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Systematic Review

Creatine Supplementation Across Health and Performance Outcomes: An Umbrella Review of Systematic Reviews and Meta-Analyses

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Abstract

Background: Creatine supplementation is widely used to enhance physical performance, but its effects across health and performance outcomes remain uncertain. Objective: To synthesise evidence from systematic reviews and meta-analyses on creatine supplementation, evaluating methodological quality, certainty of evidence, and primary-study overlap. Methods: An umbrella review was conducted according to the Preferred Reporting Items for Overviews of Reviews (PRIOR) statement and registered in PROSPERO (CRD420261501087). PubMed, Scopus, and Web of Science were searched for systematic reviews with quantitative meta-analyses published during the preceding 20 years. Methodological quality was assessed using AMSTAR-2, and primary-study overlap using the Corrected Covered Area (CCA). Results: Forty-five systematic reviews were included, and the evidence was organised into seven thematic domains. Most reviews examined healthy, physically active, or athletic populations, whereas clinical cohorts (e.g., chronic obstructive pulmonary disease, heart failure, chronic kidney disease, depression, or metabolic disease) were represented in approximately one fifth of the reviews, mainly in mixed samples of healthy and clinical participants. Creatine supplementation showed favourable effects on selected measures of muscular strength, power, lean mass, and

Academic Editor: Emanuela Gualdi-Russo

Received: 17 September 2026
Revised: 4 November 2026
Accepted: 11 November 2026
Published: 13 November 2026

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physical function, with more consistent findings when combined with resistance training. Cognitive findings suggested improvements in selected measures of memory, attention, and processing speed, whereas evidence for endurance, recovery, inflammation, and mental health outcomes remained mixed or outcome-specific. Serum creatinine increased, but Cr-EDTA-measured GFR and urinary kidney-injury markers showed no significant changes; evidence regarding long-term renal safety remains limited. No review achieved high AMSTAR-2 confidence, and nearly half were rated critically low. Primary-study overlap was slight (global CCA: 3.49%), although 395 unique studies accounted for 1001 study–review inclusions, indicating that concordance across reviews does not necessarily represent independent replication. Conclusions: Creatine supplementation appears to provide outcome-specific benefits, particularly for selected measures of strength, power, lean mass, and physical function. However, these findings are tempered by the absence of high-confidence reviews and substantial reuse of primary studies across syntheses. Interpretation should therefore account for methodological limitations, population and outcome variability, and primary-study overlap.

Keywords: creatine supplementation; systematic reviews; meta-analysis; muscle strength; exercise performance; evidence synthesis

1. Introduction

Creatine is one of the most extensively studied and widely used nutritional supplements in sport and exercise. Its biological role is closely linked to cellular energy metabolism, as creatine and phosphocreatine contribute to the rapid regeneration of adenosine triphosphate during high-intensity muscle activity [1,2]. Accordingly, creatine monohydrate supplementation has consistently been associated with improvements in high-intensity exercise capacity and adaptations to resistance training, particularly increases in muscular strength, power and lean body mass [3–5]. Beyond athletic performance, creatine has also attracted substantial interest for its potential applications in healthy ageing, rehabilitation, physical function and several clinical populations, reflecting the broader physiological relevance of the creatine-phosphocreatine system [6–8].

However, the relevance of creatine extends beyond gains in performance and muscle mass [9]. Its proposed effects on recovery from exercise-induced muscle damage, thermoregulation, inflammation, oxidative stress, physical function, and tissue protection have stimulated a rapidly expanding literature across diverse populations and exercise contexts [9–13]. At the same time, safety remains a major component of the clinical and public health discussion surrounding creatine, particularly regarding renal function and the interpretation of serum creatinine [11,13–16]. Although long-term use has generally been considered well tolerated in healthy individuals, recent evidence continues to investigate whether changes in renal biomarkers represent physiological responses to creatine ingestion or clinically meaningful impairment [13,15,16]. This question is revisited directly in the synthesis of the safety domain and in the Conclusion of this review.

This expanding evidence base has generated a large number of systematic reviews and meta-analyses addressing specific outcomes, populations, exercise modalities and supplementation strategies. Recent analyses continue to report benefits for lean mass, strength and anaerobic performance, while also highlighting variation according to training status, age and intervention context. For example, a 2024 GRADE-assessed meta-analysis including 143 studies reported small increases in body mass and fat-free mass, with larger effects when creatine supplementation was combined with resistance training [17]. A 2026 meta-analysis in young men similarly found that gains in lean mass were observed

when creatine supplementation was combined with resistance training, whereas improvements in anaerobic power were observed irrespective of training context [18]. At the population level, recent reviews have also examined older adults and individuals at risk of functional disability, as well as active females, further illustrating the increasingly specialised nature of the evidence base [19].

Despite this substantial body of literature, important uncertainties remain. Existing systematic reviews and meta-analyses vary considerably in terms of populations, intervention protocols, comparators, outcome definitions, and methodological quality, making it difficult to distinguish findings that are consistent across reviews from those that may depend on specific analytical or contextual factors. These uncertainties are particularly evident in three non-exercise domains where the findings of systematic reviews are most divergent: post-exercise recovery and inflammation, where meta-analyses disagree on whether markers other than creatine kinase are consistently affected; cognitive function, where reported benefits are limited to selected domains and supported by low-to-moderate certainty evidence; and renal safety, where increases in serum creatinine have not been accompanied by consistent changes in glomerular filtration rate. Moreover, potentially important domains such as exercise recovery and inflammation remain characterised by inconsistent findings. For example, Northeast et al. [20] found no consistent effects of creatine supplementation on muscle strength recovery, muscle soreness, range of motion, lactate dehydrogenase or inflammatory outcomes, although creatine kinase was reduced at 48 h post-exercise; substantial heterogeneity was reported across several outcomes. Similarly, Jiaming et al. [21] reported an overall reduction in creatine kinase, but not lactate dehydrogenase, and highlighted high heterogeneity and moderate risk of bias among the included trials. Beyond exercise-related outcomes, the scope of creatine research has expanded into cognitive function and renal health, with recent meta-analyses reporting potentially beneficial effects on selected cognitive domains but low-to-moderate certainty for several outcomes, while renal analyses indicate increases in serum creatinine without consistent changes in glomerular filtration rate [22]. Collectively, these findings illustrate an increasingly broad but fragmented evidence base, in which the consistency, magnitude and certainty of effects remain dependent on the outcome and population examined.

Importantly, the contemporary evidence base builds upon foundational meta-analyses published in 2003. Branch [23] conducted a meta-analysis of 96 publications reporting 100 studies, examining the effects of creatine supplementation on body composition and exercise performance, including the influence of supplementation characteristics such as loading and maintenance protocols, exercise-task characteristics, and participant-related factors. Similarly, Nissen et al. [24] investigated the effects of dietary supplements on lean mass and strength gains during resistance exercise, identifying creatine and β-hydroxy-β-methylbutyrate (HMB) as the two supplements with sufficient evidence supporting improvements in these outcomes. These publications represent important contributions to the early quantitative synthesis of creatine-related evidence and remain relevant to understanding the historical development of this research field. Nevertheless, the objective of the present umbrella review was to provide a synthesis of contemporary systematic reviews and meta-analyses published within the 20-year period preceding the search, from September 2006 to September 2026. This temporal delimitation was adopted for three reasons. First, it prioritises evidence syntheses conducted and reported within the modern era of systematic review methodology, following the widespread adoption of standardised conduct and reporting guidance, thereby ensuring a more homogeneous and critically appraisable evidence base. Second, it reflects the substantial expansion of creatine research beyond its traditional applications in exercise performance and resistance-training adaptations, encompassing additional populations and health-related outcomes, including ageing, clinical conditions, cognitive function, and safety. Third, the primary-trial

evidence underpinning the 2003 syntheses is not lost under this restriction, as pre-2006 trials remain extensively represented within the reviews included in this umbrella review. The restriction was therefore intended to define the contemporary scope of the evidence synthesis, rather than to suggest that earlier meta-analyses are methodologically unimportant or that their findings have necessarily been superseded. Accordingly, the foundational publications from 2003 are acknowledged as part of the historical evidence base, although they fall outside the predefined eligibility period of the present umbrella review.

