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ORIGINAL ARTICLE

Dietary creatine and cognitive function in U.S. adults aged 60 years and over

Sergej M. Ostojic[1] · Darinka Korovljev[1] · Valdemar Stajer[1]

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Abstract

Objectives Recent clinical trials suggested a potential benefit of dietary creatine on cognitive function for aging individuals. However, the association between creatine consumption from food and cognitive function in the older adults remained undetermined at the populational level. The present study quantified the amount of creatine consumed through a regular diet among U.S. adults aged 60 years and over, and evaluated the link between dietary creatine and cognitive function using data from the 2001–2002 National Health and Nutrition Examination Survey (NHANES).

Methods NHANES 2001–2002 round included a total of 1340 older adults (51.8% women; age 71.4 ± 7.8 years) who provided valid dietary information and cognitive testing measures. Dietary intake information was obtained from the NHANES Dietary Data component through a 24-h in-person dietary recall interview. Cognitive function was assessed using the WAIS III Digit Symbol Substitution Test (DSS) conducted during the household interview.

Results A bivariate model revealed a significant positive correlation between DSS scores and creatine intake across the whole sample ($\tau b = 0.043$; $P = 0.02$). The partial models demonstrated a significant correlation between creatine consumption and DSS score when adjusted for sociodemographic variables ($r = 0.062$; $P = 0.039$), and nutritional variables ($r = 0.055$; $P = 0.049$). The participants who consumed more than 0.95 g of creatine per day (3rd and 4th quartiles of creatine intake) were found to have higher scores on the cognitive functioning test as compared to their peers with lower creatine intake (1st and 2nd quartiles) ($P < 0.05$).

Conclusion Our findings suggest that creatine from food might be protective against reduced cognitive performance in the older population. Further research is highly warranted to investigate the role of dietary creatine amount in cognitive function in the older adults.

Keywords Creatine · Cognitive function · Aging · Cross-sectional · Meat · Diet

Introduction

Aging-associated cognitive decline is a growing public health issue, with approximately 1 in 9 adults aged 65 years and older encounter cognitive impairment [1]. Cognitive decline, even at mild stages, can significantly impact everyday activities and reduce the perceived quality of life in the older adults [2]. A relatively high prevalence of cognitive decline and its health consequences have stimulated biomedical research to find effective countermeasures that enable the older adults to protect and retain their cognitive capacities [3]. For instance, the consumption of several essential nutrients (*e.g.*, vitamin E, folate, vitamin D) has been found to be beneficial to remediate an age-related decline in cognitive function [4], implying a pivotal role of adequate nutrition in maintaining cognitive functioning in the older adults. While diet has gained considerable attention as a modifiable factor in preventing and even reversing age-related cognitive deficits [5], the effects of specific dietary compounds on cognitive function in older people have yet to be clarified. A growing research area suggests that dietary creatine, an amino acid derivative widely available in meat, fish, and poultry, may play a protective role for cognitive performance in older adults. Early evidence comes from a small-scale randomized pilot trial that reported a favorable effect of short-term creatine intake on different cognitive

✉ Sergej M. Ostojic
sergej.ostojic@chess.edu.rs

[1] Applied Bioenergetics Lab, Faculty of Sport and Physical Education, University of Novi Sad, Lovcenska 16, Novi Sad 21000, Serbia

tests in community-dwelling older adults [6]. A recent systematic review evinces the potential benefit of creatine on cognitive function for aging individuals [7]. However, a possible connection between creatine consumption and cognitive function in the older adults remains undetermined at the populational level. Therefore, the purpose of this cross-sectional study was to quantify the amount of creatine consumed through regular diet among U.S. adults aged 60 years and over, and evaluate the link between dietary creatine and cognitive function using data from the 2001–2002 National Health and Nutrition Examination Survey (NHANES).

Methods

Population

The NHANES is an annual survey conducted to monitor the health and nutritional status of U.S. children and adults, combining interviews, physical examinations, and laboratory tests on the non-institutionalized civilian resident population of the United States. Data for this cross-sectional report were acquired from the NHANES 2001–2002 round, with the round included a total of 11,039 men and women aged 0 to 85 years. The NHANES population was selected using an intricate, four-stage sample design, with sample weights were used to produce estimates of the health-related statistics that would have been obtained if the entire sampling frame had been surveyed [8]. For this report, we extracted data for adult respondents aged 60 years and over at the time of screening, who provided valid dietary information and cognitive testing measures ($n = 1{,}340$). The data were collected between January 2001 and December 2002. The ethical approval to conduct the NHANES 2001–2002 was granted by the NHANES Institutional Review Board (Protocol #98-12), with the informed consent obtained from all participants.

