Routledge
Taylor & Francis Group

Journal of the International Society of Sports Nutrition

ISSN: 1550-2783 (Online) Journal homepage: www.tandfonline.com/journals/rssn20

Safety of creatine supplementation: analysis of the prevalence of reported side effects in clinical trials and adverse event reports

Richard B. Kreider, Drew E. Gonzalez, Kelly Hines, Adriana Gil & Diego A. Bonilla

To cite this article: Richard B. Kreider, Drew E. Gonzalez, Kelly Hines, Adriana Gil & Diego A. Bonilla (2025) Safety of creatine supplementation: analysis of the prevalence of reported side effects in clinical trials and adverse event reports, Journal of the International Society of Sports Nutrition, 22:sup1, 2488937, DOI: 10.1080/15502783.2025.2488937

To link to this article: https://doi.org/10.1080/15502783.2025.2488937

JOURNAL OF THE INTERNATIONAL SOCIETY OF SPORTS NUTRITION
2025, VOL. 22, NO. S1, 2488937
https://doi.org/10.1080/15502783.2025.2488937

Taylor & Francis
Taylor & Francis Group

CREATINE FOR HEALTH AND PERFORMANCE

OPEN ACCESS Check for updates

Safety of creatine supplementation: analysis of the prevalence of reported side effects in clinical trials and adverse event reports

Richard B. Kreider[a], Drew E. Gonzalez[a], Kelly Hines[a], Adriana Gil[a] and Diego A. Bonilla[b,c]

[a]Texas A&M University, Exercise & Sport Nutrition Lab, Department of Kinesiology and Sports Management, College Station, TX, USA; [b]Dynamical Business & Science Society—DBSS International SAS, Research Division, Bogotá, Colombia; [c]University of the Basque Country (UPV/EHU), Hologenomiks Research Group, Department of Genetics, Physical Anthropology and Animal Physiology, Leioa, Spain

ABSTRACT

Background: Individual studies have indicated that creatine supplementation is generally well tolerated and not associated with clinically significant side effects. Nevertheless, anecdotal reports about side effects persist primarily from popular and social media and on the Internet.

Methods: This study evaluated side effects reported from 685 human clinical trials on creatine supplementation, worldwide adverse event report (AER) databases, and performed a social media sentiment analysis. The presence of side effects (No, Yes) in studies was evaluated using chi-squared analysis. The frequency of side effects among study participants was evaluated using a multivariate analysis of variance.

Results: A total of 13,452 participants in 652 studies ingested placebos (PLA), while 12,839 participants in 685 studies consumed creatine (Cr). Nearly all studies (95%) provided CrM at an average dose of 0.166 [0.159, 0.173] g/kg/d (about 12.5 g/d) for 64.7 [52.0, 77.3] days in studies lasting up to 14 yrs. Side effects were reported in 13.2% of studies in the PLA groups and 13.7% of studies in the Cr-supplemented groups, with no significant differences observed between the groups ($p = 0.776$). There was a slightly higher percentage of studies reporting gastrointestinal (GI) issues (PLA 4.3%, Cr 4.9%, $p < 0.001$) and muscle cramping/pain (PLA 0.9%, Cr 2.9%, $p = 0.008$) with Cr supplementation, but not when the total number of participants in these studies was evaluated (muscle cramping/pain: PLA 0.07%, Cr 0.52%, $p = 0.085$; GI issues: PLA 4.05%, Cr 5.51%, $p = 0.820$). Additionally, there was no significant multivariate difference among the 49 side effects evaluated ($p = 0.340$), no significant difference in the total frequency of side effects reported among participants (PLA 4.21%, Cr 4.60%, $p = 0.828$), and no significant differences in any of the other side effect evaluated that included

ARTICLE HISTORY

Received 19 February 2025
Accepted 28 March 2025

KEYWORDS

Ergogenic; dietary supplement; safety; adverse events

CONTACT Richard B. Kreider rbkreider@tamu.edu Exercise & Sport Nutrition Lab, Human Clinical Research Facility, 675 John Kimbrough Blvd., Building #1542, College Station, TX 77843-4253, USA

Supplemental data for this article can be accessed online at https://doi.org/10.1080/15502783.2025.2488937

markers of renal function and health. The percentage prevalence of side effects was small, with differences between groups generally within ± 0.5%. Analysis of 28.4 million AERs revealed that the mention of Cr was rare (0.00072%), 46.3% of CAERS had no Cr in the products listed, and 63% of AERs with Cr in the product involved the use of other types of Cr or ingestion with other supplements or drugs. The overall sentiment analysis was neutral about perceptions of Cr, although those with strong perceptions about Cr were slightly more negative.
Conclusion: Results demonstrate that Cr supplementation does not increase the prevalence or frequency of side effects when compared to participants ingesting PLA. Therefore, claims that Cr supplementation increases the risk of side effects are unfounded.

1. Introduction

Creatine is a naturally occurring compound that is a primary constituent of phosphocreatine (PCr) that provides cellular energy [1,2]. The daily need for creatine is about 2–4 g/d, depending on muscle mass and physical activity levels [2–4]. About half the daily need for creatine is synthesized endogenously from the amino acids arginine, glycine, and methionine [2]. The remainder is obtained primarily from meat and fish in the diet, which contains about 1–2 g/lbs [2], and/or dietary supplements containing bioavailable sources of creatine [2–4].

Low dietary availability of creatine has been associated with greater health risks. For example, analysis of the National Health and Nutrition Examination Survey (NHANES) revealed that children and adolescents with low dietary creatine intake (<1.5 g/d) were shorter and weighed less [5], had less lean body mass and bone mineral content, and had higher fat mass and body fat percentage than those consuming higher amounts of creatine in their diets [6]. Women (12 years and older) with low dietary creatine intake (<13 mg/kg/d) had a greater risk of fetal macrosomia, infections, hysterectomy, oophorectomy, and receiving hormone replacement therapy, while those consuming diets higher in creatine had lower risks of irregular menstrual periods, obstetric conditions, and pelvic pathology [7]. In older individuals (>60 yrs), lower dietary creatine intake (i.e. <0.95 g/d) has been associated with poorer cognitive function test performance [8]. Furthermore, 70% of older individuals (>65 yrs) consumed less than recommended amounts of creatine in their diets (<0.95 g/d), and low dietary creatine intake was associated with a greater risk of angina pectoris and liver conditions compared to those consuming more than 1.0 g/d of creatine [9]. Low dietary creatine intake has been associated with a greater incidence of depression in adults [10] and cancer risk [11]. These findings highlight the need to consume enough dietary creatine to promote general health throughout the lifespan.

Since meat and fish are expensive (about $4.00–$18.00 USD per pound) and high in calories (i.e. about 500 to 1,400 kcals/lbs), dietary supplementation of creatine is a cost-effective way (about $0.03 - $ 0.05 USD per gram) to ensure individuals obtain enough creatine in their diet to meet daily needs [2]. The most effective and clinically assessed source of creatine for dietary supplements is creatine monohydrate (CrM) [2]. Numerous studies indicate that CrM supplementation (e.g. 0.3 g/kg/d

for 5–7 days and 0.05 to 0.15 g/kg/d thereafter) increases muscle creatine and PCr content by 20–40%, high-intensity exercise performance and promotes greater gains in strength and muscle mass during resistance exercise training [12,13]. Creatine supplementation has also been reported to reduce the risk of injury, including the severity of concussion and traumatic brain injury in animal models [4] and in patient populations (i.e. children with TBI) [14,15]. Based on this evidence, professional organizations [12,16–18], athletic governing bodies [19]; and the Office of Dietary Supplements at the National Institutes of Health [20] recognize CrM as a safe, effective, and legal nutritional strategy to enhance performance and training adaptations.

There is also emerging evidence that CrM supplementation possesses health benefits throughout the lifespan. For example, there is evidence that creatine supplementation may benefit the third trimester of pregnancy and is needed in infants [21,22], children and adolescents [23], women [24], and older populations to help maintain strength, lean mass, and cognitive function [25]. Additionally, there is evidence that CrM supplementation enhances immunity [26] and can promote mitochondrial [27], heart [28], vascular [29], and brain health [30]. Therapeutic benefits have also been reported in the management of type 2 diabetes [31], sarcopenia [32–35], osteoporosis [33,36], patients with neuromuscular diseases [37], and rehabilitation [32,38–45]. Furthermore, data show that creatine may slow the progression of some forms of cancer [46,47] and may have therapeutic benefits in helping cancer patients maintain lean mass [48] and prevent body fat accumulation during maintenance chemotherapy that includes corticosteroids [49]. Consequently, CrM has transitioned from a performance enhancement supplement to a supplement to promote general health and help manage clinical populations who may benefit from CrM supplementation [4,12,50].

To date, hundreds of clinical trials have been conducted in humans on healthy and medically managed populations with no adverse events reported and relatively few, if any, side effects noted [2,4,12,50]. For this reason, CrM is considered Generally Recognized as Safe (GRAS) by the Food and Drug Administration (FDA) in the United States [51] and is the only form of creatine approved for sale in the United States, Canada, Europe, Australia, Japan, the Republic of Korea, and China [2]. Nevertheless, anecdotally reported side effects and claims that CrM is not as effective as other "forms" of creatine continue to permeate the Internet [2,50]. A few case study reports also appeared in the literature suggesting adverse events despite other mitigating factors unrelated to creatine supplementation [52–54] which subsequently have been debunked [15,55,56]. This misinformation has created concern among athletes, parents, physicians, medical providers, the elderly, and patient populations who may benefit from CrM supplementation regarding safety. It has also prompted some legislative efforts to limit the availability of creatine in dietary supplements to populations who may benefit. The purpose of this comprehensive analysis was to 1.) determine the presence of side effects reported in clinical trials conducted on creatine supplementation; 2.) compare the frequency of side effects reported from volunteers taking creatine and placebos in these trials; 3.) analyze the prevalence of adverse event reports (AERs) attributed to creatine supplementation reported in international surveillance systems; and 4.) compare the reported side effects to claims made about creatine supplementation on the Internet. We hypothesized that

this comprehensive analysis would confirm observations that creatine is well tolerated and does not increase the risk of untoward side effects.

2. Methods

2.1. Comprehensive review

We performed a comprehensive literature review on PubMed with the keywords "creatine" and "supplementation." This review incorporated elements of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [57].

2.1.1. Study summaries and categorization

After compiling a list of clinical trials conducted on creatine supplementation in humans, we evaluated each publication and developed a summary table of creatine studies (see Supplemental File 1). This searchable spreadsheet lists the study reference, year of publication, study n-size in each cohort, the design of the study, the length of study, absolute and relative doses investigated, demographic information on participants, main study findings, and any side effects reported for participants taking creatine and placebo supplements. Based on the side effects reported in these studies, we created a side effect list of 35 types of side effects mentioned in these studies. We categorized the presence of side effects in these studies (No, Yes) to compare the number of studies reporting side effects in participants taking PLA and Cr supplements. We then recorded the frequency of the side effects reported in each study for the creatine and placebo groups. A zero frequency was assigned if a side effect from the list was not mentioned in the study. We then summed the total frequency of side effects reported for each study. We also categorized each study by supplement groups (creatine, placebo), sex (combined cohort, male, female, unspecified), age (children/adolescents less than 18 yrs, young adults between 18 and 45 yrs, middle-aged adults between 45 and 65 yrs, older adults more than 65 yrs), training status as defined in the study (clinical population with physical health issues, clinical populations with cognitive issues, untrained, recreationally active, trained, athletes, military), health status (apparently healthy, clinical populations), clinical category (apparently healthy, cardiometabolic/cardiopulmonary conditions, neurological conditions, musculoskeletal conditions, renal conditions, and other), and type of creatine ingested (CrM compared to other forms including creatine HCl, Magnesium-Creatine, Creatine Citrate, Creatine Pyruvate, Creatine Methyl-Ester, Creatine H_20, Creatine Nitrate, Creatyl-L-Leucine). These categories were used to determine study demographics, dosages studied, whether studies reported side effects (Yes, No), and the frequency of individual side effects reported among participants in the PLA and Cr groups. If incomplete demographic information was provided (e.g. body mass), we used an average population value as an estimate to calculate relative creatine intake.