Against this background, an overarching synthesis is warranted to determine what the totality of evidence supports across the major domains in which creatine supplementation has been investigated. An umbrella review provides an appropriate framework for integrating findings from existing systematic reviews and meta-analyses while simultaneously evaluating their methodological quality, the certainty of the underlying evidence, the consistency and magnitude of effects, and the extent to which overlap among primary studies may influence the apparent strength of the evidence base. Accordingly, the present umbrella review aimed to comprehensively synthesise the evidence from systematic reviews and meta-analyses on the effects of creatine supplementation across health and performance outcomes, while evaluating the methodological quality, certainty of evidence, and overlap of primary studies.

2. Materials and Methods

2.1. Study Design and Reporting Framework

This study was conducted as an umbrella review of systematic reviews with meta-analysis evaluating the effects of creatine supplementation in human populations. The review was conducted and reported in accordance with the Preferred Reporting Items for Overviews of Reviews (PRIOR) statement [25]. The methodological approach was designed to identify, appraise, and synthesise the available evidence from systematic reviews with meta-analysis across predefined outcome domains. The unit of inclusion and synthesis was the systematic review with meta-analysis, rather than the individual primary study. No supplemental primary studies were included outside the evidence contained within the eligible systematic reviews. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261501087).

Generative artificial intelligence tools, including ChatGPT (GPT-5.6; OpenAI, San Francisco, CA, USA), were used during manuscript preparation for language editing, structural refinement, drafting support, organisation of the manuscript, and conceptual development and refinement of Figures. Generative AI tools were not used to make autonomous study-eligibility decisions, independently determine review inclusion, extract or validate study data, perform statistical analyses, assess methodological quality or certainty of evidence, or independently verify the underlying evidence. The authors independently reviewed and verified all search strategies and selection decisions, extracted data, methodological assessments, quantitative results, citations and references, figure content, statistical values, and final wording, and accept full responsibility for the accuracy, integrity, and interpretation of the published content.

2.2. Eligibility Criteria

Only systematic reviews with a quantitative meta-analysis specifically evaluating the effects of creatine supplementation, alone or in the context of concomitant exercise or training, were eligible for inclusion in this umbrella review. Eligible reviews were required to evaluate creatine supplementation in human populations, to have used systematic methods to identify and select relevant studies, and to provide at least one

quantitative meta-analytic estimate specifically attributable to creatine supplementation. Reviews were required to have been published in English within the predefined 20-year period covered by the umbrella review. No restrictions were imposed on participant age, sex, training status, health or clinical condition, exercise modality, or outcome domain, provided that the review addressed the effects of creatine supplementation within the predefined scope of the review. The eligibility assessment was informed by seven predefined thematic outcome domains used to guide the identification and classification of potentially relevant meta-analyses. Accordingly, network meta-analyses comparing multiple dietary supplements were eligible only when a pooled estimate separately attributable to creatine supplementation could be obtained; multi-supplement syntheses not meeting this condition were excluded at the full-text stage.

The intervention of interest was creatine supplementation, considered both as a standalone intervention and when administered in conjunction with exercise or training programmes. Reviews evaluating creatine alone, creatine combined with exercise or training, or creatine as part of a multi-ingredient intervention were considered eligible only when the quantitative effect specifically attributable to creatine supplementation could be isolated from the effects of exercise, training, or other interventions. Accordingly, reviews in which creatine was included but its independent quantitative effect could not be distinguished were excluded. Eligible comparators included placebo, no supplementation, no exercise, usual care, or otherwise comparable control conditions, according to the design of the original review. Reviews were eligible regardless of creatine dose, supplementation protocol, intervention duration, exercise modality, training status, or concomitant exercise or training programme. Reviews without a quantitative meta-analysis specific to creatine supplementation, narrative reviews, scoping reviews, expert reviews, protocols, guidelines, commentaries, and other non-meta-analytic evidence syntheses were excluded. No supplemental primary studies were included in the umbrella review.

2.3. Information Sources and Search Strategy

A systematic literature search was conducted in PubMed, Scopus, and Web of Science between 2 and 8 September 2026. The search covered the preceding 20 years and was restricted to English-language publications involving humans. A 20-year publication window was prespecified to capture contemporary systematic reviews and meta-analyses while limiting the inclusion of older evidence syntheses whose conclusions may have been superseded by more recent reviews. An initial search using the terms “creatine” and “meta-analysis” in the title and abstract fields was undertaken to identify the core body of evidence. The search strategy was subsequently broadened to maximise retrieval across the predefined health, performance, recovery, cognitive, and safety domains of the umbrella review. The final search strategy combined terms for the intervention, evidence-synthesis design, and predefined outcome domains. The intervention component included “creatine” and “creatine monohydrate”, while the evidence-synthesis component included “meta-analysis” and “metaanalysis”. The outcome component included terms related to strength and power, body composition and muscle mass, exercise performance and endurance, aerobic capacity, recovery and inflammation, cognition and mental health, and safety, renal, and biochemical outcomes. Population descriptors, including age, sex, athletic status, and specific clinical conditions, were not required search terms because these characteristics were used as eligibility criteria rather than as primary search concepts and could unnecessarily reduce retrieval sensitivity. Database-specific syntax, field restrictions, and filters were adapted to the requirements of each database while maintaining the same conceptual structure across sources. The complete database-specific search strategies, including the terms, fields, filters, and limits used in each database, are provided in Appendix A. The searches retrieved 273 records from PubMed, 210 from

Scopus, and 201 from Web of Science, yielding 684 records. Because the evidence-synthesis component required meta-analysis-related terms in searchable fields, reviews in which these terms did not appear in the title, abstract, or indexing fields, or in which different terminology was used, may not have been retrieved.

2.4. Study Selection

Following the database searches, duplicate records were removed before screening. The remaining records were independently screened by the three authors based on title and abstract. A total of 110 records were excluded for the following reasons: absence of a quantitative meta-analysis (n = 46), intervention not focused on creatine supplementation (n = 28), focus on creatine-related biomarkers or physiological outcomes (e.g., creatine kinase or creatinine) rather than creatine supplementation (n = 18), outside the predefined population or research scope (n = 12), and other eligibility reasons (n = 6). Records considered potentially eligible by at least one author were retained for full-text assessment. A total of 57 full-text reports were independently assessed by the three authors against the predefined inclusion and exclusion criteria. Twelve reports were excluded at this stage: four addressed creatinine-related outcomes rather than creatine supplementation, four evaluated supplements other than creatine, two did not provide a quantitative meta-analytic estimate specifically attributable to creatine supplementation, and two were outside the predefined scope of the umbrella review. The individual screening and eligibility decisions were subsequently compared during a consensus meeting, and disagreements were resolved through discussion and consensus. Reviews were not excluded because of overlap with other potentially eligible reviews. Primary-study overlap was assessed subsequently during data collection and synthesis using the citation matrix and the Corrected Covered Area (CCA), as described in Section 2.9 [26]. The final selection comprised 45 systematic reviews with quantitative meta-analysis. Figure 1 presents the study selection process in the PRISMA 2020 flow diagram [25].

2.5. Data Collection Process

Data were extracted independently by the three authors using a predefined and standardised data collection form. Each author independently extracted the relevant information from the included systematic reviews with meta-analysis, and the resulting datasets were subsequently compared. Potential discrepancies identified during data extraction were discussed in a consensus meeting involving all three authors and resolved by agreement. Data were extracted from the reports of the included systematic reviews with meta-analysis and organised in a structured database for subsequent synthesis. Information required to characterise the reviews, populations, interventions, comparators, outcomes, quantitative results, methodological quality, risk of bias, reporting bias, certainty of evidence, and primary-study overlap was collected [26]. Quantitative effect estimates were extracted only when they represented an effect specifically attributable to creatine supplementation. For reviews evaluating multiple supplements or nutritional interventions, including network meta-analyses, only estimates comparing creatine supplementation (alone or combined with exercise or training) with placebo or a non-creatine control were extracted. Depending on the review, these estimates corresponded to creatine-specific subgroup analyses, pairwise meta-analytic estimates from the creatine subset of trials, or network estimates for the creatine node versus placebo. Head-to-head comparisons between creatine and other supplements were not extracted. During data collection, the primary studies included in each systematic review with meta-analysis were identified and harmonised to construct the citation matrix. Multiple publications, reports, follow-up assessments, or intervention arms originating from the same underlying randomised controlled trial were consolidated into a single primary-study unit. Discrepancies in the

identification of primary studies across reviews were resolved through cross-checking of study characteristics and, where necessary, the original reports and reference lists. The procedures used to quantify primary-study overlap are described in Section 2.9.