Dietary creatine intake

Dietary intake information was obtained from the NHANES 2001–2002 Dietary Data component through a 24-h (midnight-to-midnight) in-person dietary recall interview. Individual data files that contained detailed information about each food item consumed (including the type and amount of food) were extracted and summarized to estimate the personal intakes of energy, macronutrients, micronutrients, and non-nutritive food components (*e.g.*, caffeine, alcohol). To calculate creatine intake, we first identified meat-based protein foods using 8-digit food codes from the U.S. Department of Agriculture (USDA) using dietary interview entries for individual foods. Meat-based protein foods (*e.g.*, red meat, poultry, fish, and seafood) are the predominant sources of dietary creatine, while other foods contain only negligible amounts of creatine [9]. We subsequently recorded the gram weight of each food component containing meat-based protein, and calculated the net intake of meat-based protein for each respondent by merging all relevant food items on a daily basis. Individual values for total grams of creatine consumed per day for each participant were computed using the average amount of creatine (3.88 g/kg) across all sources of meat-based protein, as previously described [10]. Nutrient intakes reported did not include those obtained from dietary supplements, medications, or plain drinking water. The intakes were calculated using the USDA Food and Nutrient Database for Dietary Studies, which contains the most up-to-date food composition values available for this time frame [11]. An overview of quality assurance procedures conducted during the data processing stage is available elsewhere [12]. In addition, the respondents' weight, height, and waist circumference were assessed in the mobile examination center by trained technicians, with body mass index (BMI) calculated as weight in kilograms divided by height in meters squared.

Cognitive assessment

Data for this domain were acquired from NHANES 2001–2002 Questionnaire Data on Cognitive Functioning. All NHANES 2001–2002 participants who were 60 years old or older were eligible to receive the cognitive functioning test. Cognitive function was assessed using the WAIS III Digit Symbol Substitution Test (DSS) conducted during the household interview [13], with the test administered under a licensing agreement [14]. In this coding test, the participants copied symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participants drew the symbol under the corresponding number, and the score was the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit, and the maximum score is 133. The sample items were provided for initial practice, and the participants who were unable to complete any of the sample items did not continue with the remainder of the exercise. About 10% of the forms were scored independently for a second time, and the two scores were compared and reconciled when necessary. DSS test is considered a reliable and more sensitive measure of cognitive impairment/dementia than the Mini-Mental Status Examination, and has been administered in the National Institute on Aging Health ABC study [15]. The DSS test is sensitive to the presence of cognitive dysfunction as well as to change in cognitive function across a wide range of clinical populations but has limited specificity to determine exactly which cognitive domain has been affected [16].

Variables

The primary and secondary exposures used in the analyses were the mean daily intake of creatine, and the mean daily intake of creatine categorized into quartiles, respectively. The primary outcome was the DSS test score. Potential confounders were identified based on previous research [4, 17]. The variables were extracted from NHANES 2001–2002 Demographic Data and Laboratory Data databases, including demographic information (gender, body mass index, ethnicity, educational level, and annual household income), and nutritional variables, as measured by blood levels of selected micronutrients (vitamin E, vitamin D, folate, and trans-β-carotene). Smoking and physical activity were excluded as non-relevant variables from prior analysis.

Statistical analyses

Data series were analyzed by Kolmogorov–Smirnov test for normality of distribution. A bivariate Kendall's tau-b and partial non-parametric correlation analyses were conducted to assess the association between creatine intake and cognitive functioning. The partial correlation models were adjusted for an a priori defined set of cofounders, including sociodemographic (Model 1) and nutritional variables (Model 2). Kruskal–Wallis non-parametric one-way ANOVA was used to compare DSS test scores across creatine quartiles, with post hoc pairwise comparison tests employed to identify the differences between individual quartiles of creatine intake. Multinomial logistic regression models was used to analyze the association between dietary creatine and cognitive function categorized into quartiles. Data were analyzed using SPSS Statistics for Mac (Version 24.0) (IBM, Armonk, NY), with the significance level set at $P<0.05$, and all statistical tests were two-sided.