2.2. Assessment of adverse events

The prevalence of AERs mentioning creatine reported in the United States Food and Drug Administration Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS) [58], the Canadian Vigilance Adverse Reaction Online

Database [59], the Australian Department of Health and Aged Care, Therapeutic Goods Administration [60], the European Database of Suspected Adverse Drug Reaction Reports [60], and the Side Effect Resource (SIDER) 4.1 Side Effect Resource [60] were assessed. These databases were searched for "creatine' in dietary supplements or products following accepted protocols [61,62]. Each report was evaluated to ensure creatine was in the product mentioned by conducting an Internet search for the product name and evaluating the list of ingredients. We then categorized reports on products that contained only CrM, reports that involved consuming CrM in multi-ingredient supplements, products containing other "forms" or types of creatine, and whether creatine was consumed with other products. The total number of reports was divided by the total number of reports in the database over the 25, 50, 27, 24, and 10 years of monitoring AERs, respectively, to determine the percentage of reports in the database mentioning creatine. While AERs do not indicate causality, particularly when co-ingested with other nutrients and/or products, a low percentage of mentioning a nutrient or drug in these databases suggests safety from widespread use by the general public.

2.3. Big data text analysis

To assess the public's perceptions about side effects related to creatine supplementation, we performed a sentiment analysis using the following procedures. The rationale was to determine whether there was congruence between the side effects reported in scientific literature, AERs monitoring systems, and perceptions on social media regarding the safety of creatine supplementation.

2.3.1. Registration

The big data text analysis was conducted using the YouTube application programming interface (API) version 3, provided by YouTube for developers, and was authorized by the Twitter (X) Academic Research program (San Francisco, USA) to access the Twitter (X) API. The analysis was based on the information provided by the DBSS Research Division (Project name: "*Creatine Safety*"- APP ID: 21590870).

2.3.2. Data gathering and searching

To gather social web texts, we utilized the Academic Research version of the Mozdeh software [63], which automatically anonymizes usernames (http://mozdeh.wlv.ac.uk, accessed on 15 February 2025). This program uses the YouTube and Twitter (X) APIs to extract comments and tweets, respectively [64,65]. Both YouTube and Twitter (X) are widely used social platforms that serve as key tools for information-sharing and technological communication. In this study, the query-based retrieval method used the term "creatine," with date ranges from April 2011 to February 2025 for YouTube comments and February 2007 to July 2021 for Tweets. It should be noted that, as of April 2023, free access to Twitter (X) data was discontinued, making it unfeasible to extend the analysis in Mozdeh to the present day

For YouTube, comments were extracted from videos containing the term "creatine" in the title or description. The extraction process involved several steps: only the first comment per user was included, all user identifiers were anonymized, duplicate posts with identical text were filtered out, and only comments in English were collected. Finally,

the comments were grouped by month for subsequent analysis. For Twitter (X), we specified one million as the number of sets of 500 (pages) to get all tweets. A pilot testing was performed with the string "*creatine AND (horrible OR worst OR sucks OR bad OR disappointing OR adverse OR side effects) -is retweet -happy -exciting -excited -favorite -fav -amazing -lovely -incredible*" to avoid flaws. Finally, after hiding duplicates, we explored and analyzed the downloaded texts in Mozdeh.

2.3.3. Sentiment analysis

We conducted a supervised machine learning analysis called sentiment analysis to detect and classify subjective content. This has been shown to be an effective strategy for social web text analytics [66] with large and variate applications [67,68]. The Mozdeh software uses the SentiStrength algorithm to estimate the strength of positive and negative sentiment in text using a manually curated list of over 3000 terms and term stems (SentiStrength's lexicon) and a set of extra rules [63]. This allocates each post positive/negative scores between 1 (no sentiment) and 5 (very strong sentiment). Negative values represent negative sentiment. The Mozdeh software calculates the average positive and negative SentiStrength for all posts matching the query, including 95% confidence intervals. The accuracy of this method has been published previously [69]. A comparative analysis of association word mining was conducted to identify keywords that were statistically associated with comments containing "monohydrate" or "HCl" on YouTube.

2.3.4. Ethics

According to the Mozdeh developers, informed consent for individual projects using public data is unnecessary since authors of public texts do not have the right to privacy for these texts [70]; however, we have fully anonymized users to avoid drawing attention to them.

2.4. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (International Business Machines (IBM) Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp.) and the R statistical computing environment [71]. Demographic information on participants, duration of the study, and absolute and relative dosages studied were analyzed using one-way analysis of variance (ANOVA) with Bonferroni and Welch tests of equality of means since the sample sizes of some categories differed. Using the WRS2 package [72], robust ANOVA or Yuen – Dixon tests with 20% trimmed means were also conducted to analyze the categories with unequal sample sizes. The prevalence of side effects reported in studies (categorized as yes or no) was evaluated using split file means by each category to obtain the number of studies reporting side effects. The percentage prevalence was calculated by dividing the number of studies reporting side effects by the total number of studies. We then analyzed differences in the number of studies reporting side effects for the placebo (PLA) and creatine (Cr) supplemented groups using crosstabs chi-squared tests, likelihood ratios, Fisher Exact tests, and odds ratios for supplementation, not present, and present with corresponding 95% confidence intervals presented as mean [lower bound, upper bound].

The frequency of side effects was then analyzed by categories using a General Linear Model multivariate on all side effects evaluated and univariate analysis on each side effect evaluated. Prevalence rates were determined by dividing the number of side effects reported by the total number of participants for the placebo and creatine-supplemented groups and multiplying times 100. The prevalence difference between the supplement groups was determined by subtracting the prevalence rate observed in the creatine group from the placebo group. Alpha levels and effect sizes (eta squared) are reported for each side effect. Data were considered significantly different when the probability of Type I error was 0.05 or less. However, all alpha levels are reported along with the percent prevalence of each side effect to the total number of studies conducted (prevalence data) or total number of participants studied in PLA and Cr groups. Partial Eta squared ($\eta_p 2$) tendencies were used to assess effect size where values of 0.01 represented a small effect, 0.06 represented a medium effect, and 0.14 represented a large effect size [73].

3. Results

3.1. Study selection

The results from the search algorithm were compared to an existing comprehensive database previously developed by the Principal Investigator yielding 3,445 unique references. Of these, studies were omitted that did not involve creatine supplementation (n = 539), investigated animal models (n = 1,186), were literature reviews (n = 496), meta-analyses (n = 98), patents (n = 6), or other publications (n = 6) not referenced. The remaining 1,113 articles were reviewed with 685 clinical trials on humans identified and analyzed for reported adverse events and side effects. Figure 1 shows the PRISMA flowchart.

3.2. Study demographics

Table 1 presents the demographic, study duration, and dosage-related information for the 652 clinical trials with a PLA group and 685 studies with Cr supplementation groups. Overall, the average study had 19.7 [17.4, 21.9] participants who were 30.1 [29.3, 30.9] years, 75.5 [74.9, 76.2] kg body mass, ingested the supplements for 64.7 [52.0, 77.3] days, and consumed an average of 0.166 [0.159, 0.173] g/kg/d of supplements or 480 [388, 623] g total of supplements (about 12.5 g/d). This included studies with sample sizes up to 874 participants and participants up to 77 years old in studies lasting up to 14 years. No significant differences were observed between those taking PLA and Cr supplements among demographic-related variables.

Supplemental Tables S1 – S6 show demographic data categorized by sex, age, training status, clinical population category, health status, and type of creatine evaluated, respectively. This analysis revealed that clinical populations were typically evaluated over longer supplementation periods with higher doses than healthy counterparts. Additionally, relative creatine doses were higher in children and adolescents (0.280 [0.184, 0.375] g/kg/d) and taken for longer periods of time (324.1 [23.6, 624.5] d) than older cohorts. Nearly all studies (648/685 or 95%) were conducted using CrM as the source of creatine.

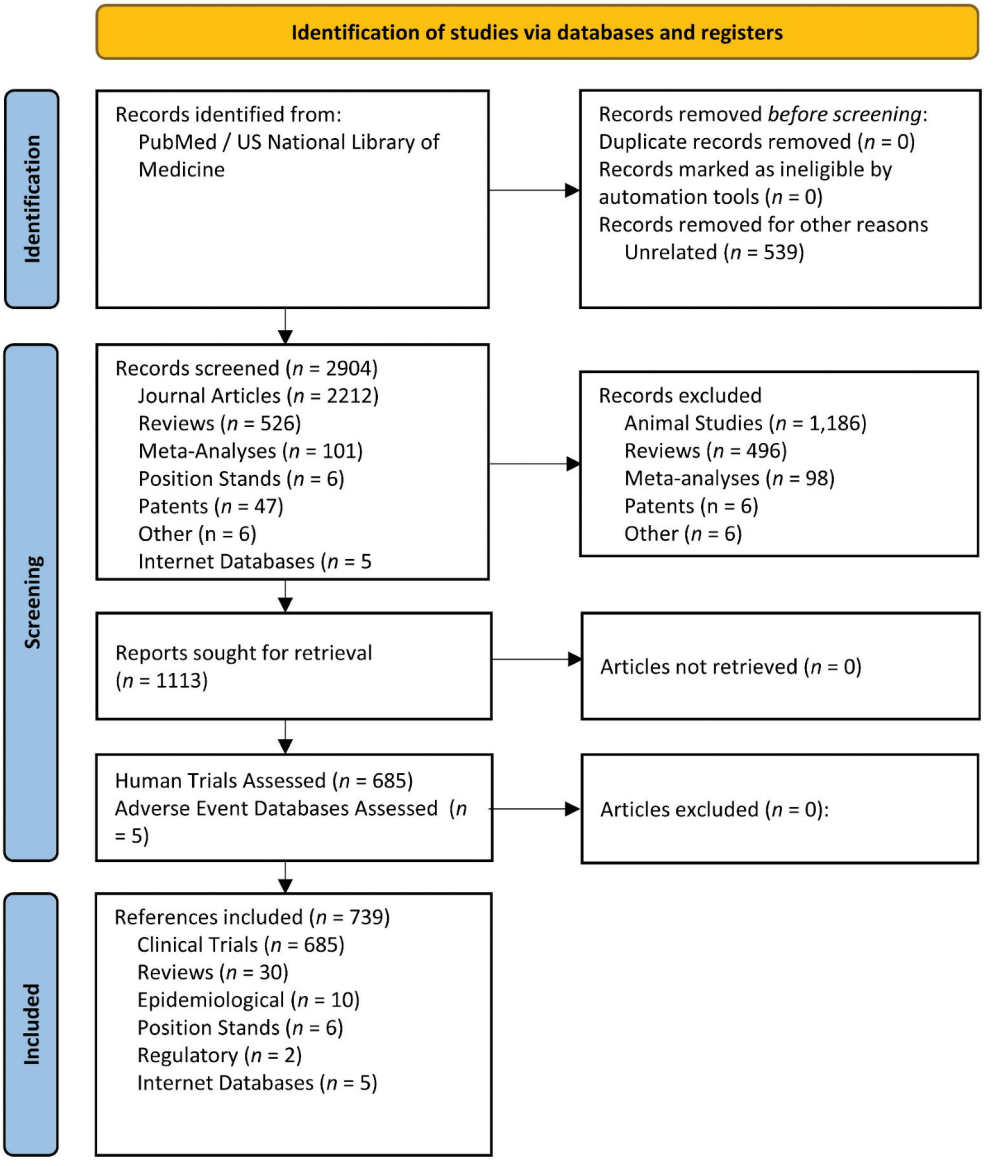

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.

