1.5 (−19.1, 16.0) $p = 0.458$ Corsi Block Test G1: 0.9 (−0.8, 2.5) G2: 1.3 (−0.9, 3.5) $p = 0.764$ Reverse Corsi Block Test G1: 1.2 (−0.5, 3.0) G2: 0.0 (−2.8, 2.8) $p = 0.472$ Differentiation Test G1: 1.3 (−2.6, 5.2) G2: 1.0 (−3.0, 5.1) $p = 0.933$ Visual Forward Digit Span G1: 3.4 (1.1, 5.6) G2: 0.5 (−3.3, 4.3) $p = 0.219$

(Continues)

TABLE B.2 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Pires et al. (2020) Brazil	RCT, double-blind, placebo-controlled, parallel Population sampled: Female Muay Thai athletes Inclusion criteria: NR Exclusion criteria: (i) were taking medications that could impact muscle or brain biology and function, (ii) had ingested creatine monohydrate within 4 weeks prior to the start of the study, (iii) were vegetarian or vegan or (iv) had pre-existing kidney or liver abnormalities Age (years): 25.9 ± 4.6 Sex: Females *N* = | *n* = G1: 14 | 13 G2: 13 | 13	Duration: 4 weeks Doses G1: Cr 3 g/days G2: Placebo Compliance: NR Participants completed a Muay Thai exhaustive training session which consisted of a 10 min warm-up, followed by 40 min of technical training and 30 min of intensive fighting. Immediately following the bout of exercise, participants completed a series of standardised cognitive performance tests	**Memory** Differentiation task test (DTT): Working memory Corsi Block Tapping test (CBT): Working memory Visual forward digit span: Short-term memory **Alertness** Visual reaction time test (VRT): reaction time **Attention** Eriksen flanker task (EFT): selective attention, executive function and inhibitory control GO/NO GO reaction time test: sustained attention, speed of processing and inhibitory control	Repeated measures two-way (Group × Time) ANOVA If a significant interaction was found an LSD post hoc analysis was performed. Absolute changes for each outcome variable (post mean – pre mean) were assessed using an independent samples *t*-test.	EFT-Arrows in same direction G1: −63.9 (−137.6, 9.8) G2: 23.5 (−23.8, 70.7) $p = 0.062$ EFT-Arrows in opposite direction G1: −41.7 (−114.4, 31.0) G2: −16.4 (−65.6, 32.8) $p = 0.577$ EFT-% correct answers same direction G1: 4.3 (1.5, 7.1) G2: 0.0 (−3.8, 3.8) $p = 0.091$ EFT-% correct answers opposite directions G1: 4.4 (0.7, 8.2) G2: 0.2 (−6.3, 6.7) $p = 0.283$ *Forced* post hoc *analyses showed a significant decrease in visual reaction time ($p = 0.01$) and GO/NO GO reaction time ($p = 0.017$) and an increase in the Erikson Flanker task performance ($p = 0.05$) with no changes observed in the placebo group (visual: $p = 0.98$; GO/NO GO: $p = 0.97$; The Erikson Flanker task: $p = 0.46$).*

TABLE B.2 (Continued)

Reference Country	Design Subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Turner et al. (2015) New Zealand	RCT, double-blind, placebo-controlled, crossover with 5-week washout period Population sampled: Healthy adult volunteers Inclusion criteria: NR Exclusion criteria: NR Age (years): 31 Sex (M/F): 10/5 *N* = 15|*n* = 15	Duration: 7 days Doses G1: Cr 20 g/days G2: Placebo Compliance: NR *A familiarisation session was conducted to collect baseline neuropsychological data and to introduce participants to the hypoxia intervention.* Participants were exposed to **severe experimental hypoxia** using a gas breathing intervention to induce acute energy disruption after dietary Cr supplementation.	**Computerised test battery of 7 neuropsychological function tests** **Composite Memory** Adapted Rey Auditory verbal learning test (RAVLT) and the Rey Visual design learning tests (RVDLT): Verbal and visual memory **Complex Attention** Continuous performance test (CPT) ± test of shifting attention (SAT) ± Stroop test: Complex attention (vigilance/sustained attention) Stroop test: Information processing speed (reaction time) **Psychomotor speed** Finger tapping test (FTT) & symbol digit coding (SDC) Stroop test & (SAT): Cognitive flexibility *Experimental sessions were completed the day after dietary supplementation was complete.*	Paired-samples *t* tests for between-treatment comparisons of normalised scores	Composite memory (RAVLT + RVDLT): Baseline scores: 106.0 ± 13.1 G1: 97.8 ± 21.2 G2: 96.1 ± 16.7 $p = 0.4$ Psychomotor speed (FTT ± SDC): Baseline scores: 118.8 ± 18.5 G1: 114.5 ± 23.0 G2: 112.0 ± 22.9 $p = 0.279$ Reaction time (Stroop test): Baseline scores: 103.2 ± 10.6 G1: 100.7 ± 12.6 G2: 98.9 ± 13.8 $p = 0.332$ Complex attention (CPT ± SAT ± Stroop test): Baseline scores: 93.7 ± 16.8 G1: 86.4 ± 22.7 G2: 70.7 ± 51.5 $p = 0.049$ Cognitive flexibility (SAT ± Stroop test): Baseline scores: 98.8 ± 18.2 G1: 98.9 ± 19.3 G2: 88.9 ± 31.7 $p = 0.072$ *Raw scores for individual cognitive tests for correct and incorrect responses were also reported. With the exception of CPT commission error score ($p = 0.02$), the effect of supplementation was NS on all individual scores.*