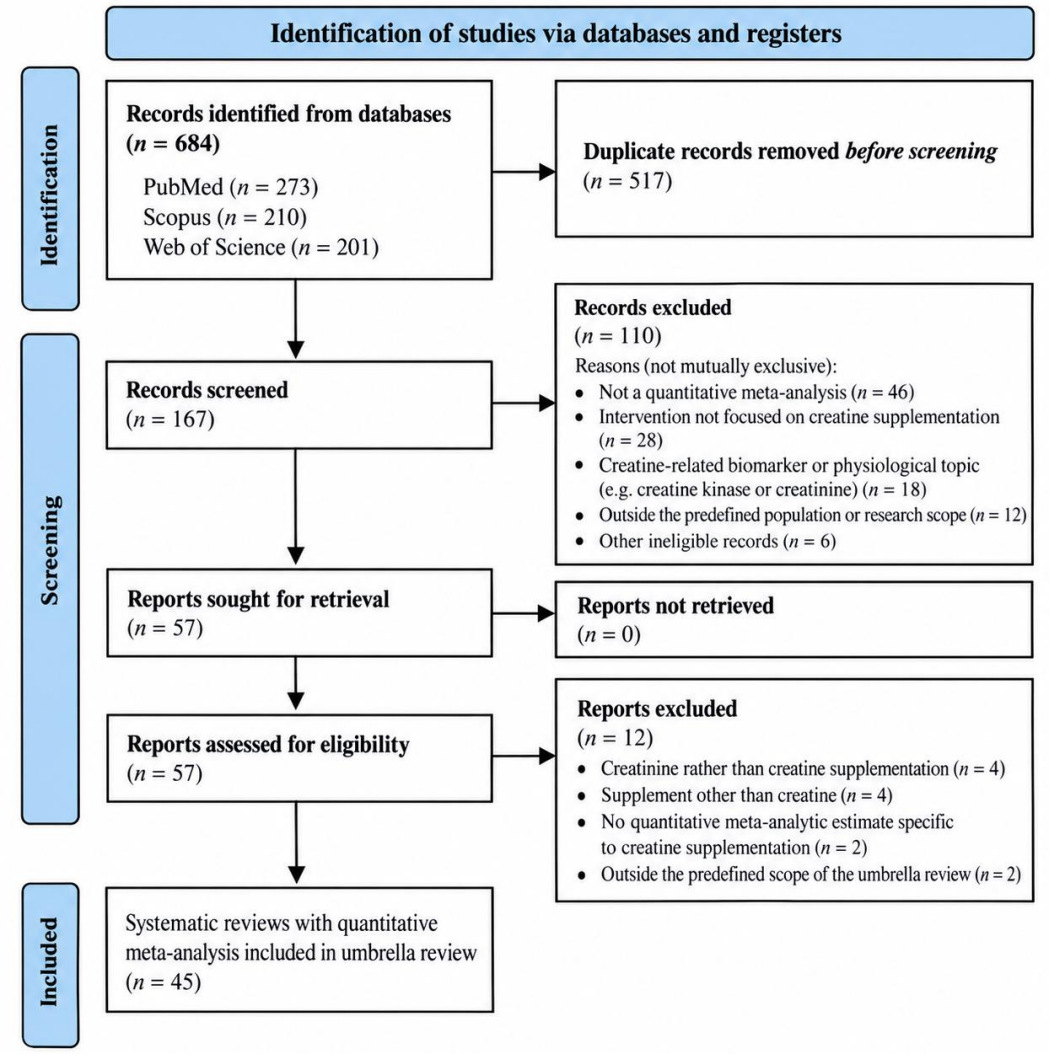


Figure 1. PRISMA 2020 flow diagram of the identification, screening, eligibility assessment, and inclusion of systematic reviews with meta-analysis.

2.6. Data Items

A predefined data collection framework was used to extract information from each included systematic review with meta-analysis. Data items were organised into five broad categories: characteristics of the review; characteristics of the populations, interventions and comparators; quantitative outcome data; methodological and reporting characteristics; and information required for assessment of primary-study overlap. Review characteristics included first author, publication year, journal, number of primary studies included in the systematic review, number of participants, population characteristics, principal thematic domain, protocol registration status, and funding sources or conflicts of interest reported by the systematic review. Information on the interventions included the type of creatine supplementation, dosage, loading and maintenance protocols (when reported), duration of supplementation, and concomitant exercise or training programmes. Comparator characteristics were also recorded.

For each outcome, the extracted quantitative information included the outcome definition, number of primary studies and participants contributing to the meta-analysis,

effect measure, pooled effect estimate specifically attributable to creatine supplementation, corresponding measure of precision (95% confidence interval or credible interval, as applicable), direction of effect, statistical significance, and measures of statistical heterogeneity when reported. Subgroup analyses, sensitivity analyses, and other relevant secondary analyses reported by the systematic reviews were also recorded. Methodological and reporting characteristics included the risk-of-bias or methodological appraisal tool used by each systematic review, assessments of reporting or publication bias and small-study effects, and the certainty of evidence, including GRADE ratings when reported [27].

For assessment of primary-study overlap, the primary studies included in each systematic review with meta-analysis were recorded together with relevant identifying characteristics, including author, publication year, sample size, intervention characteristics, population, and other trial identifiers when available. Multiple reports arising from the same underlying randomised controlled trial were subsequently consolidated as described in the assessment of primary-study overlap. When information was not reported, this was recorded as "not reported" rather than inferred. Where information was unclear or inconsistent within a systematic review, the relevant report was re-examined, and the discrepancy was discussed among the three authors during the data verification process. Unclear information was not replaced with assumptions or estimates that were not provided by the original review.

2.7. Predefined Outcome Domains and Thematic Classification

The scope of the umbrella review was structured a priori around seven predefined thematic domains reflecting the principal areas in which the effects of creatine supplementation have been investigated: (1) strength and power; (2) body composition; (3) population-specific outcomes; (4) dose–response and safety; (5) recovery and inflammation; (6) endurance and VO_2max; and (7) cognitive and mental health. These domains were used to guide the classification of the included systematic reviews and to organise data extraction and subsequent evidence synthesis. Each included systematic review was assigned to a single primary thematic domain according to its principal outcome focus and the main question addressed by the review. The seven domains were therefore mutually exclusive at the systematic-review level, allowing the 45 included reviews to be classified into a single primary thematic cluster. Individual systematic reviews could evaluate multiple outcomes and quantitative meta-analyses; however, these analyses remained within the primary thematic domain assigned to the corresponding review.

Quantitative meta-analyses reported within each systematic review were subsequently extracted and synthesised according to their specific outcome, population, intervention, comparator, and analytical characteristics. Thus, thematic classification was performed at the systematic-review level, whereas quantitative effect estimates were retained and analysed at the individual meta-analysis and outcome level. This approach preserved the methodological and clinical characteristics of the original evidence syntheses while allowing results addressing distinct outcomes to be examined separately. The predefined domains provided a structured framework for the synthesis while preserving differences in population, intervention, comparator, outcome definition, and analytical approach across the included meta-analyses. Findings were therefore interpreted within their respective thematic domains rather than being combined into a single overall estimate of the effect of creatine supplementation.

2.8. Assessment of Methodological Quality and Risk of Bias

The methodological quality of the included systematic reviews with meta-analysis was assessed using the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews 2) instrument [28]. AMSTAR-2 comprises 16 items addressing key methodological aspects

of systematic reviews, including protocol registration, adequacy of the literature search, duplicate study selection and data extraction, assessment of risk of bias in the included primary studies, appropriateness of the meta-analytical methods, consideration of publication bias, and disclosure of potential conflicts of interest (Supplementary Data S1). Overall confidence in the methodological quality of each systematic review was rated as high, moderate, low, or critically low according to the AMSTAR-2 guidance, based on the presence and severity of weaknesses across its critical domains. No numerical summary score was calculated. AMSTAR-2 assessments were initially performed by one researcher and subsequently reassessed independently and in full by the other two authors, who were unaware of the initial ratings. Discrepancies between the independent appraisals were discussed among the three authors and resolved by consensus. Information on the risk of bias of the primary studies included in each systematic review was extracted as reported by the corresponding review. The risk-of-bias assessment tool used by each systematic review and the resulting assessments were recorded. Primary studies were not reassessed independently within the present umbrella review. When risk-of-bias information was incomplete or unavailable in an included review, this was recorded accordingly rather than inferred or reassessed [28,29].