3.3. Prevalence of studies reporting side effects

Table 2 presents the analysis of the prevalence of studies reporting side effects or not. In the placebo group, 86/652 studies (13.2%) reported side effects, while 94/685 (13.7%) reported side effects in creatine-supplemented ($p = 0.776$). The prevalence of studies reporting gastrointestinal (GI) issues (PLA 4.3%, Cr 4.9%, $p < 0.001$) and muscle cramping/pain (PLA 0.9%, Cr 2.9%, $p = 0.008$) were significantly higher in the Cr group. However, the difference in the prevalence of studies reporting side effects was small and differences between groups were very small. No other significant differences were observed in the

Table 1. Creatine study demographics by supplementation groups.

Descriptives						95% Confidence Interval for Mean			Statistics		Welch Test
		Studies (n)	Mean	SD	SE	Lower Bound	Upper Bound	*Post-hoc*	p-level	Eta-squared	p-level
Sample Size	Placebo a	652	20.6	45.2	1.8	17.2	24.1		0.407	0.001	0.409
	Creatine b	685	18.7	37.8	1.4	15.9	21.6				
	Total	1337	19.7	41.6	1.1	17.4	21.9				
Age (years)	Placebo a	652	30.3	14.9	0.6	29.1	31.4		0.620	0.000	0.620
	Creatine b	685	29.9	14.9	0.6	28.8	31.0				
	Total	1337	30.1	14.9	0.4	29.3	30.9				
Weight (kg)	Placebo a	652	75.5	11.0	0.4	74.7	76.4		0.942	0.000	0.942
	Creatine b	685	75.5	12.8	0.5	74.5	76.5				
	Total	1337	75.5	12.0	0.3	74.9	76.2				
Study Duration (d)	Placebo a	652	52.6	140.9	5.5	41.8	63.4		0.067	0.003	0.063
	Creatine b	685	76.2	299.0	11.4	53.8	98.6				
	Total	1337	64.7	235.8	6.4	52.0	77.3				
Loading Dose Duration (d)	Placebo a	652	4.0	5.1	0.2	3.6	4.4		0.626	0.000	0.625
	Creatine b	685	4.2	6.1	0.2	3.7	4.6				
	Total	1337	4.1	5.6	0.2	3.8	4.4				
Non-Loading Dose Duration (d)	Placebo a	652	46.2	138.0	5.4	35.6	56.8		0.067	0.003	0.063
	Creatine b	685	69.2	291.8	11.1	47.3	91.1				
	Total	1337	58.0	230.2	6.3	45.6	70.3				
Loading Dose (g/kg/d)	Placebo a	652	0.169	0.173	0.007	0.156	0.182		0.692	0.000	0.693
	Creatine b	685	0.165	0.150	0.006	0.154	0.177				
	Total	1337	0.167	0.161	0.004	0.158	0.176				
Loading Dose (g)	Placebo a	652	73.9	74.4	2.9	68.2	79.6		0.517	0.000	0.513
	Creatine b	685	77.3	111.4	4.3	68.9	85.6				
	Total	1337	75.6	95.1	2.6	70.5	80.7				
Non-Loading Dose (g/kg/d)	Placebo a	652	0.055	0.081	0.003	0.049	0.061		0.656	0.000	0.653
	Creatine b	685	0.058	0.113	0.004	0.049	0.066				
	Total	1337	0.056	0.098	0.003	0.051	0.062				
Non-Loading Dose (g)	Placebo a	652	297	1137	45	210	384		0.142	0.002	0.135
	Creatine b	685	509	3534	135	244	775				
	Total	1337	406	2652	73	263	548				
Total Daily Dose (g/kg/d)	Placebo a	652	0.166	0.124	0.005	0.157	0.176		0.896	0.000	0.896
	Creatine b	685	0.165	0.134	0.005	0.155	0.175				
	Total	1337	0.166	0.129	0.004	0.159	0.173				
Absolute Total Dose (g)	Placebo a	652	370	1129	44	283	457		0.138	0.002	0.130
	Creatine b	685	585	3531	135	320	850				
	Total	1337	480	2648	72	338	623				

Table 2. Prevalence of studies reporting side effects from ingesting the placebo and creatine containing supplements.

	Studies Reporting Side Effects							Chi-Square Tests					Risk Estimate								
	Placebo			Creatine			Prevelence							95% Confidence Interval			95% Confidence Interval			95% Confidence Interval	
Variable	Not Present (n)	Present (n)	Prevelance (%)	Not Present (n)	Present (n)	Present %	Difference %	X^2 Value	X^2 p level	Likelihood Ratio	Likelihood p-level	Fisher Exact Test p-level	Odds Ratio for Supplement	Lower	Upper	Odds Ratio for Not Present	Lower	Upper	Odds Ratio for Present	Lower	Upper
Studies with Participants Reporting Side Effects	566	86	13.19	591	94	13.72	0.53	0.08	0.776	0.776		0.776	0.96	0.70	1.31	1.01	0.97	1.05	1.00	0.96	1.06
Gastrointestinal/ Abdominal	624	28	4.29	622	63	9.20	4.90	12.66	<.001	13.003	<.001	<.001	2.26	1.43	3.57	1.05	1.02	1.09	0.47	0.30	0.72
Vertigo	652	0	0.00	682	3	0.44	0.44	2.86	0.091	4.019	0.045	0.250				1.00	1.00	1.01			
Hypertension	652	0	0.00	682	0	0.00	0.00														
Headache	647	5	0.77	672	13	1.90	1.13	3.22	0.073	3.342	0.068	0.096	2.50	0.89	7.06	1.01	1.00	1.02	0.40	0.15	1.13
Dizziness	648	4	0.61	680	5	0.73	0.12	0.07	0.795	0.068	0.794	0.794	1.19	0.32	4.46	1.00	0.99	1.01	0.84	0.23	3.12
Light Headed	651	1	0.15	683	2	0.29	0.14	0.29	0.592	0.293	0.588	1.000	2.00	0.18	22.17	1.00	1.00	1.01	0.50	0.05	5.50
Nausea	644	8	1.23	667	18	2.63	1.40	3.44	0.064	3.536	0.060	0.075	2.17	0.94	5.03	1.01	1.00	1.03	0.47	0.20	1.07
Diarrhea	646	6	0.92	677	8	1.17	0.25	0.20	0.657	0.199	0.656	0.790	1.27	0.44	3.69	1.00	0.99	1.01	0.79	0.28	2.26
Impaired Concentration	650	2	0.31	684	1	0.15	−0.16	0.39	0.535	0.392	0.531	0.616	0.48	0.04	5.25	1.00	0.99	1.00	2.10	0.19	23.12
Muscle Cramping/ Pain	646	6	0.92	665	20	2.92	2.00	7.00	0.008	7.414	0.006	0.009	3.24	1.29	8.12	1.02	1.01	1.04	0.32	0.13	0.78
Sleep Disturbances	650	2	0.31	681	4	0.58	0.28	0.58	0.448	0.587	0.444	0.687	1.91	0.35	10.46	1.00	1.00	1.01	0.53	0.10	2.86
Poor Appetite	650	2	0.31	682	3	0.44	0.13	0.15	0.694	0.156	0.693	1.000	1.43	0.24	8.58	1.00	1.00	1.01	0.70	0.12	4.18
Fatigue	651	1	0.15	681	4	0.58	0.43	1.66	0.197	1.789	0.181	0.375	3.82	0.43	34.30	1.00	1.00	1.01	0.26	0.03	2.34
Excessive Sweating	651	1	0.15	683	2	0.29	0.14	0.29	0.592	0.293	0.588	1.000	1.91	0.17	21.07	1.00	1.00	1.01	0.53	0.05	5.78
Edema	651	1	0.15	682	5	0.73	0.57	2.49	0.115	2.728	0.099	0.219	4.79	0.56	41.08	1.01	1.00	1.01	0.21	0.03	1.79
Palpitations	652	0	0.00	684	1	0.15	0.15	0.95	0.329	1.338	0.247	1.000				1.00	1.00	1.00			
Thromboembolic Events	651	1	0.15	683	2	0.29	0.14	0.29	0.592	0.293	0.588	1.000	1.91	0.17	21.07	1.00	1.00	1.01	0.53	0.05	5.78
Kidney Related Issues	650	2	0.31	682	3	0.44	0.13	0.15	0.694	0.156	0.693	1.000	1.43	0.24	8.58	1.00	1.00	1.01	0.70	0.12	4.18
Elevated Liver Enzymes	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Neoplasm †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76

(*Continued*)

Table 2. (Continued).

	Studies Reporting Side Effects							Chi-Square Tests					Risk Estimate								
	Placebo			Creatine			Prevelence							95% Confidence Interval			95% Confidence Interval			95% Confidence Interval	
Variable	Not Present (n)	Present (n)	Prevelance (%)	Not Present (n)	Present (n)	Present %	Difference %	χ^2 Value	χ^2 p level	Likelihood Ratio	Likelihood p-level	Fisher Exact Test p-level	Odds Ratio for Supplement	Lower	Upper	Odds Ratio for Not Present	Lower	Upper	Odds Ratio for Present	Lower	Upper
Nerve & Muscle Complaints †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Nervous System Issues †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Infections and Infestations †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Renal/Urinary Issues †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Psychiatric Disorders †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Respiratory †	650	2	0.31	683	2	0.29	−0.01	0.00	0.961	0.002	0.961	1.000	0.95	0.13	6.78	1.00	0.99	1.01	1.05	0.15	7.44
Vascular	650	2	0.31	684	1	0.15	−0.16	0.39	0.535	0.392	0.531	0.616	0.48	0.04	5.25	1.00	0.99	1.00	2.10	0.19	23.12
Bone Joint †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Metabolism and Nutrition †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Skin †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Cardiac †	650	2	0.31	684	1	0.15	−0.16	0.39	0.535	0.392	0.531	0.616	0.48	0.04	5.25	1.00	0.99	1.00	2.10	0.19	23.12
Eye Disorders †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Reproductive †	651	1	0.15	684	1	0.15	−0.01	0.00	0.972	0.001	0.972	1.000	0.95	0.06	15.25	1.00	1.00	1.00	1.05	0.07	16.76
Pregnancy	652	0	0.00	684	1	0.15	0.15	0.95	0.329	1.338	0.247	1.000				1.001	0.999	1.004			
Other	647	5	0.77	679	6	0.88	0.11	0.05	0.825	0.049	0.825	1.000	1.14	0.35	3.77	1.00	0.99	1.01	0.88	0.27	2.86

Data are means and standard deviations of the number of clinical trials reporting side effects. † = Only reported in one clinical trial on 1,741 Parkinson's patients consuming 10 g/d of a placebo or creatine monohydrate for up to 8-years (Kieburtz et al. 2015).

number of studies reporting the remaining 33 side effects between the placebo and creatine-supplemented groups, with the difference in prevalence reported typically ±0.4%. This includes the number of studies reporting vertigo, hypertension, headache, dizziness, lightheadedness, nausea, diarrhea, impaired concentration, sleep disturbances, poor appetite, fatigue, excessive sweating, edema, palpitations, thromboembolic events, kidney-related issues, elevated liver enzymes, pregnancy, and other complaints. This also includes one large long-term clinical trial conducted on Parkinson's patients, providing 10 g/d of CrM for up to 8 years [74] that reported the incidence of neoplasm, nerve and muscle complaints, nervous system issues, infections and infestations, renal/urinary issues, psychiatric disorders, respiratory complaints, vascular issues, bone and joint problems, metabolism and nutrition issues, skin complications, cardiac conditions, eye disorders, and reproductive issues.