Note: Data are presented as mean ± standard deviation and 95% confidence interval (95% CI), unless when otherwise stated.

Abbreviations: ANCOVA, analysis of covariance; CBT, Corsi Block Tapping test; CI, confidence interval; CPT, Complex attention test; DTT, differentiation task test; EFT, Eriksen flanker task; F, female; FTT, finger tapping test; G, group; HSD, honestly significant difference; LSD, least significant difference; M, male; *n*, number analysed; *N*, number randomised; NR, not reported; NS, non-significant; RAVLT, Rey Auditory verbal learning test; RCT, randomised controlled trial; RVDLT, Rey Visual Design Learning Tests; SAT, test of shifting attention; SDC, symbol digit coding; SD, standard deviation; VRT, Visual reaction time test.

TABLE B.3 Human intervention studies in diseased individuals.

Reference Country	Design subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Alves, Santiago, et al. (2013) Brazil	RCT, double-blind, placebo-controlled, parallel. Population sampled: Women diagnosed with primary fibromyalgia. Inclusion criteria: NR Exclusion criteria: (i) Cardiovascular involvement (e.g. arrhythmias, arterial hypertension, heart failure, conduction disturbances, myocarditis and pericarditis); (ii) Tobacco usage; and (iii) All other chronic diseases (e.g. rheumatic diseases, cardiovascular diseases, metabolic diseases and chronic kidney diseases) Age (years): G1: 49.0 ± 10.1 G2: 48.7 ± 8.4 Sex: F (100%) *N* = |*n* = G1: 16|13 G2: 16|15	Duration: 16 weeks Doses G1: Placebo G2: Cr 5 g/days *G2 received 20 g of Cr (4 × 5 g/days) for the first five days followed by 5 g/days as a single dose throughout the trial.* Compliance: 100% self-reported adherence to supplementation protocol.	**Memory** Delayed Recall Test of the Brief Cognitive Screening Battery (BBCS): Immediate and delayed recall memory. Digit Span Test: Short-term memory and working memory. **Attention** Stroop test (Victoria version): Selective attention, inhibitory control and executive function Trail Making Test: Executive function, attention, working memory, visual search and planning.	All values converted into delta scores and tested by unpaired Student's *t*-test. Cohen's *d* used to determine the effect size for the dependent variables. Baseline data were compared using Fisher's exact test.	**Delay recall of BBCS (mean ± SD):** **Δ (95% CI)** Naming (0–10) G1: 0.1 ± 0.3 G2: 0.0 ± 0.4 *p*: 0.23 Incidental memory (0–10) G1: −0.1 ± 1.7 G2: 0.8 ± 1.4 *p*: 0.07 Immediate memory (0–10) G1: 0.0 ± 1.3 G2: 0.0 ± 1.0 *p*: 0.50 Learning (0–10) G1: −0.1 ± 1.0 G2: 0.0 ± 1.0 *p*: 0.40 Delayed recall (0–10) G1: −0.2 ± 1.0 G2: −0.1 ± 1.0 *p*: 0.39 **Digit Span Test (mean ± SD):** **Δ (95% CI)** Forward order (0–7) G1: −0.2 ± 0.6 G2: −0.1 ± 0.7 *p*: 0.34 Backward order (0–7) G1: −0.3 ± 1.5 G2: −0.1 ± 1.1 *p*: 0.21