2.9. Assessment of Primary-Study Overlap Across Meta-Analyses

Primary-study overlap across the included systematic reviews was assessed using a citation matrix and the Corrected Covered Area (CCA) index [26]. The citation matrix was constructed with unique primary studies represented as rows and the 45 included systematic reviews represented as columns. Each cell indicated whether a given primary study was included in the corresponding systematic review. Multiple publications, follow-up reports, or intervention arms originating from the same underlying randomised controlled trial were consolidated into a single primary-study unit before calculation of the overlap measures. Primary studies were identified and harmonised across reviews using author, year, sample characteristics, intervention, population, and, where available, trial identifiers.

The CCA was calculated according to the following formula: $CCA = (N - r)/(rc - r)$, where N represents the total number of study–review inclusions in the citation matrix, including repeated appearances of the same primary studies across different reviews; r represents the number of unique primary studies; and c represents the number of systematic reviews included in the matrix. Thus, the global CCA was calculated using the complete matrix of included systematic reviews rather than the number of individual quantitative meta-analyses. This approach follows the established CCA methodology, in which primary publications are represented in rows and systematic reviews in columns.

For the present umbrella review, the global matrix comprised 1001 study–review inclusions, 395 unique primary studies, and 45 systematic reviews, resulting in a global CCA of 3.49%. Because a global CCA may mask substantial variation in overlap across individual reviews and outcome domains, pairwise overlap and study-level reuse were also examined descriptively. These analyses were used to identify systematic reviews drawing on substantially overlapping sets of primary studies and to inform the interpretation of apparent concordance across evidence syntheses. Accordingly, concordant findings across reviews were not considered independent replications when the underlying primary studies substantially overlapped. The complete citation matrix, pairwise overlap estimates, and CCA calculations are provided in the Supplementary Data S2. Overlap was treated as an interpretive characteristic of the evidence base and was not used as an exclusion criterion.

2.10. Synthesis Methods

The findings were synthesised descriptively and comparatively across the included meta-analyses, without re-pooling primary study data or performing a new meta-analysis of the estimates reported by the included reviews [30]. Results were organised according to the seven predefined thematic outcome domains and examined at the level of the individual meta-analysis and outcome. For each outcome, the pooled effect estimate specifically attributable to creatine supplementation was extracted together with its corresponding measure of precision, direction of effect, statistical significance, and measure of statistical heterogeneity when available [30,31]. Effect estimates were retained in the metric reported by the original meta-analysis, including mean differences, weighted mean differences, standardised mean differences, Hedges' g, odds ratios, and other reported effect measures. Results from frequentist and Bayesian meta-analyses were retained according to the analytical framework of the original meta-analysis, with credible intervals reported for Bayesian estimates where applicable [32].

Where multiple meta-analyses evaluated the same or closely related outcomes, their findings were compared with respect to the direction and magnitude of the reported effects, statistical significance, and heterogeneity [33]. No statistical transformation or recalculation of effect estimates was undertaken solely to enable direct pooling across meta-analyses using different effect measures or analytical models. Reported subgroup analyses were extracted and considered when they examined differences according to relevant characteristics such as age, sex, training status, population, intervention dose or duration, or other reported moderators. Potential sources of heterogeneity identified within the original meta-analyses were recorded and summarised where reported. Sensitivity analyses reported by the original meta-analyses were extracted and considered as part of the evidence synthesis; no additional sensitivity analyses were conducted in the present umbrella review [31,33].

When multiple systematic reviews addressed the same or closely related outcome, the interpretation of their findings was informed by a predefined hierarchy of methodological and evidential characteristics. The review providing the most reliable synthesis was considered the principal basis for interpretation. Priority was given first to the AMSTAR-2 confidence rating and, when reviews had similar ratings, to the recency and comprehensiveness of the evidence base, the relevance of the population, intervention, comparator and outcome characteristics, and the extent to which risk of bias and heterogeneity were considered in the synthesis. The degree of primary-study overlap between reviews was also considered when interpreting apparent concordance or discordance.

This prioritisation was used to guide interpretation rather than to exclude eligible evidence. All included reviews were retained in the evidence map and considered in the assessment of consistency. Reviews addressing the same outcome but providing a less methodologically robust or substantially overlapping synthesis were interpreted as corroborative evidence rather than as independent replications of the findings of the principal review. Conversely, concordant findings across reviews with limited overlap were considered more informative regarding the robustness of an observed association. The prioritisation criteria were applied at the outcome level and, where appropriate, within specific population or intervention contexts. The synthesis prioritised the results of quantitative meta-analyses specifically attributable to creatine supplementation while preserving differences in populations, interventions, comparators, outcome definitions, analytical methods, and statistical heterogeneity across reviews. Results were not collapsed into a single pooled estimate across meta-analyses, and statistical significance was not used as the sole criterion for assessing consistency across the evidence base [34].

2.11. Assessment of Reporting Bias and Small-Study Effects

Information on reporting bias and small-study effects was extracted from the included meta-analyses. Where reported, assessments included funnel plot asymmetry, Egger's regression test, Begg's test, trim-and-fill procedures, and other statistical or graphical methods used by the original meta-analyses to investigate potential small-study effects or missing results. The corresponding statistical results and conclusions reported by the original meta-analyses were recorded for the relevant outcomes [35]. No new analyses of reporting bias or small-study effects were conducted within the present umbrella review. When multiple assessments of reporting bias were available for different outcomes or subgroups within the same meta-analysis, these were recorded separately for the corresponding outcome. Findings suggesting possible reporting bias or small-study effects were considered alongside the reported effect estimates, statistical heterogeneity, methodological quality of the corresponding systematic review, and certainty of evidence. Reporting-bias assessments were not used in isolation to determine the consistency of the evidence [35,36].

2.12. Assessment of Certainty of Evidence

Certainty of evidence was extracted from the included systematic reviews with meta-analysis when formally assessed and reported [27]. The certainty ratings assigned by the original reviews, including assessments based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, were recorded for each relevant outcome. No independent recalculation or reassessment of certainty of evidence was performed within the present umbrella review. When certainty assessments were available for specific outcomes, the reported rating was retained alongside the corresponding meta-analytic estimate and other relevant methodological characteristics [17,27]. Certainty ratings were not aggregated across outcomes or reviews; instead, they were presented at the outcome level to preserve differences in populations, interventions, comparators, heterogeneity, risk of bias, imprecision, and other considerations underlying the original assessments. When certainty of evidence was not reported by an included meta-analysis, this was recorded as "not reported".

3. Results

A total of 45 systematic reviews and meta-analyses published between 2009 and 2026 were identified as eligible for inclusion in the present umbrella review. The included reviews examined the effects of creatine supplementation, predominantly compared with placebo or an otherwise comparable control condition, across a broad range of health and performance outcomes. The evidence was organised into seven thematic clusters: (1) strength and power (11 reviews); (2) body composition (six reviews); (3) population-specific outcomes (13 reviews); (4) safety and physiological responses (six reviews); (5) recovery and inflammation (four reviews); (6) endurance/VO_2max (two reviews); and (7) cognitive and mental health outcomes (three reviews). The distribution of included reviews according to publication year and thematic cluster is presented in Figure A1.

3.1. Selection and General Characteristics of the Included Meta-Analyses

Thirty-seven reviews (82.2%) were published from 2021 onwards. The number of primary studies included in individual reviews ranged from four to 143, and the number of participants ranged from 151 to 3655. The populations examined included elite and recreational athletes, healthy trained and untrained adults, older adults, postmenopausal women, and clinical populations, including individuals with chronic obstructive pulmonary disease and heart failure. Creatine monohydrate was the predominant form of

supplementation. Primary studies used different dosing regimens, including loading and maintenance protocols, as well as varying intervention durations. Risk-of-bias assessment methods differed across reviews and included the PEDro scale, Cochrane Risk of Bias 2 (RoB 2), the original Cochrane Risk of Bias tool, CONSORT, Jadad, Downs and Black, SIGN, and combinations with instruments such as the Newcastle–Ottawa Scale and the Joanna Briggs Institute tool. Six reviews included multiple supplements or nutritional interventions [6,7,35–38]. For the present umbrella review, only comparisons involving creatine supplementation alone versus placebo or an otherwise comparable control condition were extracted; creatine combined with other supplements and creatine derivatives were excluded. The main characteristics of the included reviews are presented in Table 1. The distribution of reviews by publication year and thematic cluster is shown in Appendix Figure A1.

Table 1. Characteristics of the 45 systematic reviews and meta-analyses included.