Table 1 Demographic and nutritional characteristics of study sample ($n=1{,}340$)

NHANES 2001–2002	Total	Men	Women
Age, years	71.4 ± 7.8	71.2 ± 7.6	71.5 ± 8.1
n	1340	646	694
Ethnicity (%)			
Mexican American	15.7	15.0	16.4
Other Hispanic	3.1	2.5	3.6
Non-Hispanic White	63.7	65.0	62.5
Non-Hispanic Black	15.5	15.8	15.3
Other race	1.9	1.7	2.2
Education level (%)*			
Less than high school	35.1	35.4	34.6
High school or equivalent	24.4	21.1	27.6
Some college	22.0	18.7	25.0
College graduate or above	18.5	24.8	12.7
Annual household income (%)			
Less than $14,999	21.0	17.6	24.3
$15,000 to $44,999	46.7	45.5	48.0
More than $45,000	31.9	36.9	27.7
Body mass index category (%)*			
Underweight	1.9	1.1	2.5
Normal	27.7	24.6	28.7
Overweight	40.8	42.1	36.4
Obese	29.6	24.6	32.4
Body mass index (kg/m^2)*	28.1 ± 5.5	27.8 ± 4.7	28.3 ± 5.9
Daily dietary intake			
Energy (kcal)*	1738 ± 806	1985 ± 646	1507 ± 694
Protein (g)*	67.9 ± 34.1	78.5 ± 38.9	58.0 ± 25.4
Carbohydrate (g)*	218.4 ± 102.9	242.0 ± 118.3	196.5 ± 80.2
Total fat (g)*	66.2 ± 40.6	76.9 ± 48.3	56.4 ± 28.4
Creatine (g)*	1.13 ± 1.00	1.36 ± 1.16	0.92 ± 0.78

Asterisk (*) indicates significant difference at $P<0.05$ between genders

Results

The final study population includes 1,340 older adults (646 men and 694 women). Table 1 depicts the demographic and nutritional characteristics of the sample, with significant differences found for education level, BMI and BMI category, and dietary outcomes between genders ($P<0.05$). 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). The DSS score range was 0 to 100 points, with the mean score of 43.2 ± 18.2 points (95% CI from 42.3 to 44.2). A bivariate crude model revealed a significant positive correlation between DSS scores and creatine intake across the whole sample ($\tau b=0.043$; $P=0.02$). The partial models demonstrated a significant correlation between creatine consumption and DSS score when adjusted for sociodemographic variables ($r=0.062$; $P=0.039$), and nutritional variables ($r=0.055$; $P=0.049$).

Mean daily creatine intake was categorized into quartiles, ranging from 0.00 to 0.40 g (1st quartile; mean ± SD = 0.13 ± 0.14 g), 0.41–0.94 g (2nd quartile; 0.68 ± 0.15), 0.95 to 1.57 g (3rd quartile; 1.21 ± 0.18), and 1.58–10.83 g (4th quartile; 2.45 ± 0.99). A significant variation has been found in DSS scores across creatine quartiles categories ($P=0.019$). The scores were significantly lower in participants in the 1st and 2nd quartiles of dietary creatine consumption than scores among participants in the 3rd and 4th quartiles, respectively (Fig. 1).

The average DSS scores was also categorized into quartiles, ranging from 0–30 points (1st quartile;