3.4. Frequency of side effects reported

Table 3 shows the frequency of side effects reported in creatine supplementation studies. This analysis provides a more detailed assessment of whether creatine supplementation increased the incidence of side effects among participants taking creatine supplements compared to those consuming placebos. Multivariate analysis of all side effects evaluated revealed no significant differences in the frequency of side effects reported between participants taking placebo and creatine supplements ($p = 0.340$, $n_p 2 = 0.023$). Univariate analysis revealed that 13,452 participants ingested placebos, while 12,839 consumed creatine supplements ($p = 0.411$). Of these, 4.21% of participants ingesting placebos reported having a side effect, while 4.60% of participants consuming creatine supplements reported side effects ($p = 0.828$). Most of the reported side effects were reported from one large clinical trial that involved high-dose creatine supplementation for up to 8 years (i.e. 437/566 or 77.2% PLA, 478/591 or 80.9% Cr) [74]. When the number of participants reporting side effects was considered from all studies, no significant differences were observed in the frequency of GI issues (PLA 4.05%, Cr 5.51%, $p = 0.820$), muscle cramping/pain (PLA 0.07%, Cr 0.52%, $p = 0.085$), or any other of the 33 side effects evaluated, including clinical markers of health and renal function. Similarly, the percentage prevalence in the frequency of reported side effects was very small between those taking creatine and placebos overall, as well as when categorized by sex (Table S7), age (Table S8), and comparing healthy and clinical populations (Table S9). Although some significant differences were noted among sex and age categories, the percent differences in the frequency of side effects between participants consuming placebos and creatine were, in most cases, less than ±0.5% and, in some cases, higher in those consuming placebos. No significant differences were observed when comparing the frequency of side effects among healthy and clinical populations, even though clinical populations generally consumed a greater amount of creatine for longer periods of time.

3.5. Adverse event report analysis

Table 4 shows a summary of the reported AERs in worldwide databases. Although AERs do not provide enough detail to assess causality and may not be attributed to creatine supplementation, only 203 adverse events mention creatine among 28.4 million reports

Table 3. Frequency of side effects reported in creatine studies for participants consuming placebos and creatine containing supplements.

	All Participants										Prevalence Difference	Statistics Supplement	
	Placebo Supplements					Creatine Supplements							
Variable	Studies (*n*)	Number	Mean	SD	Prevalence (%)	Studies (*n*)	Number	Mean	SD	Prevalence (%)	%	*p* level	Eta 2
Sample Size	652	13,452	20.63	45.22		685	12,839	18.74	37.84			0.411	0.001
Participants Reporting Side Effects	652	566	0.870	0.34	4.21	685	591	0.860	0.34	4.60	0.39	0.828	0.000
Gastrointestinal/Abdominal	652	545	0.836	15.98	4.05	685	708	1.033	15.98	5.51	1.46	0.820	0.000
Vertigo	652	0	0.000	0.00	0.00	685	4	0.010	0.09	0.03	0.03	0.111	0.002
Hypertension	652	0	0.000	0.00	0.00	685	0	0.000	0.00	0.00	0.00	.	.
Headache	652	22	0.034	0.57	0.16	685	15	0.022	0.28	0.12	−0.05	0.635	0.000
Dizziness	652	23	0.040	0.72	0.17	685	17	0.020	0.43	0.13	−0.04	0.747	0.000
Light Headed	652	0	0.000	0.00	0.00	685	1	0.000	0.04	0.01	0.01	0.329	0.001
Nausea	652	51	0.078	0.91	0.38	685	54	0.079	0.89	0.42	0.04	0.986	0.000
Diarrhea	652	28	0.043	0.84	0.21	685	51	0.075	1.32	0.40	0.19	0.605	0.000
Impaired Concentration	652	50	0.080	1.84	0.37	684	32	0.050	1.22	0.25	−0.12	0.726	0.000
Muscle Cramping/Pain	652	9	0.014	0.15	0.07	685	67	0.097	1.23	0.52	0.45	0.085	0.002
Sleep Disturbances †	652	0	0.000	0.00	0.00	685	2	0.000	0.05	0.02	0.02	0.167	0.001
Poor Appetite †	652	2	0.004	0.08	0.02	685	3	0.004	0.08	0.02	0.00	0.962	0.000
Fatigue	652	41	0.060	1.61	0.30	685	35	0.050	1.23	0.27	−0.03	0.881	0.000
Excessive Sweating	652	2	0.000	0.08	0.01	685	3	0.000	0.09	0.02	0.01	0.769	0.000
Increased Urination	652	5	0.010	0.20	0.04	685	5	0.010	0.19	0.04	0.00	0.973	0.000
Edema	652	2	0.000	0.08	0.01	685	13	0.020	0.20	0.10	0.09	0.055	0.003
Palpitations	652	0	0.000	0.00	0.00	685	12	0.020	0.32	0.09	0.09	0.167	0.001
Thromboembolic Events	652	2	0.000	0.08	0.01	685	3	0.000	0.09	0.02	0.01	0.769	0.000
High Urine Albumin Creatinine Ratio	652	0	0.000	0.00	0.00	685	2	0.000	0.08	0.02	0.02	0.329	0.001
High Urine Microalbumin	652	6	0.010	0.24	0.04	685	3	0.000	0.12	0.02	−0.02	0.632	0.000
Hemoglobin in Urine	652	8	0.010	0.31	0.06	685	3	0.000	0.12	0.02	−0.04	0.538	0.000
Low Creatinine Clearance	652	2	0.000	0.08	0.01	685	1	0.000	0.04	0.01	−0.01	0.632	0.000
Protein in urine	652	6	0.010	0.24	0.04	685	0	0.000	0.00	0.00	−0.04	0.306	0.001
High Urine Creatine	652	0	0.000	0.00	0.00	685	6	0.010	0.23	0.05	0.05	0.329	0.001
Low Estimated Glomerular Filtration Rate	652	0	0.000	0.00	0.00	685	4	0.010	0.15	0.03	0.03	0.329	0.001
Low Urine Creatinine	652	1	0.000	0.04	0.01	685	0	0.000	0.00	0.00	−0.01	0.306	0.001
Kidney Infection	652	0	0.000	0.00	0.00	685	2	0.000	0.05	0.02	0.02	0.167	0.001
Kidney Cysts	652	1	0.000	0.04	0.01	685	0	0.000	0.00	0.00	−0.01	0.306	0.001
High Liver Enzymes	652	3	0.000	0.12	0.02	685	6	0.010	0.23	0.05	0.02	0.936	0.000
Neoplasm †	652	142	0.220	5.56	1.06	685	133	0.190	5.08	1.04	−0.02	0.678	0.000
Bilirubin in Urine	652	0	0.000	0.00	0.00	685	1	0.000	0.04	0.01	0.01	0.329	0.001

(*Continued*)

Table 3. (Continued).

	All Participants										Prevalence	Statistics	
	Placebo Supplements					Creatine Supplements					Difference	Supplement	
Variable	Studies (*n*)	Number	Mean	SD	Prevalence (%)	Studies (*n*)	Number	Mean	SD	Prevalence (%)	%	*p* level	Eta 2
Low Albumin	652	2	0.000	0.08	0.01	685	1	0.000	0.04	0.01	−0.01	0.632	0.000
Nerve & Muscle Complaints †	652	437	0.670	17.11	3.25	685	478	0.700	18.26	3.72	0.47	0.976	0.000
Nervous System Issues †	652	409	0.630	16.02	3.04	685	458	0.670	17.50	3.56	0.52	0.963	0.000
Infections and Infestations †	652	368	0.560	14.41	2.74	685	353	0.520	13.49	2.75	0.01	0.950	0.000
Renal/Urinary Issues †	652	368	0.560	14.41	2.74	685	321	0.470	12.27	2.50	−0.24	0.897	0.000
Psychiatric Disorders †	652	322	0.490	12.61	2.39	685	335	0.490	12.80	2.61	0.21	0.995	0.000
Respiratory †	652	325	0.500	11.97	2.42	685	373	0.540	12.77	2.90	0.49	0.945	0.000
Vascular	652	295	0.450	11.51	2.19	685	254	0.370	9.71	1.98	−0.22	0.889	0.000
Bone Joint †	652	233	0.360	9.13	1.73	685	215	0.310	8.22	1.67	−0.06	0.928	0.000
Metabolism and Nutrition †	652	228	0.350	8.93	1.69	685	233	0.340	8.90	1.81	0.12	0.985	0.000
Skin †	652	222	0.340	8.69	1.65	685	226	0.330	8.64	1.76	0.11	0.983	0.000
Cardiac †	652	189	0.290	7.40	1.40	685	172	0.250	6.57	1.34	−0.07	0.920	0.000
Eye Disorders †	652	155	0.240	6.07	1.15	685	162	0.240	6.19	1.26	0.11	0.998	0.000
Reproductive †	652	143	0.220	5.60	1.06	685	123	0.180	4.70	0.96	−0.11	0.889	0.000
Pregnancy	652	0	0.000	0.00	0.00	685	3	0.000	0.12	0.02	0.02	0.329	0.001
Other	652	29	0.040	0.58	0.22	685	30	0.040	0.67	0.23	0.02	0.986	0.000

Data are means and standard deviations of the frequency of side effects reported in studies involving creatine supplementation. The overall multivariate analysis revealed no significant differences between placebo and creatine supplements ($p = 0.340$, np 2 $= 0.023$) .Univariate p-levels, effect sizes, and prevalence frequency observed/total sample size) values are also reported. † = Only reported in one clinical trial on 1,741 Parkinson's patients consuming 10 g/d of a placebo or creatine monohydrate for up to 8-years (Kieburtz et al. 2015).

Table 4. Reported adverse events listing creatine.