Cluster	Review	Population	No. Studies	No. Participants	Design	AMSTAR-2	Main Outcomes	Risk-of-Bias Tool
Population-specific outcomes	Al-Ghimlas et al. [12]	Adults with COPD undergoing pulmonary rehabilitation	4	151	MA	Critically low (Q2, Q7)	Exercise capacity, strength, quality of life	Cochrane
Dose–response and safety	Lopez et al. [11]	Physically active individuals	10	167	MA	Critically low (Q2, Q7)	Body temperature, hydration in heat	PEDro
Population-specific outcomes	Devries et al. [9]	Adults >45 yr undergoing resistance training	10	357	MA	Critically low (Q2, Q7)	FFM, strength, physical function	Jadad
Strength and power	Lanhers et al. [37]	Healthy adults	60	1297	MA	Critically low (Q2, Q7, Q9)	Lower-limb strength	CONSORT
Strength and power	Lanhers et al. [38]	Healthy adults	53	1138	MA	Critically low (Q2, Q7, Q9)	Upper-limb strength	CONSORT
Population-specific outcomes	Mielgo-Ayuso et al. [8]	Football players	9	168	MA	Critically low (Q2, Q7, Q15)	Anaerobic and aerobic performance	Cochrane
Dose–response and safety	de Souza et al. [14]	General population, healthy and clinical	26	497	MA	Critically low (Q2, Q7)	Serum creatinine, creatinine clearance, urea	PEDro/JBI
Dose–response and safety	de Guingand et al. [13]	Post-menarche females	29	951	MA	Low (Q7)	Safety, adverse events	Cochrane Handbook
Population-specific outcomes	Forbes et al. [39]	Adults >50 yr, with or without chronic disease	20	NR	MA	Critically low (Q2, Q7)	Lean mass, strength	NR
Population-specific outcomes	Dos Santos et al. [4]	Older/postmenopausal women undergoing resistance training	10	211	MA	Low (Q7)	Strength, muscle mass	PEDro
Population-specific outcomes	Choi et al. [40] §	Adults ≥60 yr undergoing resistance training plus nutrition	22	NR	NMA	Low (Q7)	LBM, strength, physical function	RoB 2

Recovery and inflammation	Jiaming et al. [21]	Young healthy adults	9	630	MA	Critically low (Q2, Q7)	CK, LDH, exercise-induced muscle damage	Cochrane
Recovery and inflammation	Northeast et al. [20]	Adults	13	278	MA	Low (Q7)	Strength, DOMS, CK, LDH	Cochrane
Body composition	Delpino et al. [41]	Healthy adults	35	1192	MA	Low (Q7)	Lean mass	Cochrane
Recovery and inflammation	Doma et al. [10]	Trained healthy adults	23	469	MA	Critically low (Q2, Q7)	Muscle damage, inflammation, oxidative stress, DOMS	Modified PEDro
Strength and power	Glaister et al. [42]	Young trained adults	14	NR	MA	Low (Q7)	Repeated-sprint power	PEDro
Body composition	Burke et al. [2]	Healthy adults, young and older, undergoing resistance training	10	NR	MA	Low (Q7)	Regional muscle hypertrophy	Modified Downs and Black
Body composition	Candow et al. [43]	Adults <50 yr undergoing resistance training	12	266	MA	Critically low (Q7)	Body-fat percentage, fat mass	RoB 2
Endurance/VO_2max	Fernández-Landa et al. [5]	Trained/elite athletes	13	277	MA	Low (Q7)	Endurance performance	PEDro
Endurance/VO_2max	Gras et al. [44]	Healthy adults and patients with heart failure	19	424	MA	Critically low (Q2, Q7)	VO_2max, ventilatory threshold	SIGN/PEDro
Cognitive and mental health	Prokopidis et al. [45]	Healthy individuals	8	225	MA	Low (Q7)	Memory	RoB 2
Population-specific outcomes	Davies et al. [19]	Older adults and adults with chronic disease at risk of disability	33	1076	MA	Low (Q7)	Physical function, strength, lean mass	Cochrane
Body composition	Desai et al. [3]	Healthy non-athletes undergoing resistance training	12	362	MA	Low (Q7)	LBM, body-fat percentage, fat mass	RoB 2
Body composition	Pashayee-Khamene et al. [17]	Healthy adults	143	3655	MA	Critically low (Q2, Q7)	Body mass, FFM, FM, body-fat %, BMI	Cochrane
Strength and power	Wang et al. [46]	Adults <50 yr undergoing resistance training	23	509	MA	Low (Q7)	Upper- and lower-limb strength	PEDro
Population-specific outcomes	Huang et al. [47]	Swimmers	17	361	MA	Critically low (Q2, Q7)	Swimming performance, physiological responses, body composition	PEDro
Cognitive and mental health	Xu et al. [22]	Healthy adults and adults with specific diseases	16	492	MA	Low (Q7)	Overall cognition, memory, executive function, attention, processing speed	RoB 2

Body composition	Ashtary-Larky et al. [1]	Adults undergoing resistance training	61	1457	MA	Low (Q7)	FFM, body mass, FM, body-fat %, BMI	RoB 2
Strength and power	Kazeminasab et al. [48]	Adults with or without metabolic disease	69	1937	MA	Moderate	Strength, jump, power	PEDro
Strength and power	Zhang et al. [49]	General population	14	523	MA	Low (Q7)	Muscle strength	Cochrane
Dose–response and safety	Naeini et al. [16]	General population	21	NR	MA	Critically low (Q2, Q7)	Serum creatinine, GFR	RoB 2/NOS
Population-specific outcomes	Sharifian et al. [50]	Adults ≥55 yr undergoing exercise training	20	1093	MA	Low (Q7)	1RM, body-fat %, BMD	PEDro/RoB 2
Population-specific outcomes	Domínguez et al. [7] §	Competitive swimmers	23	422	MA	Critically low (Q2, Q7)	Swimming performance	PEDro/Cochrane
Strength and power	Luo et al. [6] §	Elite combat-sport athletes	67	1026	NMA	Moderate	Mean/peak power, lactate	Cochrane
Strength and power	Luo et al. [51] §	Football players	80	1425	NMA	Moderate	Jump, sprint, power, distance	Revised Cochrane
Cognitive and mental health	Eckert et al. [52]	Individuals with or without depression	11	1093	MA	Low	Depressive symptoms, remission, treatment response	RoB 2
Strength and power	Bai et al. [53] §	Physically active adults and trained/competitive athletes	52	NR	NMA	Critically low (Q2, Q7)	Anaerobic performance (sprint, jump, repeated-sprint ability, muscular endurance)	PEDro
Strength and power	Gu et al. [18]	Healthy men aged 18–30 yr	37	NR	MA	Critically low (Q7)	1RM, FFM/LBM, Wingate power, CMJ	RoB 2
Population-specific outcomes	Naddafha et al. [15]	Postmenopausal women	7	608	MA	Critically low (Q2, Q7)	Lean mass, strength, BMD	RoB 2
Recovery and inflammation	de Camargo et al. [54]	General population	8	NR	MA	Low (Q7)	CRP, IL-6	RoB 2
Dose–response and safety	Tsiaras et al. [55]	Adults, healthy/physically active	20	786	MA	Low (Q7)	Serum creatinine, urea, eGFR	RoB 2
Dose–response and safety	de Souza Almeida et al. [56]	Healthy adults and patients with CKD	26	1036	MA	Low (Q7)	Serum creatinine, GFR, urea, albuminuria, proteinuria, urinary creatinine	RoB 2
Strength and power	Wang et al. [57] §	Trained athletes and active individuals	35	1211	NMA	Critically low (Q2)	Strength, endurance, recovery	RoB 2
Population-specific outcomes	Yao et al. [58]	Adults ≥60 yr undergoing resistance training	11	NR	MA	Low (Q7)	Muscle strength, muscle mass,	ROBUST-RCT

							physical function	
Population-specific outcomes	Lin et al. [59]	Females engaged in exercise/training	34	692	MA	Critically low (Q2, Q7)	Exercise performance, body composition, physiological outcomes	RoB 2

Note: All included papers were systematic reviews with a quantitative meta-analysis, as a pooled estimate attributable to creatine was an eligibility criterion; no systematic review without meta-analysis was included. MA, pairwise meta-analysis; NMA, network meta-analysis. AMSTAR-2 critical items: Q2, protocol registered before commencement of the review; Q4, adequacy of the literature search; Q7, list of excluded studies with justification; Q9, risk-of-bias assessment of included studies; Q11, appropriateness of meta-analytical methods; Q13, consideration of risk of bias when interpreting results; Q15, assessment of publication bias. BMD, bone mineral density; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; CRP, *C*-reactive protein; DOMS, delayed-onset muscle soreness; FFM, fat-free mass; FM, fat mass; GFR/eGFR, glomerular filtration rate/estimated glomerular filtration rate; IL-6, interleukin-6; LBM, lean body mass; NR, not reported; RoB, risk of bias; RCT, randomised controlled trial; RSA, repeated-sprint ability; 1RM, one-repetition maximum; VO_2max, maximal oxygen uptake. § Multi-supplement review or network meta-analysis; only the estimate specifically attributable to creatine supplementation (alone or with exercise or training) versus placebo or control was extracted.