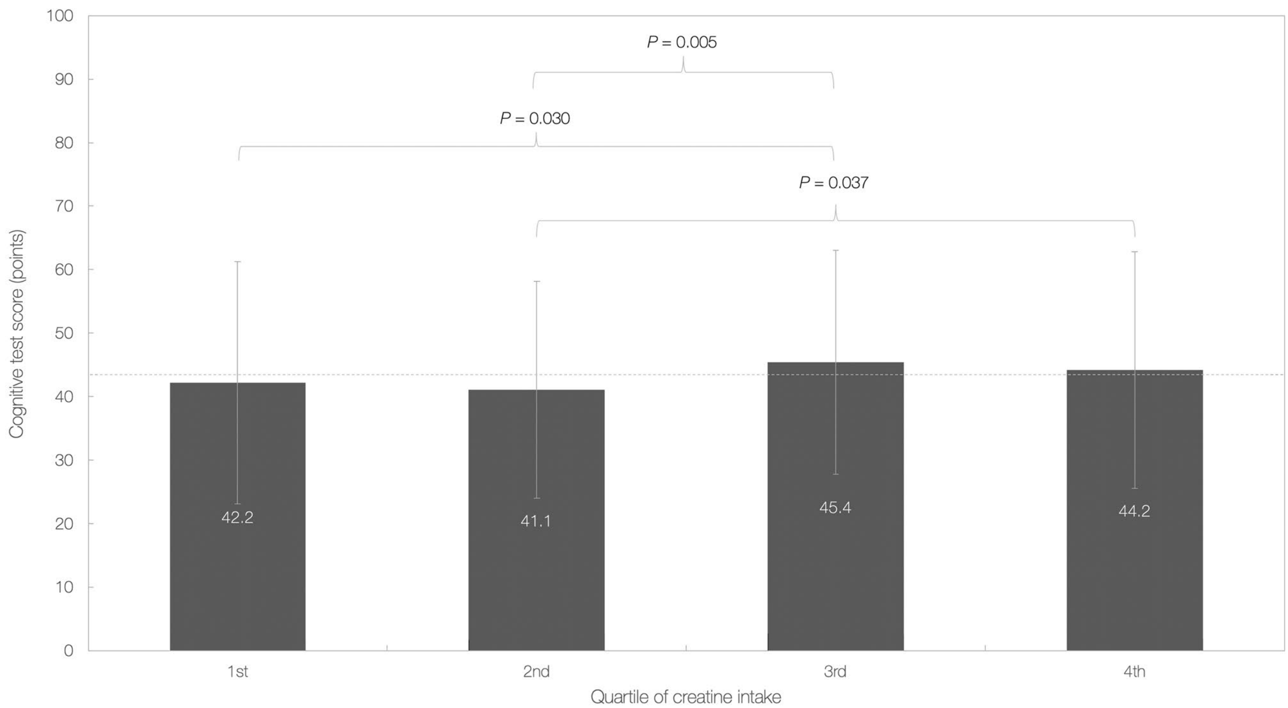

Fig. 1 Cognitive functioning evaluated with WSII DSS test (error bars indicate SD) across quartiles of average daily dietary intake of creatine in NHANES 2001–2002 participants aged 60 years and over. The dashed line represents the mean DSS score for the whole sample

mean ± SD = 20.2 ± 7.5 points), 31–41 points (2nd quartile; 36.1 ± 3.2 points), 42–55 points (3rd quartile; 48.4 ± 4.0 points), and 56–100 points (4th quartile; 66.5 ± 9.0 points). Multinominal logistic regression model revealed no association between dietary creatine and cognitive function across DSS quartiles ($P = 0.579$).

Discussion

To our knowledge, this is the first population-based study that examined the relationship between creatine consumed through regular diet and cognitive function in the older adults. We found that dietary creatine intake is positively associated with cognitive functioning in U.S. adults aged 60 years and over. The link between creatine consumption and cognitive function remained robust even when adjusted for main demographic and nutritional confounders. Furthermore, the participants who consumed more than 0.95 g of creatine per day (3rd and 4th quartiles of creatine intake) were found to have higher scores on the cognitive functioning test as compared to their peers with the lower intake (1st and 2nd quartiles). This suggests that additional creatine from food might be protective against reduced cognitive performance in the older population. Further research is highly warranted to investigate the role of dietary creatine amount in cognitive function in the older adults.

Arguably, the first study that examined the effect of dietary creatine on older adults' cognitive performance was a small-scale multicentre placebo-controlled trial conducted in UK and Poland [6]. Healthy older volunteers (eight men and seven women; age 76.4 ± 8.5 years) who received supplemental creatine during 2 weeks performed significantly better in several cognitive tests (*e.g.*, forward and backward number and spatial recall, long-term memory tasks) than their peers who received placebo. The authors hypothesized that dietary creatine enhances cognitive performance in the older adults by several means, including cell energy replenishment, mitochondrial membrane stimulation, antioxidant protection, and glutamate uptake. Avgerinos et al. [7] summarized the impact of creatine consumption on cognitive function in a systematic review of randomized controlled trials. The authors identified 6 relevant trials with 281 healthy individuals (249 young and 32 older adults), and concluded that dietary creatine might improve short-term memory and intelligence/reasoning, but its effect on other cognitive domains remains unclear. The findings of this systematic review suggested a potential benefit of dietary creatine for aging and stressed individuals, with creatine dose recognized as a significant factor that accounts for different responses in various cognitive tasks. The current cross-sectional study broadens the previous research to a population-wide sample of the older adults, confirming the association between creatine consumption and cognitive functioning within the context of a regular diet. We found that the incremental increase in dietary creatine goes with better cognitive functioning in a nationally representative U.S. sample of men and women aged 60 years and over, even after controlling for main confounders, including micronutrients known to have an impact on cognitive function among older adults [17]. Surprisingly, even a moderately higher daily creatine intake corresponds to better cognitive performance. For example, older adults in the third quartile of dietary creatine who consume 0.95 to 1.57 g per day demonstrated significantly better cognitive functioning than individuals who consume less than 0.40 g of creatine per day (1st quartile) and 0.41 to 0.94 g (2nd quartile). Those findings perhaps support the idea that the older adults may benefit from increasing dietary intake of creatine in aim to preserve their cognitive abilities, either via fostering diets rich in creatine-containing foods (*e.g.*, meat, poultry, fish, and seafood), creatine supplementation, and/or food fortification with creatine.