TABLE B.3 (Continued)

Reference Country	Design subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
					Stroop conditions (mean ± SD): **Δ (95% CI)** Colour (s) G1: −2.3 ± 4.5 G2: −1.5 ± 2.3 *p*: 0.27 Non-colour word (s) G1: 0.0 ± 7.5 G2: −1.1 ± 2.9 *p*: 0.31 Colour word (s) G1: 1.2 ± 10 G2: −1.3 ± 7.3 *p*: 0.22 **Trail Making Test (mean ± SD):** **Δ (95% CI)** Part A G1: −4.4 ± 30.2 G2: −8.3 ± 11.5 *p*: 0.32 Part B G1: −18.3 ± 35.5 G2: −1.5 ± 72.6 *p*: 0.23

(Continues)

TABLE B.3 (Continued)

Reference Country	Design subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Toniolo et al. (2017) Brazil	Randomised, double-blind, placebo-controlled trial. Population sampled: patients with bipolar depression. Inclusion criteria: Subjects aged 18–59 years who met DSM-IV criteria for bipolar disorder type I or II currently depressed as assessed using the Structural Clinical Interview for DSM-IV Axis I Disorders – Patient version and whose score on the Montgomery-Åsberg Depression Rating Scale (MADRS) was ≥ 20. Patients taking antipsychotics or mood stabilisers were included in the trial if the dosages had been stable for at least 2 weeks; those who were on antidepressants were included if the dosages had been stable for at least 4 weeks. Exclusion criteria: alcohol/other substance abuse in the past 2 weeks/dependence in the past two months, dementia, delirium, epilepsy or mental retardation, clinically unstable medical conditions, history of hypersensitivity to creatine, high risk for suicidal, homicidal or automutilatory behaviour, pregnant or lactating women. Age (years): G1: 43.4 ± 8.4 G2: 44.1 ± 10.7 Sex: F (72%) + M (28%) *N* = |*n* = G1: 9|9 G2: 9|9	Duration: 6 weeks Doses: G1: Cr 6 g/days G2: placebo Compliance: NR	**Working/short-term memory** Digit Span subtest of the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III): Participants see a sequence of numerical digits and are tasked to recall the sequence correctly, with increasingly longer sequences being tested in each trial. The participant's span is the longest number of sequential digits that can accurately be remembered. **Selective attention:** Stroop colour-word test: It includes three conditions that consist in naming the colour of dots (i.e. 'colour'), neutral words (i.e. 'noncolor word') and colour words printed in incongruent colours (i.e. 'colour word'). Performance is assessed based on the time to complete each condition. **Executive function:** Wisconsin Card Sorting Test (WCST): test of 'set-shifting'. A number of stimulus cards are presented to the participant. The participant is told to match the cards, but not how to match; however, he or she is told whether a particular match is right or wrong. Rey–Osterrieth complex figure test (ROCF): Examinees are asked to reproduce a complicated line drawing, first by copying it freehand (recognition) and then by drawing from memory. **Verbal fluency** Verbal fluency (F, A, S): Participants have to say as many words that begin with letters F, A or S (a semantic category) as possible in 60 s.	Student's *t*-tests were used to compare normally distributed continuous variables, while Mann–Whitney test was used for non-normally distributed continuous variables. Qui square and Fisher's exact tests used for categorical variables. Cognitive test scores are presented as medians, comparisons between the groups are made using the Mann–Whitney test. The effect size corresponding to the statistically significant finding of this study is calculated as Cohen's *d*.	**Stroop test 1 (Median, (IQR)):** G1: −1 (5) G2: 2 (7) *P*: 0.268 **Stroop test 2 (Median, (IQR)):** G1: −2 (9) G2: −3 (8) *P*: 0.329 **Stroop test 3 (Median, (IQR)):** G1: −3 (8) G2: 2 (8) *P*: 0.111 **Stroop test 1 – errors (Median, (IQR)):** G1: 0 (0) G2: 0 (0) *P*: 1.000 **Stroop test 2 – errors (Median, (IQR)):** G1: 0 (0) G2: 0 (0) *P*: 0.654 **Stroop test 3 – errors (Median, (IQR)):** G1: 0 (2) G2: 0 (2) *P*: 0.547 **Verbal fluency test (Median, (IQR)):** G1: 3 (9) G2: −2 (6) *P*:0.030 **ROCF test (Median, (IQR)):** G1: 0 (1) G2: 0 (2) *P*: 0.585

TABLE B.3 (Continued)