3.2. Strength and Power

The strength and power cluster comprised 11 systematic reviews and meta-analyses and represents the domain in which the evidence showed the greatest overall convergence. Across healthy adults, resistance-trained individuals, physically active populations, and sport-specific cohorts, creatine supplementation was consistently associated with improvements in maximal muscular strength, particularly in upper- and lower-body multi-joint exercises. This pattern was evident across both earlier and more recent evidence syntheses, with favourable effects reported for squat, leg-press, bench-press, and chest-press performance and generally low statistical heterogeneity for the principal strength outcomes [37,38,46,48]. The persistence of this effect across successive meta-analyses, despite differences in participant characteristics and training protocols, strengthens the inference that the strength-enhancing effect of creatine is robust rather than dependent on a particular generation of trials. At the same time, the magnitude of the strength response does not appear to be uniform across individuals or performance tests. Evidence from subgroup analyses suggests that training status may influence responsiveness, with larger effects observed in untrained than in trained participants [49]. However, these differences should be interpreted cautiously, as subgroup estimates are based on fewer studies and may reflect differences in participant characteristics, training exposure, or other between-study factors rather than a true modification of the creatine effect. Similarly, the most recent meta-analysis restricted to healthy men aged 18–30 years reported moderate-certainty evidence for an increase in squat 1RM, while no significant effect was observed for leg-press 1RM and the certainty for this outcome was low [18]. Thus, the consistency of the overall strength signal should not be interpreted as evidence that creatine improves every measure of muscular strength to the same extent.

The evidence for power is directionally consistent with that for strength but appears more dependent on the specific characteristics of the task. Across the available meta-analyses, creatine supplementation improved repeated-sprint mean power, jumping performance, repeated-sprint ability, upper-limb muscular endurance, and Wingate peak and mean power [18,42,48,53]. However, null findings for selected outcomes, including

repeated-sprint peak power and some measures of jumping or strength performance, indicate that the effect is not equally expressed across all tests. This task specificity is further illustrated by sport-specific analyses, in which relatively large effects were observed for mean and peak power in elite combat-sport athletes, whereas in football players the evidence was more selective, with an improvement in jump height but no clear benefit for muscular strength [6,51]. Importantly, the convergence across strength and power outcomes is supported not only by statistical significance but also by the reproducibility of the direction of effect across different populations, analytical approaches, and generations of evidence synthesis. Nevertheless, the heterogeneity observed for selected power outcomes and the differences according to training status and task characteristics suggest that the effect is better understood as context- and task-dependent rather than universal. The direction of effects was generally consistent across reviews, particularly for activities requiring maximal force production and rapid or repeated high-intensity energy turnover. However, this convergence should be interpreted in light of the methodological limitations and primary-study overlap among the contributing reviews. The magnitude of benefit for specific exercises or sporting tasks remains less certain. This interpretation is consistent with the underlying role of the phosphocreatine system in rapidly regenerating ATP during high-intensity exercise and repeated bouts of muscular effort [2]. The quantitative findings for the principal strength and power outcomes are summarised in Table 2.

Table 2. Synthesis of the principal effects of creatine supplementation on strength and power outcomes.

Review	Population	n Studies	Outcome	Measure	Effect Estimate (95% CI)	*p*	I^2	Direction
Lanhers et al. [37]	Healthy adults	60	Squat 1RM	SMD	0.336 (0.047 to 0.625)	0.023	0%	Favourable
		60	Leg press	SMD	0.297 (0.098 to 0.496)	0.003	0%	Favourable
Lanhers et al. [38]	Healthy adults	53	Bench press 1RM	SMD	0.238 (0.098 to 0.377)	<0.001	0%	Favourable
		53	Chest press	SMD	0.289 (0.160 to 0.419)	<0.0001	2.4%	Favourable
Glaister et al. [42]	Young trained adults	14	Mean power, repeated sprints	SMD	0.61 (0.23 to 1.00)	0.002	27%	Favourable
		14	Peak power, repeated sprints	SMD	0.41 (−0.08 to 0.90)	0.10	75%	Neutral
Wang et al. [46]	Adults <50 years undergoing RT	23	Maximal upper-body strength	WMD (kg)	4.43 (3.12 to 5.75)	<0.001	0%	Favourable
		23	Maximal lower-body strength	WMD (kg)	11.35 (8.44 to 14.25)	<0.001	0%	Favourable
Kazeminasab et al. [48]	Adults, with/without metabolic disease	69	Bench/chest press	WMD (kg)	1.43 (0.53 to 2.34)	0.002	15.07%	Favourable
		69	Squat	WMD (kg)	5.64 (3.87 to 7.40)	<0.001	4.12%	Favourable
		69	Vertical jump	WMD (cm)	1.48 (0.30 to 2.66)	0.01	70.84%	Favourable
		69	Wingate peak power	WMD (W)	47.81 (15.55 to 80.06)	0.004	47.61%	Favourable
Zhang et al. [49]	General adult population	14	Overall muscle strength, post-intervention	SMD	0.43 (0.25 to 0.61)	<0.01	43%	Favourable

		6	Muscle strength, untrained subgroup	SMD	1.06 (0.67 to 1.45)	<0.01	52%	Favourable
		6	Muscle strength, trained subgroup	SMD	0.32 (0.00 to 0.63)	0.05	0%	Favourable
		6	Muscle strength, low-dose subgroup	SMD	0.88 (0.29 to 1.46)	<0.01	63%	Favourable
		3	Muscle strength, high-dose subgroup	SMD	0.24 (−0.16 to 0.65)	0.24	0%	Neutral
Luo et al. [6] (NMA)	Elite combat-sport athletes	67	Mean power (creatine)	SMD	1.0 (0.38 to 1.6) CrI	<0.05	0%	Favourable
		67	Peak power (creatine)	SMD	1.1 (0.45 to 1.7) CrI	<0.05	0%	Favourable
Luo et al. [51] (NMA)	Football players	80	Jump height (creatine)	SMD	0.33 (0.051 to 0.63) CrI	<0.05	NR	Favourable
		80	Muscle strength (creatine)	SMD	0.35 (−0.49 to 0.64) CrI	>0.05	NR	Neutral
Bai et al. [53] (NMA)	Active athletes/adults	52	Sprint <10 s	SMD	−0.64 (−1.27 to −0.01)	0.04	73.2%	Favourable †
		52	Jump height	SMD	0.33 (0.11 to 0.56)	0.002	14.8%	Favourable
		52	Repeated-sprint ability	SMD	−0.78 (−1.40 to −0.17)	0.01	24.7%	Favourable †
		52	Upper-limb muscular endurance	SMD	0.43 (0.09 to 0.77)	0.01	46.7%	Favourable
Wang et al. [57] (NMA)	Trained/active athletes	35	Muscle strength (creatine)	SMD	0.46 (0.29 to 0.63)	<0.001	38.6%	Favourable
Gu et al. [18]	Healthy men aged 18–30 years	16	Squat 1RM	MD (kg)	11.90 (7.60 to 16.20)	<0.001	43.1%	Favourable
		12	Leg press 1RM	MD (kg)	3.58 (−7.85 to 15.01)	0.539	39.1%	Neutral
		12	Wingate peak power	MD (W)	71.27 (38.09 to 104.45)	<0.001	13.8%	Favourable
		11	Wingate mean power	MD (W)	39.69 (15.83 to 63.56)	0.001	40.5%	Favourable
		11	Countermovement jump	MD (cm)	2.70 (0.18 to 5.21)	0.04	89%	Favourable

Abbreviations: CrI, 95% Bayesian credible interval; MD, mean difference; NMA, network meta-analysis; NR, not reported; RT, resistance training; SMD, standardised mean difference; WMD, weighted mean difference. † Negative SMDs for sprint and repeated-sprint ability indicate faster completion times and were therefore classified as favourable.