Not all studies confirmed favorable effects of dietary creatine on cognitive function in the older adults. A Brazilian group reported that 24-week creatine supplementation (20 g/day for 5 days followed by 5 g/day) did not promote any significant change in cognitive function and emotional parameters in apparently healthy older women [18]. The variation in the follow-up period of intake, amount of creatine consumed per day, demographic discrepancies across studies, and diversity in testing cognitive function are among the main factors that might be responsible for the conflicting results with respect to the creatine effects on cognitive function. In terms of dosage, a relatively high amount of creatine administered through interventional studies (*e.g.*, 20 g per day) may adversely affect N-acetyl-containing compounds in the cerebellum and thalamus as well as of choline-containing compounds in the thalamus [19]; this 'creatine overload' can potentially compromise brain metabolism and curb nootropic potential of creatine, in contrast to modest amounts provided by regular food. The optimal load of creatine acquired from food sources that is safe and effective for supporting cognitive performance in the older adults has yet to be established.

Several limitations have to be considered when the study findings are interpreted. First, this study's cross-sectional design prevents any conclusions about a cause-and-effect link between exposures (dietary creatine intake) and outcomes (cognitive functioning), or to analyze temporal changes in those variables occurring with age. Second, dietary creatine intake has been calculated using a single-day self-reported interview, which could be susceptible to recall bias and cannot account for a day-to-day variation. Third, the creatine calculation method omitted to consider variability in creatine content across various meat-based foods and non-meat sources of creatine, also possibly missed data coming from creatine supplements. Having in mind that milk is a poor source of creatine, while < 0.1% of the U.S. population uses supplemental creatine, leaving out those food components probably has a marginal consequence on study findings [20]. Fourth, we could not size endogenous creatine production, a possible modifying variable that could account for a total daily creatine load (a sum of creatine synthesized de novo inside the body plus creatine consumed from a diet). Fifth, we employed a single test of cognitive performance that may not address exactly which cognitive domains have suffered the age-specific impairment.

Conclusion

In summary, our study indicates that dietary creatine intake is positively associated with cognitive functioning in U.S. men and women aged ≥ 60 years. This association appears to be independent of sociodemographic and nutritional factors that might impact cognitive function among older adults. The findings reported here corroborate previous clinical trials with creatine and give grounds for further exploration of dietary creatine and cognitive function in the older adults. The most practical future work on this topic will need to track down a threshold of creatine intake demonstrating cognitive benefits or lack of harm in this delicate population.

Funding None received.

Declarations

The study procedures were structured in line with the Declaration of Helsinki.

Conflict of Interest S.M.O. serves as a member of the Scientific Advisory Board on creatine in health and medicine (AlzChem LLC). S.M.O. owns patent "Sports Supplements Based on Liquid Creatine" at European Patent Office (WO2019150323 A1), and active patent application "Synergistic Creatine" at UK Intellectual Property Office (GB2012773.4). S.M.O. has served as a speaker at Abbott Nutrition, a consultant of Allied Beverages Adriatic and IMLEK, and an advisory board member for the University of Novi Sad School of Medicine, and has received research funding related to creatine from the Serbian Ministry of Education, Science, and Technological Development, Provincial Secretariat for Higher Education and Scientific Research, AlzChem GmbH, KW Pfannenschmidt GmbH, and ThermoLife International LLC. S.M.O. is an employee of the University of Novi Sad and does not own stocks and shares in any organization. D.K. and V.S. declare no conflict of interest.

Ethical approval The ethical approval to conduct the NHANES 2001–2002 was granted by the NHANES Institutional Review Board (Protocol #98-12).

Statement of human and animal rights The study procedures were structured in line with the Declaration of Helsinki.

Informed consent The informed consent was obtained from all participants.

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