Variable	USA	Canada	Australia	Europe	SIDER 4.1	Total
Total AERS reported from 1999 – 2024	1,40,566	1,75,940	6,39,835	2,74,00,000	1,39,756	2,83,56,341
Total AERS reports mentioning creatine 1999 – 2024	307	32	6	0	0	345
Number of AERS reports mentioning creatine that do not contain creatine in product	142	0	0	0	0	142
Number of AERS reports with creatine in the product	165	32	6	0	0	203
Percentage of AERS reports mentioning creatine that do not contain creatine (%)	46.3	0.0000	0.0000	0.0000	0.0000	0.00000
Percentage of AERS reports mentioning creatine in database (%)	0.2184	0.0182	0.0009	0.0000	0.0000	0.00122
Percentage of AERS reports that actually have creatine in the products (%)	0.1174	0.0182	0.0009	0.0000	0.0000	0.00072
Years evaluated in database	25	50	27	24	10	27.20
Average AERS Reported per year	6.6	0.64	0.22	0.00	0.00	7.46

(0.00072%). In the United States CAERS database, 46.3% of reports listing creatine did not contain creatine when evaluating the ingredients of the product listed. Among the CAERS that contained creatine as an ingredient, 37% listed CrM as the only product the individual was consuming, and 63% contained other nutrients consumed with CrM. Of these, only 15.8% involved ingestion of CrM with other nutrients, 47.3% involved other types of creatine, and 43.6% involved ingesting creatine with nutritional products or drugs, which makes attribution of CAERS to CrM alone impossible. Similar findings were seen when looking at the products associated with AERs from other databases.

3.6. Social media sentiment analysis

Results of the sentiment analysis based on YouTube data are presented in Table 5. A total of 129,782 comments were collected from YouTube videos published between April 2011 and February 2025 that contained the term "creatine" in their title or description. The majority of comments exhibit no strong sentiment, suggesting that many are informational rather than opinion-based. Overall, positive comments (blue) outnumber negative ones (orange), though neutral comments show a slightly higher proportion of negativity (Figure 2(a)). As sentiment strength increases, the number of comments decreases, with positive comments remaining more prevalent. The narrow confidence intervals and the

Table 5. Results of the sentiment analysis in YouTube (April 2011 to February 2025).

	Overall (129,782 [100%])		Creatine Monohydrate (2,253 [1.7%])		Creatine HCl (1,026 [0.8%])	
Score (strength)	Positive	Negative	Positive	Negative	Positive	Negative
1 (none)	67.90%	74.34%	53.93%	62.58%	54.48%	57.89%
2 (weak)	18.52%	14.41%	26.01%	21.44%	28.27%	21.25%
3 (moderate)	12.24%	8.33%	17.93%	11.23%	15.40%	13.65%
4 (strong)	1.28%	2.78%	2.04%	4.57%	1.75%	6.73%
5 (very strong)	0.06%	0.14%	0.09%	0.18%	0.10%	0.49%
Sentiment	**Mean score**	**95% CI**	**Mean score**	**95% CI**	**Mean score**	**95% CI**
Positive	1.4708	1.4667, 1.4749	1.6835	1.6488, 1.7183	1.6472	1.5977, 1.6966
Negative	1.3997	1.3955, 1.4039	1.5832	1.5471, 1.6193	1.7066	1.6472, 1.7660

Data are results of the SentiStrength algorithm. 95% CI: 95% confidence interval.

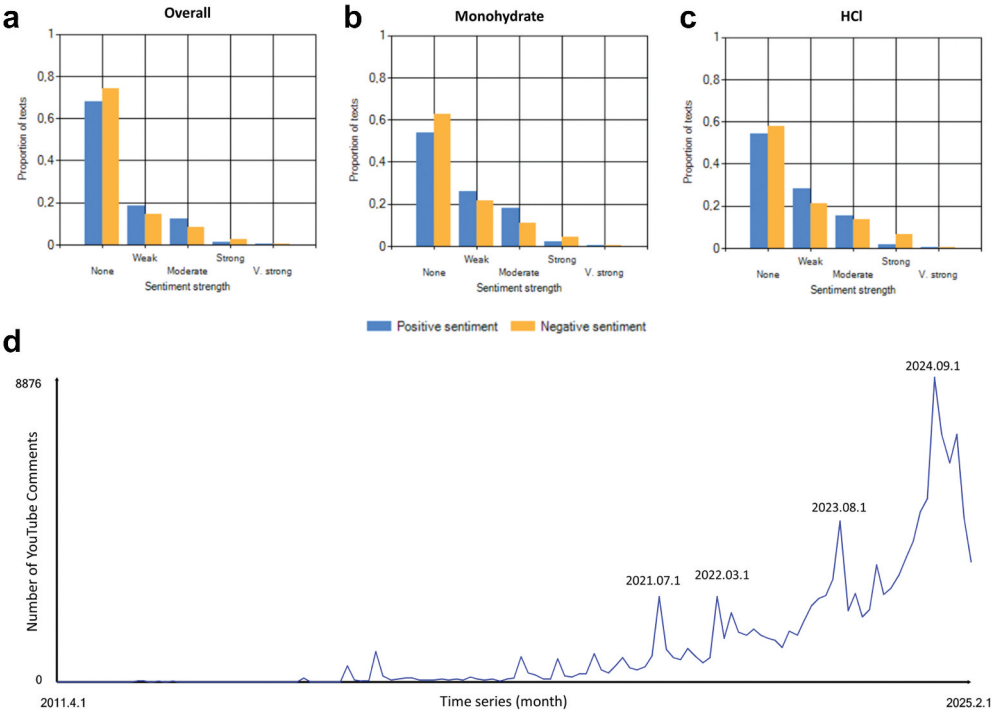

Figure 2. Plots for the set of YouTube comments results on creatine. *Above*. Bar plot presenting the proportion of texts (Y-axis) and the sentiment strength scores (X-axis) for all collected comments (a), as well as for those including the words "monohydrate" (b) or "HCl" (c). *Below*. Time series graph displaying all YouTube comments from videos containing the word "creatine" in title or description, organized by publication date (d). The plots were generated using Mozdeh software.

small difference suggest that the overall sentiment is relatively balanced, with a marginal tendency toward positivity (average positive − average negative = 0.0711). Thus, most YouTube discussions on creatine seem neutral or slightly positive. Interestingly, comments containing the word "monohydrate" remain generally neutral despite having a higher percentage of comments with weak and moderate positive sentiments (average positive − average negative = 0.1033); however, negative sentiments were predominant when the estimated sentiment strength was classified as strong or very strong (Figure 2(b)). Comments containing the word "HCl" were more likely to express strong negative sentiments compared to the overall average, which could indicate greater dissatisfaction or criticism in these comments (average positive − average negative = −0.0595) (Figure 2(c)). The time series scanning revealed a continuous increase in YouTube comments with important peaks in July 2021, March 2022, August 2023, and September 2024 (Figure 2(d)).

The word mining analysis (Table S10) revealed statistically significant associations ($p < 0.001$) between the term "monohydrate" and words such as "creatine," "micronized," "creapure," "better," "cheapest," and "effective," as well as with "bloating," "stomach," and "issue." In the case of "HCl," significant associations were found with words like "stomach," "better," "bloating," "superior," "expensive," "cost" and "soluble." Both "HCl"

and "monohydrate" were highly associated with each other, but the match percentage was lower for the latter. This might indicate that when people comment on HCl, they generally also mention monohydrate (37%), whereas the opposite occurs less frequently (17%).

Regarding Twitter (X) data up to 2021, a total of 657,039 tweets (90.5%) matched out after the search for "creatine" in the initial gathered data of 725,788 tweets. No significant differences were found on average sentiment; therefore, there was a neutral sentiment on creatine if we consider the mean values of the analyzed population (mean positive – mean negative = 0.0098). However, there is a higher prevalence of strong negative sentiment (2.09%) compared to a strong positive sentiment (0.69%) (Table S11).

4. Discussion

Although creatine has been studied since the early 1900s, CrM became a popular dietary supplement in the early 1990s after Harris, Hultman, Greenhaff, and colleagues [63–66] published several papers demonstrating that CrM supplementation could increase muscle PCr and influence high-intensity exercise performance. Additionally, reports in the media that several British Olympians used creatine during the 1992 Olympics piqued interest in the ergogenic value of creatine supplementation and its use in dietary supplements. About the same time, Earnest and colleagues [75] and Kreider and coworkers [76–79] demonstrated that creatine supplementation during training could augment gains in strength, power, and lean mass. This was followed by seminal studies by Volek and colleagues [80] and Willoughby et al. [81,82], which showed that gains in weight were attributed to gains in lean mass. These studies and others conducted during the mid-1990s to late 1990s propelled interest in CrM as a performance-enhancing dietary supplement for athletes.

While no side effects were observed in these early studies involving as much as 25 g/d of CrM for 84 days in American football players undergoing intense training [79], anecdotal reports began appearing in the media about purported side effects (e.g. cramping, dehydration, muscle strains/pulls, concern about kidney function, etc.). As a result, Kreider [83] published what we believe is the first paper to address some of these anecdotal side effects, noting that no study had reported any of these purported side effects mentioned in the media. At about the same time, several studies were conducted to assess whether athletes taking creatine experienced a greater risk of anecdotally reported side effects and/or adverse health outcomes [84–90]. Other studies directly assessed the merit of anecdotal reports of side effects and found that creatine supplementation did not increase the incidence of musculoskeletal injuries [84–87], dehydration [85,86,91–96], muscle cramping [80,85,86,92,97], gastrointestinal issues [84–87], promote renal dysfunction [87,89,98–107], or have long-term detrimental effects [50,87,106,108,109]. Consequently, the ISSN concluded in its 2007 [16] and the 2017 position stands [12] that CrM was safe and effective for all ages and that additional research should evaluate the potential therapeutic benefits of creatin in clinical populations that may benefit. The 2017 position noted that given the known benefits and safety profile of creatine supplementation, government legislatures and sports organizations who restrict and/or discourage the use of creatine may be placing athletes at greater risk [12].

One would expect that given the large safety profile of CrM [2], the position stands from the ISSN [12,16]; the fact that the FDA considers CrM GRAS [51] and it is the only source of creatine that is approved for sale in worldwide markets [2]; international athletic governing bodies and professional organizations consider CrM safe, effective, and legal for use [12,16–20]; and there has been increased awareness about the dietary need for creatine and reported health benefits throughout the lifespan [4–9,22], and for clinical populations [1,4,13,21,23–26,28–31,110–114] concerns about the safety of creatine supplementation would have diminished. Yet, inaccurate information on the Internet and social media platforms has persisted, confusing the public and healthcare professionals. To address this misinformation, creatine scholars published two papers regarding misconceptions about creatine supplementation [15,56]. Additionally, a Creatine for Health website was established [115] and a special issue on creatine in health and disease was published [1,4,13,21,23–26,28–31,110–114] to educate the public and healthcare professionals about the safety and efficacy of creatine supplementation. While these efforts have helped, concerns over the safety of creatine and legislative efforts to limit access to dietary supplements containing creatine continue. So much so that the ISSN issued a press release that was endorsed by nearly 40 creatine scholars to raise concerns about the potential negative health impact of limiting access to CrM, including to children and adolescents [116,117].

Given persistent concerns about the safety of creatine supplementation, we conducted this comprehensive analysis to better inform the public and governing bodies about the safety of creatine supplementation in various populations. Our literature search revealed that over 680 clinical trials have been conducted in humans on creatine supplementation (95% as creatine monohydrate) on over 26,000 participants. These studies are summarized in a searchable database provided in Supplement File 1. Most studies show that creatine supplementation can benefit healthy active populations as they age and provide therapeutic benefits in some clinical populations [2,4]. Additionally, we identified over 400 scholarly reviews and 100 meta-analyses about creatine supplementation. Most of those reviews conclude that creatine supplementation can provide some performance and/or clinical benefit, and most meta-analyses report some efficacy.