3.3. Body Composition

The body-composition cluster comprised six systematic reviews and meta-analyses and revealed a broadly consistent increase in lean or fat-free mass following creatine supplementation, although the magnitude and interpretation of this effect differed according to the presence of resistance training, participant characteristics, and the method used to assess muscle mass. These estimates are derived predominantly from indirect body-composition methods, such as dual-energy X-ray absorptiometry and bioelectrical impedance, rather than from direct imaging assessments of muscle cross-sectional area or volume.

Across the evidence base, the most reproducible finding was an increase in lean or fat-free mass, whereas evidence for reductions in fat mass or body-fat percentage was considerably less consistent (Table 3). Delpino et al. [41], for example, reported an overall increase in lean body mass of 0.68 kg, with a substantially greater effect when creatine was combined with resistance training (1.10 kg) and virtually no effect in the absence of exercise (0.03 kg). Similar findings were subsequently reported by Desai et al. [3] in non-athletic adults undertaking resistance training and by Pashayee-Khamene et al. [17] in a much larger evidence base of 143 studies, which identified increases in lean or fat-free mass with minimal statistical heterogeneity for the latter outcome. Ashtary-Larky et al. [1] further reinforced this pattern, reporting an overall increase of 1.39 kg in fat-free mass across 61 trials.

The consistency of these findings suggests that the effects of creatine on indirectly estimated lean mass are relatively consistent across analyses. However, these surrogate measures cannot distinguish gains in contractile tissue from increases in intracellular water. However, it also indicates that supplementation should be understood primarily as an adjunct to exercise-induced adaptation rather than as an independent stimulus for substantial increases in lean mass. The larger effect observed when creatine was combined with resistance training in Delpino et al. [41], together with the consistent benefits observed in resistance-training populations in subsequent reviews, supports the interpretation that the interaction between creatine availability and mechanical loading is an important component of the observed response. Nevertheless, the evidence does not indicate that this interaction is restricted to trained individuals. Ashtary-Larky et al. [1] reported increases in fat-free mass in both trained and untrained participants, although the estimated effect was numerically greater in trained individuals and the between-subgroup difference was not statistically significant. Thus, the available evidence supports a general increase in lean or fat-free mass, while leaving the extent to which training status modifies responsiveness unresolved.

Importantly, the magnitude of the increase in lean or fat-free mass should not be interpreted as being synonymous with skeletal muscle hypertrophy. This distinction becomes evident when the evidence is restricted to studies using direct imaging measures of regional muscle hypertrophy. Burke et al. [2], based on 10 studies, reported a pooled standardised effect of only 0.11 (95% CrI −0.02 to 0.25) for regional muscle hypertrophy, with a somewhat larger estimate in younger adults than in older adults. The discrepancy between the relatively consistent increases in whole-body lean or fat-free mass and the more modest evidence for directly measured regional hypertrophy suggests that changes in fat-free mass may encompass components beyond new contractile tissue. This is particularly relevant for creatine because supplementation can alter intracellular water distribution, meaning that increases in fat-free mass should not be interpreted mechanistically as equivalent to increases in skeletal muscle protein accretion. Accordingly, the current evidence provides stronger support for an increase in fat-free or lean mass than for a quantitatively equivalent increase in measured muscle hypertrophy. By contrast, the evidence for adiposity is less coherent. Some resistance-training studies reported reductions in body-fat percentage and, in the case of Desai et al. [3], a modest reduction in absolute fat mass; however, these findings were accompanied by substantial heterogeneity, particularly for body-fat percentage and fat mass. Candow et al. [43] similarly observed a reduction in body-fat percentage without a significant change in absolute fat mass, while Pashayee-Khamene et al. [17] found no significant effect on fat mass despite evidence of increased fat-free mass. This pattern argues against interpreting creatine as a direct fat-loss intervention. Rather, the apparent improvement in body-fat percentage may partly reflect changes in the relative composition of body mass associated with greater lean tissue, while evidence for an independent reduction in adipose tissue remains limited.

Table 3. Synthesis of the principal effects of creatine supplementation on body composition outcomes.

Review	Population	n Studies	Outcome	Measure	Effect Estimate (95% CI)	*p*	I^2	Direction
Delpino et al. [41]	Healthy adults	35	LBM, overall	MD (kg)	0.68 (0.26 to 1.11)	NR	0%	Favourable
		35	LBM, creatine + RT	MD (kg)	1.10 (0.56 to 1.65)	NR	0%	Favourable
		35	LBM, no exercise	MD (kg)	0.03 (−0.65 to 0.70)	NR	0%	Neutral
Burke et al. [2]	Adults undertaking RT	10	Regional muscle hypertrophy	SMD	0.11 (−0.02 to 0.25) CrI	0.961 ‡	NR †	Neutral
Candow et al. [43]	Adults <50 years undertaking RT	12	Body-fat percentage	MD (%)	−1.19 (−2.03 to −0.34)	0.006	0%	Favourable
		12	Fat mass	MD (kg)	−0.18 (−1.32 to 0.96)	0.76	0%	Neutral
Desai et al. [3]	Non-athletic adults undertaking RT	12	LBM	MD (kg)	1.14 (0.69 to 1.59)	<0.01	45.1%	Favourable
		12	Body-fat percentage	MD (%)	−0.88 (−1.66 to −0.11)	0.03	91.5%	Favourable
		12	Fat mass	MD (kg)	−0.73 (−1.34 to −0.11)	0.02	67.1%	Favourable
Pashayee-Khamene et al. [17]	Adults	143	FFM	WMD (kg)	0.82 (0.57 to 1.06)	<0.001	0%	Favourable
		143	Fat mass	WMD (kg)	0.05 (−0.24 to 0.35)	0.703	0%	Neutral
Ashtary-Larky et al. [1]	Adults undertaking RT	61	FFM, overall	WMD (kg)	1.39 (1.07 to 1.70)	<0.001	47%	Favourable
		61	FFM, trained	WMD (kg)	1.82 (1.10 to 2.55)	<0.001	14.4%	Favourable
		061	FFM, untrained	WMD (kg)	1.23 (0.91 to 1.56)	<0.001	0%	Favourable

Note. CrI, credible interval; FFM, fat-free mass; LBM, lean body mass; MD, mean difference; NR, not reported; RT, resistance training; SMD, standardised mean difference; WMD, weighted mean difference. † Burke et al. [2] reported Bayesian heterogeneity using τ; therefore, I^2 is not applicable. ‡ For Burke et al. [2], the value of 0.961 represents the posterior probability of a positive effect [P(effect > 0)], not a conventional *p*-value.

3.4. Population-Specific Outcomes

Within this domain, the population is the stratifying variable: reviews are organised into older adults and postmenopausal women, clinical populations, females engaged in exercise or training, and athletes and sport-specific cohorts, with outcomes presented in a consistent order within each group (strength, body composition, physical function, and other outcomes). This structure was retained because the primary question addressed by this domain is whether the effects of creatine generalise beyond young, healthy, predominantly male populations, which requires comparing the same outcomes across populations rather than the same population across outcomes.

Thirteen systematic reviews and meta-analyses examined the effects of creatine supplementation across older adults, clinical populations, postmenopausal women, females engaged in exercise or training, and sport-specific cohorts, providing an important extension of the evidence beyond the predominantly young and healthy populations traditionally represented in creatine research (Table 4). Overall, the findings suggest that the effects of creatine across population-specific outcome groups are broadly consistent with its established musculoskeletal actions, particularly for lean tissue and strength, but that the magnitude and certainty of benefit vary substantially according to age, health status, sex, training context, and outcome assessed. Among older adults, the evidence shows a relatively coherent pattern favouring creatine for lean mass, muscular strength, and selected measures of physical function, particularly when supplementation is combined with

resistance exercise. Earlier reviews reported increases in fat-free or lean mass together with improvements in leg-press strength and chair-stand performance [9,39], while subsequent analyses extended these findings to sit-to-stand performance and lean tissue mass in older adults and individuals at risk of functional impairment [19]. The creatine-specific analysis within Choi et al. [40] similarly reported increases in lean body mass and knee-extension strength among adults aged ≥60 years. Taken together, these findings indicate that the benefits observed in younger adults may extend to ageing populations and may be particularly relevant for maintaining or increasing the components of physical capacity most directly related to functional independence.