Reference Country	Design subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
					ROCF recall (Median, (IQR)): G1: 8 (5) G2: 5 (9) *P*: 0.374 **WCST – categories achieved (Median, (IQR)):** G1: 1 (1) G2: 1 (1) *P*: 0.810 **WCST – correct answers (Median, (IQR)):** G1: 4 (8) G2: 1 (10) *P*:0.594 **WCST – total number of errors (Median, (IQR)):** G1: −4 (8) G2: −1 (10) *P*: 0.594 **WCST – perseverative errors (Median, (IQR)):** G1: 0 (2) G2: 0 (3) *P*: 0.817 **WCST – perseverative answers (Median, (IQR)):** G1: 0 (3) G2: 0 (1) *P*: 0.715 **WCST – loss of set (Median, (IQR)):** G1: 0 (0) G2: 0 (1) *P*: 0.197 **Digit Span test (Median, (IQR)):** G1: 1 (3) G2: 1 (2) *P*: 0.893

(Continues)

TABLE B.3 (Continued)

Reference Country	Design subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
Verbessem et al. (2003) Belgium	Randomised, double blind, placebo-controlled trial. Population sampled: patients with Huntington's disease. Inclusion criteria: classification into stages I to III and stable medication intake for a period of at least 3 months. Exclusion criteria: prehistory of renal pathology or existing albuminuria, prior oral Cr supplementation, pregnancy. Age (years): G1: 50.1 ± 2.6 G2: 49.6 ± 1.9 Sex: F (63%) + M (37%) *N* = |*n* = G1: 15|15 G2: 27|26	Duration: 1 year Doses G1: Placebo G2: Cr 5 g/days Compliance: NR	**Cognition:** Symbol Digit Modalities Test: NR **Attention** Stroop test: Selective attention, inhibitory control and executive function. **Verbal fluency** Verbal fluency (F, A, S): Participants have to say as many words that begin with letters F, A or S (a semantic category) as possible in 60 s.	All statistical analyses were done according to the intention-to-treat principle. Primary analysis: Group × time analysis of variance. Secondary analysis: one-way analysis of variance Differences between the experimental groups at baseline: unpaired Student *t*-test. Differences in the frequency distributions between groups were tested by means of x^2 test.	**Within groups comparisons:** **Symbol Digit Modalities Test (mean ± SEM):** *At baseline:* G1: 21 ± 3 G2: 20 ± 2 *At 6 months:* G1: 19 ± 3 G2: 19 ± 2 *At 12 months:* G1: 19 ± 3 G2: 18 ± 2 **Stroop test (mean ± SEM):** Colour: *At baseline:* G1: 35 ± 4 G2: 34 ± 2 *At 6 months:* G1: 36 ± 4 G2: 34 ± 2 *At 12 months:* G1: 36 ± 4 G2: 33 ± 2 Word: *At baseline:* G1: 51 ± 6 G2: 58 ± 3 *At 6 months:* G1: 51 ± 6 G2: 54 ± 3

TABLE B.3 (Continued)

Reference Country	Design subject characteristics *N* = number randomised *n* = number analysed	Intervention	Cognitive domain(s) assessed and methods	Statistical analyses	Results
					At 12 months: G1: 51 ± 6 G2: 55 ± 3 Interference: *At baseline:* G1: 18 ± 4 G2: 18 ± 2 *At 6 months:* G1: 22 ± 4 G2: 18 ± 2 *At 12 months:* G1: 19 ± 4 G2: 17 ± 2 **Verbal Fluency (mean ± SEM):** *At baseline:* G1: 11 ± 2 G2: 11 ± 2 *At 6 months:* G1: 10 ± 2 G2: 11 ± 2 *At 12 months:* G1: 11 ± 2 G2: 12 ± 2 No between- group comparisons of performances reported.

Note: Data are presented as mean ± standard deviation and 95% confidence interval (95% CI), unless when otherwise stated.

Abbreviations: BBCS, Brief Cognitive Screening Battery; CI, Confidence Interval; Cr, creatine; DSM, Diagnostic and Statistical Manual of Mental Disorders; F, Female; G, group; IQR, Interquartile Range; M, Male; MADRS, Montgomery-Åsberg Depression Rating Scale; *N*, number of randomised participants; *n*, number of analysed participants; NR, Not Reported; RCT, Randomised Controlled Trial; ROCF, Rey–Osterrieth complex figure test; SEM, Standard Error of the Mean; SD, Standard deviation; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.