Analysis of the side effects reported in clinical trials was conducted in several ways. First, we evaluated the prevalence of studies reporting side effects for placebo and creatine-supplemented groups. This analysis revealed that no AERs have been reported from clinical trials lasting up to 14 years in healthy and medically managed populations ranging from infants to older adults. Additionally, the number (prevalence) of studies reporting side effects was not significantly different between studies reporting side effects in placebo versus creatine groups (13.2% versus 13.7%). While more studies reported GI issues (PLA 28/652 or 4.3%, Cr 63/685 or 9.2%, $p < 0.001$) and muscle cramping/pain (PLA 6/652 or 0.9%, Cr 20/685 or 2.9%, $p = 0.008$) with creatine supplementation, there were no significant differences in these side effects when the number of participants experiencing GI issues (PLA 545/13,452 or 4.2%, Cr 708/12,839 or 5.51%, $p = 0.820$) or muscle cramping/pain (PLA 9/13,452 or 0.07%, Cr 67/12,839 or 0.52%, $p = 0.085$) is evaluated in all of these studies. These findings indicate that while more clinical trials reported these issues in creatine users versus non-users, the percentage incidence was small, and the total number of participants experiencing these issues in all studies was not significantly different between those taking creatine and placebos. This means that while

individuals taking creatine supplements may experience GI issues and muscle cramping/pain, the incidence is low and not different from those taking placebos. Additionally, the number of studies and frequency of participants experiencing other side effects were very low and not significantly different than placebos (±0.5%). This includes assessment of side effect symptomology and markers of health and renal function.

Present findings are similar to results reported in our long-term creatine safety study on American football players [86,87], where we showed that up to 21 months of creatine supplementation (5–10 g/d) in division I American football players did not significantly affect markers of health or renal function [87] and the incidence of side effects and injury in creatine users were proportional or lower than the percentage of athletes not taking creatine [86]. They are also consistent with other safety studies on creatine supplementation [50,80,84–87,89,91–109] and the long-term study conducted in Parkinson's patients [74]. Collectively, these findings indicate that creatine supplementation is well tolerated and not associated with a disproportion increase in any purported side effect or clinical marker of health.

Our second analysis assessed adverse events reported in worldwide databases going back 10–50 years. This analysis revealed that the incidence of reported AERs mentioning creatine is rare (0.00072%). It also revealed evidence of inaccurate reporting and linking creatine to AERs. In the CAERS database, 46.3% of AERs inaccurately listed creatine as a contributor despite the products not actually having any creatine mentioned in the list of ingredients. This suggests that the individuals completing these AERs had little knowledge about the known effects of creatine supplementation. Additionally, several AERs reported issues seemingly unrelated to the known physiological and psychological effects of creatine, which also raises questions regarding accuracy, whether those attributing AERs were familiar with creatine research, were influenced by inaccurate information about creatine supplementation on the Internet or assumed that creatine had steroid-like effects (which it does not). Given creatine has been taken billions of times since it became a popular dietary supplement in the early 1990s, the lack of AERs reported in worldwide databases is consistent with the lack of side effects observed in clinical trials. Comparatively, according to the U.S. Center for Disease Control, more than 1.5 million individuals required emergency room visits for adverse drug effects from anticoagulant (21%), diabetes (14%) and antibiotic (13%) medications among others resulting in over 500,000 hospitalizations [118].

Finally, we conducted an interesting analysis of perceptions about creatine on popular social media platforms (YouTube and Twitter). While the overall assessment was the public was neutral about their positive and negative perceptions of creatine supplementation, negative sentiments were predominant when the estimated sentiment strength was classified as strong or very strong (especially in Twitter). While this difference was small, it suggests a disconnect between public perceptions about the safety profile established in the literature about creatine supplementation and information learned through the popular media and/or advertisements. Much of the misinformation about creatine comes from companies and influencers who are promoting different types of creatine as more effective than CrM with fewer "side effects" [2]. This type of misinformation only confused the public. Importantly, several activities led by the *Creatine For Health* initiative may have drawn public attention on YouTube, as the significant peaks in the

time series analysis (July 2021, March 2022, August 2023, and September 2024) strongly coincide with key events. These include the special issue "Creatine Supplementation for Health and Clinical Diseases" (with several papers published during the first half of 2021), the Creatine Conference 2022 held in Alpharetta, USA, from March 16 to 19, 2022, increased activity and publications on the YouTube channel @creatineforhealth (first half of 2023), and the paid advertising strategy launched in early 2024 to boost the channel's reach, resulting in videos surpassing one million views.

Although further efforts are needed to continue educating the public and combating misinformation, these data objectively support the positive impact of bridging the gap between high-level researchers (e.g. *Creatine For Health* is an initiative that brings together the world's leading creatine researchers to accelerate awareness of the role of creatine supplementation in health and clinical diseases) and the general population through social media. As artificial intelligence (AI) methodologies improve, it may provide interesting ways to compare the science to public perceptions about creatine and other health strategies.

5. Limitations

This analysis is limited to the information provided in publications about the safety of creatine supplementation. In some cases, full details about study dosages, demographics of participants, and side effects were not provided. Some studies only mentioned side effects from those taking creatine with no mention of side effects from taking placebos which would overinflate the frequency reported with creatine supplementation. It is also unclear how anecdotal reports of side effects may have influenced researchers in reporting these side effects. It should also be noted that full details are not provided in AERs to assess causality. Additionally, given a large percentage of AERs mention creatine but were not actually in the products listed, creatine was taken with other nutrients and/or drugs, and some of the side effects reported appear unrelated to the known effects of creatine supplementation, which makes interpretation difficult. Finally, the big data text analysis has several limitations. First, the Twitter (X) API has time and size restrictions that affect the process of data gathering. Also, the query strategy normally matches many irrelevant YouTube comments and tweets as well. Finally, all social research has imperfect data and further studies on other social media platforms are needed (e.g. Facebook, LinkedIn). However, it must be noted that big data text analysis enables us to use manual judgments to identify parameters for disambiguating instances of automatically identified clues [119].

6. Conclusions

This comprehensive analysis reveals that CrM supplementation does not increase the prevalence or frequency of 35 side effects evaluated when compared to the frequency reported from participants taking placebos. This includes assessment of general health markers, renal function, and anecdotally reported side effects attributed to creatine supplementation in the media and on the Internet. Additionally, the mention of creatine in worldwide AERs is rare (0.00072%), mostly associated with co-ingestion of other nutrients and/or drugs, and in some cases report symptoms creatine studies never observed in any

clinical trial or are unrelated to the known effects of creatine supplementation. Finally, while the sentiment analysis suggests that a small percentage of the public may have a stronger negative view about creatine supplementation, it is unclear how misinformation may have influenced these perceptions. Nevertheless, these findings indicate that CrM is well tolerated in children through older adults and healthy and medically managed patient populations. We urge lobbyists, policymakers, and health agencies to consult with leading creatine scientists and to consider the full spectrum of scientific data before implementing restrictions that would have adverse public health and performance implications.

Acknowledgments

The authors would like to thank the research participants, scholars, and funding agencies who have contributed to the research cited in this manuscript. Big data text mining and social network analyses in this study are part of the Creatine REsearch And information System (CREAS), a DBSS project that implements bibliometrics, scientometrics, and other AI-assisted analyses to routinely inform, develop, improve and support research endeavors and clinical practice (available at: www.CREAS.pro).

Disclosure statement

R.B.K. has conducted industry-sponsored research on creatine through grants awarded to the univesities he has been affiliated, received financial support for presenting invited lectures at conferences about sports nutrition and creatine, and has served as an expert witness throughout his career on cases related to exercise, dietary supplements, and safety. Additionally, he serves as Chair of the Scientific Advisory Board for AlzChem (a company that makes creatine monohydrate), is a co-founder of the International Society of Sports Nutrition (ISSN) which is a non-profit professional academic organization, and a member of the scientific advisory boards for Oath Nutrition and Trace Minerals. He does not own any patents, receive royalties for the sale of creatine or any dietary supplement, or have any ownership in a company that sells creatine or any dietary supplements. D. A.B. serves as the Scientific and Managing Director of KreaFood, an R&D&I project, and is a member of the "Creatine for Health" scientific advisory board for Alzchem Group AG. Additionally, he has served as a scientific consultant for dietary supplement brands in Europe and Colombia, researched nutritional supplements funded by academic institutions, and received honoraria for presenting on nutritional supplements at international conferences and private courses. D.E.G., K.H., and A.G. report no conflicts of interest.

Funding

The Exercise and Sports Nutrition Lab at Texas A&M University supported lab personnel to conduct this study. The APC charges for the publication of this paper will be funded by Alzchem Group AG (Trostberg, Germany) as part of a special issue for the Creatine for Health 2025 conference. The funders had no role in the analysis of data, writing of the manuscript, interpretation of the results, or decision to publish the results.

ORCID

Richard B. Kreider http://orcid.org/0000-0002-3906-1658
Drew E. Gonzalez http://orcid.org/0000-0002-7279-4968
Diego A. Bonilla http://orcid.org/0000-0002-2634-1220

Author contributions

Conceptualization, R.B.K and D.A.B.; writing – original draft preparation, R.B.K.; literature review and preparation of tables, R.B.K., D.E.G., K.H., A.G., and D.A.B.; writing – review and editing, R.B.K., D.E.G., and D.A.B. All authors have read and agreed to the published version of the manuscript.

Consent for publication

All authors have reviewed and approved the publication.

Data availability statement

Provided in supplemental files.

References

1. Bonilla DA, Kreider RB, Stout JR, et al. Metabolic basis of creatine in health and disease: a bioinformatics-assisted review. Nutrients. 2021;13(4):1238. doi: 10.3390/nu13041238
2. Kreider RB, Jager R, Purpura M. Bioavailability, efficacy, safety, and regulatory status of creatine and related compounds: a critical review. Nutrients. 2022;14(5):1035. doi: 10.3390/nu14051035
3. Brosnan ME, Brosnan JT. The role of dietary creatine. Amino Acids. 2016;48(8):1785–1791. doi: 10.1007/s00726-016-2188-1
4. Kreider RB, Stout JR. Creatine in health and disease. Nutrients. 2021;13(2):447. doi: 10.3390/nu13020447
5. Korovljev D, Stajer V, Ostojic SM. Relationship between dietary creatine and growth indicators in children and adolescents aged 2–19 years: a cross-sectional study. Nutrients. 2021;13(3):1027. doi: 10.3390/nu13031027
6. Korovljev D, Todorovic N, Stajer V, et al. Food creatine and DXA-Derived body composition in boys and girls aged 8 to 19 years. Nutr Metab Insights. 2021;14:11786388211059368.
7. Ostojic SM, Stea TH, Ellery SJ, et al. Association between dietary intake of creatine and female reproductive health: evidence from NHANES 2017–2020. Food Sci Nutr. 2024;12(7):4893–4898. doi: 10.1002/fsn3.4135
8. Ostojic SM, Korovljev D, Stajer V. Dietary creatine and cognitive function in U.S. adults aged 60 years and over. Aging Clin Exp Res. 2021;33(12):3269–3274. doi: 10.1007/s40520-021-01857-4
9. Ostojic SM, Korovljev D, Stajer V. Dietary intake of creatine and risk of medical conditions in U.S. older men and women: data from the 2017–2018 national health and nutrition examination survey. Food Sci Nutr. 2021 Oct;9(10):5746–5754.
10. Bakian AV, Huber RS, Scholl L, et al. Dietary creatine intake and depression risk among U.S. adults. Transl Psychiatry. 2020 Feb 3;10(1):52. doi: 10.1038/s41398-020-0741-x
11. Jiang J, Zhao H, Chen J, et al. The association between dietary creatine intake and cancer in U.S. adults: insights from NHANES 2007–2018. Front Nutr. 2024;11:1460057. doi: 10.3389/fnut.2024.1460057
12. Kreider RB, Kalman DS, Antonio J, et al. International society of sports nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr. 2017;14:18.
13. Wax B, Kerksick CM, Jagim AR, et al. Creatine for exercise and sports performance, with recovery considerations for healthy populations. Nutrients. 2021 Jun 2;13(6).
14. Sakellaris G, Kotsiou M, Tamiolaki M, et al. Prevention of complications related to traumatic brain injury in children and adolescents with creatine administration: an open label randomized pilot study. J Trauma. 2006 Aug;61(2):322–329. doi: 10.1097/01.ta.0000230269.46108.d5

15. Antonio J, Brown AF, Candow DG, et al. Part II. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show? J Int Soc Sports Nutr. 2025 Dec;22(1):2441760. doi: 10.1080/15502783.2024.2441760
16. Buford TW, Kreider RB, Stout JR, et al. International society of sports nutrition position stand: creatine supplementation and exercise. J Int Soc Sports Nutr. 2007 Aug 30;4(1):6. doi: 10.1186/1550-2783-4-6
17. Rodriguez NR, DiMarco NM, Langley S, et al. Position of the American dietetic association, dietitians of Canada, and the American college of sports medicine: nutrition and athletic performance. J Am Diet Assoc. 2009 Mar;109(3):509–527.
18. Thomas DT, Erdman KA, Burke LM. Position of the academy of nutrition and dietetics, dietitians of Canada, and the American college of sports medicine: nutrition and athletic performance. J Acad Nutr Diet. 2016 Mar;116(3):501–528. doi: 10.1016/j.jand.2015.12.006
19. Maughan RJ, Burke LM, Dvorak J, et al. IOC consensus statement: dietary supplements and the high-performance athlete. Int J Sport Nutr Exerc Metab. 2018;28(2):104–125. doi: 10.1123/ijsnem.2018-0020
20. National Institutes of Health. Office of dietary supplements, dietary supplement fact sheets: dietary supplements for exercise and athletic performance. U.S. Department of Health and Human Services; 2021 [cited 2021 Mar 29]. Available from: https://ods.od.nih.gov/factsheets/ExerciseAndAthleticPerformance-HealthProfessional/
21. Muccini AM, Tran NT, de Guingand DL, et al. Creatine metabolism in female reproduction, pregnancy and newborn health. Nutrients. 2021 Feb 2;13(2).
22. Ostojic SM. Establishing reference intakes for creatine in infants aged 0 to 12 months. Nutr Rev. 2024 Sep 13.
23. Jagim AR, Kerksick CM. Creatine supplementation in children and adolescents. Nutrients. 2021 Feb 18;13(2).
24. Smith-Ryan AE, Cabre HE, Eckerson JM, et al. Creatine supplementation in women's health: a lifespan perspective. Nutrients. 2021;13(3).
25. Candow DG, Forbes SC, Kirk B, et al. Current evidence and possible future applications of creatine supplementation for older adults. Nutrients. 2021 Feb 26;13(3):745. doi: 10.3390/nu13030745
26. Bredahl EC, Eckerson JM, Tracy SM, et al. The role of creatine in the development and activation of immune responses. Nutrients. 2021 Feb 26;13(3):751. doi: 10.3390/nu13030751
27. Marshall RP, Droste JN, Giessing J, et al. Role of creatine supplementation in conditions involving mitochondrial dysfunction: a narrative review. Nutrients. 2022 Jan 26;14(3):529. doi: 10.3390/nu14030529
28. Balestrino M. Role of creatine in the heart: health and disease. Nutrients. 2021;13(4):1215. doi: 10.3390/nu13041215
29. Clarke H, Hickner RC, Ormsbee MJ. The potential role of creatine in vascular health. Nutrients. 2021;13(3):857. doi: 10.3390/nu13030857
30. Roschel H, Gualano B, Ostojic SM, et al. Creatine supplementation and brain health. Nutrients. 2021;13(2).
31. Solis MY, Artioli GG, Gualano B. Potential of creatine in glucose management and diabetes. Nutrients. 2021;13(2):570. doi: 10.3390/nu13020570
32. Dolan E, Artioli GG, Pereira RMR, et al. Muscular atrophy and sarcopenia in the elderly: Is there a role for creatine supplementation? Biomolecules. 2019;9(11):642. doi: 10.3390/biom9110642
33. Candow DG, Forbes SC, Chilibeck PD, et al. Effectiveness of creatine supplementation on aging muscle and bone: focus on falls prevention and inflammation. J Clin Med. 2019;8(4):488. doi: 10.3390/jcm8040488
34. Chilibeck PD, Kaviani M, Candow DG, et al. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. Open Access J Sports Med. 2017;8:213–226.
35. Riesberg LA, Weed SA, McDonald TL, et al. Beyond muscles: the untapped potential of creatine. Int Immunopharmacol. 2016;37:31–42.

36. Stares A, Bains M. The additive effects of creatine supplementation and exercise training in an aging population: a systematic review of randomized controlled trials. J Geriatr Phys Ther. 2020;43(2):99–112. doi: 10.1519/JPT.0000000000000222
37. Tarnopolsky MA. Clinical use of creatine in neuromuscular and neurometabolic disorders. Subcell Biochem. 2007;46:183–204.
38. Dover S, Stephens S, Schneiderman JE, et al. The effect of creatine supplementation on muscle function in childhood myositis: a randomized, double-blind, placebo-controlled feasibility study. J Rheumatol. 2020.
39. Balestrino M, Adriano E. Beyond sports: efficacy and safety of creatine supplementation in pathological or paraphysiological conditions of brain and muscle. Med Res Rev. 2019;39 (6):2427–2459.
40. Balestrino M, Sarocchi M, Adriano E, et al. Potential of creatine or phosphocreatine supplementation in cerebrovascular disease and in ischemic heart disease. Amino Acids. 2016;48 (8):1955–1967. doi: 10.1007/s00726-016-2173-8
41. Neves MJr., Gualano B, Roschel H, et al. Beneficial effect of creatine supplementation in knee osteoarthritis. Med Sci Sports Exerc. 2011;43(8):1538–1543.
42. Cornelissen VA, Defoor JG, Stevens A, et al. Effect of creatine supplementation as a potential adjuvant therapy to exercise training in cardiac patients: a randomized controlled trial. Clin Rehabil. 2010;24(11):988–999. doi: 10.1177/0269215510367995
43. Al-Ghimlas F, Todd DC. Creatine supplementation for patients with COPD receiving pulmonary rehabilitation: a systematic review and meta-analysis. Respirology. 2010;15(5):785–795. doi: 10.1111/j.1440-1843.2010.01770.x
44. Hespel P, Derave W. Ergogenic effects of creatine in sports and rehabilitation. Subcell Biochem. 2007;46:245–259.
45. Hespel P, Op't Eijnde B, Van Leemputte M, et al. Oral creatine supplementation facilitates the rehabilitation of disuse atrophy and alters the expression of muscle myogenic factors in humans. J Physiol. 2001;536(2):625–633. doi: 10.1111/j.1469-7793.2001.0625c.xd
46. Di Biase S, Ma X, Wang X, et al. Creatine uptake regulates CD8 T cell antitumor immunity. J Exp Med. 2019;216(12):2869–2882. doi: 10.1084/jem.20182044
47. Campos-Ferraz PL, Gualano B, Das Neves W, et al. Exploratory studies of the potential anti-cancer effects of creatine. Amino Acids. 2016;48(8):1993–2001. doi: 10.1007/s00726-016-2180-9
48. Fairman CM, Kendall KL, Hart NH, et al. The potential therapeutic effects of creatine supplementation on body composition and muscle function in cancer. Crit Rev Oncol Hematol. 2019;133:46–57. doi: 10.1016/j.critrevonc.2018.11.003
49. Bourgeois JM, Nagel K, Pearce E, et al. Creatine monohydrate attenuates body fat accumulation in children with acute lymphoblastic leukemia during maintenance chemotherapy. Pediatr Blood Cancer. 2008;51(2):183–187.
50. Jager R, Purpura M, Shao A, et al. Analysis of the efficacy, safety, and regulatory status of novel forms of creatine. Amino Acids. 2011 May;40(5):1369–1383.
51. GRN No. 931 Creatine Monohydrate. U.S. Department of health and human services. U.S. Food and Drug Administration; 2020.
52. Pritchard NR, Kalra PA. Renal dysfunction accompanying oral creatine supplements. Lancet. 1998 Apr 25;351(9111):1252–1253. doi: 10.1016/S0140-6736(05)79319-3
53. Révai T, Sápi Z, Benedek S, et al. Severe nephrotic syndrome in a young man taking anabolic steroid and creatine long term. Orv Hetil. 2003 Dec 7;144(49):2425–2427.
54. Robles EL, Pache KM, Gluck JS. Acute compartment syndrome of the leg caused by cocaine use, creatine supplementation and vigorous exercise. J Surg Case Rep. 2022 Nov;2022(11): rjac502. doi: 10.1093/jscr/rjac502
55. Rawson ES, Clarkson PM, Tarnopolsky MA. Perspectives on exertional Rhabdomyolysis. Sports Med. 2017;47(Suppl 1):33–49.
56. Antonio J, Candow DG, Forbes SC, et al. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show? J Int Soc Sports Nutr. 2021;18(1):13. doi: 10.1186/s12970-021-00412-w

57. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021.
58. FDA. CFSAN adverse event reporting system (CAERS): U.S. Food & drug administration. 2025 [cited 2025 Jan 28]. Available from: https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers
59. Canada Vigilance Adverse Reaction Online Database [Internet]. Health Canada. 2025 [cited 2025 Jan 28]. Available from: https://cvp-pcv.hc-sc.gc.ca/arq-rei/index-eng.jsp
60. Database of Adverse Event Notifications (DAEN) - medicines [Internet]. Australian Government, Department of Health and Aged Care, Therapeutic Goods Administration. 2025 [cited 2025 Jan 28]. Available from: https://daen.tga.gov.au/medicines-search/
61. Timbo BB, Chirtel SJ, Ihrie J, et al. Dietary supplement adverse event report data from the FDA center for food safety and applied nutrition adverse event reporting system (CAERS), 2004–2013. Ann Pharmacother. 2018;52(5):431–438.
62. Ng JY, Munford V, Thakar H. Web-based online resources about adverse interactions or side effects associated with complementary and alternative medicine: a systematic review, summarization and quality assessment. BMC Med Inform Decis Mak. 2020;20(1).
63. Thelwall M. Social web text analytics with Mozdeh. Wolverhampton: University of Wolverhampton; 2018.
64. Thelwall M. Social media analytics for YouTube comments: potential and limitations. Int J Soc Res Methodol. 2017;21(3):303–316. doi: 10.1080/13645579.2017.1381821
65. Thelwall M, Buckley K, Paltoglou G. Sentiment strength detection for the social web. J Am Soc Inf Sci Technol. 2011;63(1):163–173.
66. Kumar A, Garg G. Systematic literature review on context-based sentiment analysis in social multimedia. Multimedia Tools Appl. 2019;79(21–22):15349–15380. doi: 10.1007/s11042-019-7346-5
67. Chenworth M, Perrone J, Love JS, et al. Methadone and suboxone® mentions on twitter: thematic and sentiment analysis. Clin Toxicol. 2021:1–14.
68. Saha G, Roy S, Maji P. Sentiment analysis of twitter data related to COVID-19. Impac AI data sci in response to coronavirus pandemic. Algoritms Intell Syst 2021. 169–191.
69. Thelwall M, Buckley K, Paltoglou G. Sentiment strength detection for the social web. J Am Soc Inf Sci Technol. 2012;63(1):163–173.
70. Wilkinson D, Thelwall M. Researching personal information on the public web. Soc Sci Comput Rev. 2010;29(4):387–401. doi: 10.1177/0894439310378979
71. R Core Team. R: a language and environment for statistical computing [computer software]. Vienna, Austria: R Foundation for Statistical Computing; 2017. Available from: https://www.R-project.org/
72. Mair P, Wilcox R. Robust statistical methods in R using the WRS2 package. Behav Res Methods. 2020;52(2):464–488. doi: 10.3758/s13428-019-01246-w
73. Cohen J. Statistical power analysis for the behavioral sciences. Lawrence Erlbaum. Hillsdale, NJ; 1988. p. 75–108.
74. Writing Group for the NETiPDI, Kieburtz K, Tilley BC. Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: a randomized clinical trial. JAMA. 2015;313(6):584–593.
75. Earnest CP, Snell PG, Rodriguez R, et al. The effect of creatine monohydrate ingestion on anaerobic power indices, muscular strength and body composition. Acta Physiol Scand. 1995;153(2):207–209. doi: 10.1111/j.1748-1716.1995.tb09854.x
76. Kreider RB, Klesges R, Harmon K, et al. Effects of ingesting supplements designed to promote lean tissue accretion on body composition during resistance training. Int J Sport Nutr. 1996;6(3):234–246.
77. Grindstaff PD, Kreider R, Bishop R, et al. Effects of creatine supplementation on repetitive sprint performance and body composition in competitive swimmers. Int J Sport Nutr. 1997;7(4):330–348. doi: 10.1123/ijsn.7.4.330

78. Kreider RB, Ferreira M, Wilson M, et al. Effects of creatine supplementation on body composition, strength, and sprint performance. Med Sci Sports Exercise. 1998;30(1):73–82. doi: 10.1097/00005768-199801000-00011
79. Kreider RB, Klesges R, Lotz D, et al. Effects of nutritional supplementation during off-season college football training on body composition and strength. J Exerc Physiol Online. 1999;2(2):24–39.
80. Volek JS, Mazzetti SA, Farquhar WB, et al. Physiological responses to short-term exercise in the heat after creatine loading. Med Sci Sports Exerc. 2001 Jul;33(7):1101–1108.
81. Willoughby DS, Rosene J. Effects of oral creatine and resistance training on myosin heavy chain expression. Med Sci Sports Exerc. 2001;33(10):1674–1681.
82. Willoughby DS, Rosene JM. Effects of oral creatine and resistance training on myogenic regulatory factor expression. Med Sci Sports Exerc. 2003;35(6):923–929.
83. Kreider RB. Creatine, the next ergogenic supplement? Sportscience training & technology. 1998. Available from: http://www.sportsci.org/traintech/creatine/rbk.html
84. Greenwood M, Farris J, Kreider R, et al. Creatine supplementation patterns and perceived effects in select division I collegiate athletes. Clin J Sport Med. 2000 Jul;10(3):191–194.
85. Greenwood M, Kreider RB, Greenwood L, et al. Cramping and injury incidence in collegiate football players are reduced by creatine supplementation. J Athl Train. 2003;38(3):216–219.
86. Greenwood M, Kreider RB, Melton C, et al. Creatine supplementation during college football training does not increase the incidence of cramping or injury. Mol Cell Biochem. 2003 Feb;244(1–2):83–88.
87. Kreider RB, Melton C, Rasmussen CJ, et al. Long-term creatine supplementation does not significantly affect clinical markers of health in athletes. Mol Cell Biochem. 2003 Feb;244(1–2):95–104.
88. Schilling BK, Stone MH, Utter A, et al. Creatine supplementation and health variables: a retrospective study. Med Sci Sports Exerc. 2001;33(2):183–188. doi: 10.1097/00005768-200102000-00002
89. Vandenberghe K, Goris M, Van Hecke P, et al. Long-term creatine intake is beneficial to muscle performance during resistance training. J Appl Physiol (1985). 1997;83(6):2055–2063. doi: 10.1152/jappl.1997.83.6.2055
90. Mayhew DL, Mayhew JL, Ware JS. Effects of long-term creatine supplementation on liver and kidney functions in American college football players. Int J Sport Nutr Exerc Metab. 2002;12(4):453–460. doi: 10.1123/ijsnem.12.4.453
91. Hile AM, Anderson JM, Fiala KA, et al. Creatine supplementation and anterior compartment pressure during exercise in the heat in dehydrated men. J Athl Train. 2006 Jan-Mar;41(1):30–35.
92. Watson G, Casa DJ, Fiala KA, et al. Creatine use and exercise heat tolerance in dehydrated men. J Athl Train. 2006 Jan-Mar;41(1):18–29.
93. Easton C, Turner S, Pitsiladis YP. Creatine and glycerol hyperhydration in trained subjects before exercise in the heat. Int J Sport Nutr Exerc Metab. 2007 Feb;17(1):70–91.
94. Dalbo VJ, Roberts MD, Stout JR, et al. Putting to rest the myth of creatine supplementation leading to muscle cramps and dehydration. Br J Sports Med. 2008;42(7):567–573.
95. Lopez RM, Casa DJ, McDermott BP, et al. Does creatine supplementation hinder exercise heat tolerance or hydration status? A systematic review with meta-analyses. J Athl Train. 2009 Mar-Apr;44(2):215–223.
96. Rosene JM, Matthews TD, McBride KJ, et al. The effects of creatine supplementation on thermoregulation and isokinetic muscular performance following acute (3-day) supplementation. J Sports Med Phys Fitness. 2015;55(12):1488–1496.
97. Santos RV, Bassit RA, Caperuto EC, et al. The effect of creatine supplementation upon inflammatory and muscle soreness markers after a 30km race. Life Sci. 2004 Sep 03;75(16):1917–1924.
98. Poortmans JR, Auquier H, Renaut V, et al. Effect of short-term creatine supplementation on renal responses in men. Eur J Appl Physiol Occup Physiol. 1997;76(6):566–567. doi: 10.1007/s004210050291

99. Robinson TM, Sewell DA, Casey A, et al. Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function. Br J Sports Med. 2000 Aug;34(4):284–288. doi: 10.1136/bjsm.34.4.284
100. Groeneveld GJ, Beijer C, Veldink JH, et al. Few adverse effects of long-term creatine supplementation in a placebo-controlled trial. Int J Sports Med. 2005 May;26(4):307–313.
101. Gualano B, Ugrinowitsch C, Novaes RB, et al. Effects of creatine supplementation on renal function: a randomized, double-blind, placebo-controlled clinical trial. Eur J Appl Physiol. 2008;103(1):33–40.
102. Lugaresi R, Leme M, de Salles Painelli V, et al. Does long-term creatine supplementation impair kidney function in resistance-trained individuals consuming a high-protein diet? J Int Soc Sports Nutr. 2013 May 16;10(1):26. doi: 10.1186/1550-2783-10-26
103. Farquhar WB, Zambraski EJ. Effects of creatine Use on the athlete's kidney. Curr Sports Med Rep. 2002 Apr;1(2):103–106. doi: 10.1249/00149619-200204000-00007
104. Sipila I, Rapola J, Simell O, et al. Supplementary creatine as a treatment for gyrate atrophy of the choroid and retina. N Engl J Med. 1981 Apr 09;304(15):867–870. doi: 10.1056/NEJM198104093041503
105. Schroder H, Terrados N, Tramullas A. Risk assessment of the potential side effects of long-term creatine supplementation in team sport athletes. Eur J Nutr. 2005 Jun;44(4):255–261.
106. Bender A, Samtleben W, Elstner M, et al. Long-term creatine supplementation is safe in aged patients with Parkinson disease. Nutr Res. 2008;28(3):172–178. doi: 10.1016/j.nutres.2008.01.001
107. Aguiar AF, Januario RS, Junior RP, et al. Long-term creatine supplementation improves muscular performance during resistance training in older women. Eur J Appl Physiol. 2013;113(4):987–996. doi: 10.1007/s00421-012-2514-6
108. Bender A, Klopstock T. Creatine for neuroprotection in neurodegenerative disease: end of story? Amino Acids. 2016 Aug;48(8):1929–1940.
109. Vannas-Sulonen K, Sipila I, Vannas A, et al. Gyrate atrophy of the choroid and retina. A five-year follow-up of creatine supplementation. Ophthalmology. 1985 Dec;92(12):1719–1727.
110. Wallimann T, Hall CHT, Colgan SP, et al. Creatine supplementation for patients with inflammatory bowel diseases: a scientific rationale for a clinical trial. Nutrients. 2021 Apr 23;13(5).
111. van der Veen Y, Post A, Kremer D, et al. Chronic dialysis patients are depleted of creatine: review and rationale for intradialytic creatine supplementation. Nutrients. 2021 Aug 6;13(8):2709. doi: 10.3390/nu13082709
112. Ostojic SM. Diagnostic and pharmacological potency of creatine in post-viral fatigue syndrome. Nutrients. 2021 Feb 4;13(2).
113. Li B, Yang L. Creatine in T cell antitumor immunity and cancer immunotherapy. Nutrients. 2021 May 13;13(5):1633. doi: 10.3390/nu13051633
114. Harmon KK, Stout JR, Fukuda DH, et al. The application of creatine supplementation in medical rehabilitation. Nutrients. 2021;13(6):1825. doi: 10.3390/nu13061825
115. Creatine for Health. 2025. Available from: https://creatineforhealth.com/
116. Creatine supplementation is safe, beneficial throughout the lifespan, and should not be restricted [Internet]. Stuart, FL USA: International Society of Sports Nutrition; 2025 [cited 2025 Dec 2;. Available from: https://www.sportsnutritionsociety.org/PDFuploads/ISSN-PDF-U p l o a d - 3 9 4 . p d f ? f b c l i d = I w Y 2 x j a w I b H Q B l e H R u A 2 F l b Q I x M A A B H c 9 - 1rLVDhNmKGNmJTvkinA9G-mQmDeSk41IxEjUOzvqFd3iBynHDtqt0Q_aem_vuz1MxZck-dcrDDSTgmtpg
117. Kreider RB, Jagim AR, Antonio J, et al. Creatine supplementation is safe, beneficial throughout the lifespan, and should not be restricted. Front Nutr. 2025;12(1578564).
118. CDC Medication Safety Program. FastStats: medication safety data: U.S. Centers for Disease Control and Prevention. 2024 [cited 2024 Apr 17]. Available from: https://www.cdc.gov/medication-safety/data-research/facts-stats/index.html
119. Wiebe J, Wilson T, Bruce R, et al. Learning subjective language. Comput Linguistics. 2004;30(3):277–308. doi: 10.1162/0891201041850885