However, the evidence becomes less consistent when the outcome is moved from muscle mass and strength towards broader functional or structural outcomes. Yao et al. [58], for example, identified a moderate-certainty benefit for muscle strength in older adults undertaking resistance training, but no statistically significant effect on muscle mass or physical function, with low and very low certainty, respectively. Similarly, Sharifian et al. [50] reported an improvement in 1RM performance but no significant effect on total-body bone mineral density. These findings suggest that the most reproducible effects of creatine in older adults remain concentrated on muscle-related outcomes, whereas evidence for downstream functional or skeletal benefits is less established. This distinction is important because improvements in strength or lean mass may be clinically relevant, but they should not automatically be interpreted as evidence of reduced disability, improved mobility, or enhanced bone health. The contrast between ageing populations and specific clinical conditions further emphasises the importance of population context. In adults with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation, creatine did not significantly improve exercise capacity, lower-body strength, or quality of life [12]. Thus, the favourable effects observed in otherwise healthy older adults cannot simply be extrapolated to clinical populations with disease-specific limitations. The absence of benefit in COPD may indicate that the physiological determinants of exercise intolerance in chronic disease extend beyond the substrate availability and muscle energetics that can be influenced by creatine supplementation. More broadly, these findings argue against treating "older adults" and "clinical populations" as a homogeneous category and instead support a more phenotype-specific interpretation of responsiveness.

Evidence in women is increasingly available but remains comparatively less mature. In postmenopausal women, Naddafha et al. [15] reported a modest increase in lean mass and a meaningful improvement in leg-press 1RM, but no evidence of benefit for bone mineral density. Similarly, the broader synthesis by Lin et al. [59] involving females engaged in exercise or training found an overall favourable effect, with significant improvements in exercise or sport performance and body composition, whereas physiological outcomes were not significantly altered; importantly, certainty was rated low for the performance and body-composition outcomes and very low for physiological outcomes. These findings provide encouraging evidence that the benefits of creatine are not restricted to male populations, but the relatively low certainty indicates that sex-specific conclusions should remain cautious until larger, adequately powered trials become available. The sport-specific evidence further illustrates how the effect of creatine depends on the physiological demands of the activity. In football players, creatine improved overall anaerobic performance and Wingate performance but had no effect on aerobic performance [8], whereas in competitive swimmers one meta-analysis reported faster time-trial completion but another found no significant differences in single-sprint performance, repeated-interval performance, physiological responses, or body composition [7,47]. This apparent inconsistency is unlikely to reflect a simple contradiction in the biological effects of creatine. Rather, it highlights the importance of task specificity, with potential benefits more likely to emerge when performance depends on repeated high-intensity efforts, anaerobic

power, or the ability to reproduce force and power over multiple bouts. The heterogeneity across sport-specific outcomes therefore reinforces the interpretation developed for the broader strength and power literature: creatine is unlikely to enhance all components of sport performance to the same degree.

An important feature of the evidence in specific populations is therefore the distinction between generalisation of direction and generalisation of magnitude. Across older adults, postmenopausal women, female exercisers, and several athletic populations, the direction of effects for strength, lean tissue, or selected performance outcomes is generally favourable. However, the magnitude of benefit and its practical relevance vary considerably, while outcomes such as bone mineral density, aerobic performance, quality of life, and broader physiological responses frequently remain null or uncertain. Accordingly, the evidence does not support a single population-wide effect of creatine; instead, it suggests that responsiveness is strongly conditioned by the interaction between the individual's physiological phenotype, the training stimulus, and the outcome being measured.

Table 4. Synthesis of the principal effects of creatine supplementation in specific populations.

Review	Population	n Studies	Outcome	Measure	Effect Estimate (95% CI)	*p*	I^2	Direction
Older adults and postmenopausal women								
Devries et al. [9]	Adults >45 years undergoing RT	10	FFM	MD (kg)	1.33 (0.79 to 1.86)	<0.001	75%	Favourable
		10	Leg press 1RM	MD (kg)	3.25 (0.47 to 6.03)	0.02	42%	Favourable
		10	Chair-stand, 30 s	MD (repetitions)	1.93 (0.19 to 3.67)	0.03	62%	Favourable
Forbes et al. [39]	Adults >50 years	20	Lean mass	MD (kg)	1.32 (0.93 to 1.72)	<0.001	23%	Favourable
		20	Chest press	SMD	0.28 (0.09 to 0.47)	0.004	0%	Favourable
		20	Leg press	SMD	0.20 (0.00 to 0.39)	0.05	28%	Favourable
Dos Santos et al. [4]	Older women undergoing RT	10	Upper-body strength	SMD	0.35 (0.02 to 0.69)	0.04	0%	Favourable
		10	Muscle mass	SMD	0.24 (−0.10 to 0.59)	0.16	0%	Neutral
Choi et al. [40] (NMA)	Adults ≥60 years; creatine-specific subgroup	5 ‡	LBM	MD (kg)	2.61 (0.51 to 4.72)	<0.05	9%	Favourable
		5 ‡	Knee extension	SMD	0.74 (0.09 to 1.38)	<0.05	7%	Favourable
Davies et al. [19]	Older adults/clinical populations	33	Sit-to-stand	SMD	0.51 (0.01 to 1.00)	0.04	62%	Favourable
		33	Lean tissue mass	MD (kg)	1.08 (0.77 to 1.38)	<0.01	26%	Favourable
Naddafha et al. [15]	Postmenopausal women	7	Lean mass	MD (kg)	0.37 (0.05 to 0.69)	0.05	25%	Favourable
		7	Leg press 1RM	MD (kg)	7.5 (2.2 to 12.8)	<0.05	0%	Favourable
		7	Bone mineral density	MD (g/cm^2)	≈0.00 (CI crosses null)	NS	NR	Neutral
		20	1RM strength	MD	2.122	0.001	0%	Favourable

Sharifian et al. [50]	Adults ≥55 years undergoing exercise training	20	Body-fat percentage	MD (%)	−0.548	0.026	0%	Favourable
		20	Bone mineral density	MD	0.009	0.557	41%	Neutral
Yao et al. [58]	Adults ≥60 years undergoing resistance training	11	Muscle strength	Hedges' g	0.31 (0.18 to 0.45)	NR	NR	Favourable
		11	Muscle mass	Hedges' g	0.35 (−0.09 to 0.78)	NR	NR	Neutral
		11	Physical function	Hedges' g	0.47 (−0.08 to 1.03)	0.086	NR	Neutral
Clinical populations								
Al-Ghimlas et al. [12]	Adults with COPD undergoing pulmonary rehabilitation	4	Exercise capacity	SMD	−0.01 (−0.42 to 0.22)	NS	0%	Neutral
Females engaged in exercise or training								
Lin et al. [59]	Females engaged in exercise/training	34	Overall effect	Hedges' g	0.23 (0.09 to 0.37)	0.003	70.95 %	Favourable
		21 †	Exercise performance	Hedges' g	0.30 (0.06 to 0.54)	0.019	NR	Favourable
		21 #	Body composition	Hedges' g	0.24 (0.06 to 0.43)	0.011	NR	Favourable
		21 #	Physiological outcomes	Hedges' g	0.10 (−0.17 to 0.38)	0.361	NR	Neutral
Athletes and sport-specific cohorts								
Mielgo-Ayuso et al. [8]	Football players	9	Overall anaerobic performance	SMD	1.23 (0.55 to 1.91)	<0.001	81%	Favourable
		9	Aerobic performance	SMD	−0.05 (−0.37 to 0.28)	0.78	0%	Neutral
Domínguez et al. [7]	Competitive swimmers	23	Time-trial performance	ES (Hedges g)	−0.46 (−0.75 to −0.17)	0.002	11%	Favourable †
Huang et al. [47]	Swimmers	17	Single-sprint swimming performance	SMD	−0.05 (−0.26 to 0.15)	0.61	0%	Neutral
		17	Repeated-interval swimming performance	SMD	−0.11 (−0.46 to 0.25)	0.56	0%	Neutral
		17	Physiological responses	SMD	0.04 (−0.16 to 0.23)	0.71	0%	Neutral
		17	Body composition	SMD	0.18 (−0.05 to 0.41)	0.12	0%	Neutral

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ES, effect size; FFM, fat-free mass; LBM, lean body mass; MD, mean difference; NMA, network meta-analysis; NR, not reported; NS, not statistically significant; RT, resistance training; SMD, standardised mean difference. ‡ The broader Choi NMA included 22 studies, but the creatine-specific estimates shown here were derived from five RCTs. † Negative values represent shorter time to complete the time trial and therefore favour creatine. # For Lin, et al. [59], 34 studies were included in the review, whereas 21 studies (424 participants) contributed to the quantitative multilevel meta-analysis.

3.5. Dose–Response and Safety

Six systematic reviews and meta-analyses addressed dose-related effects, renal function, adverse outcomes, and physiological responses to creatine supplementation [11,13,14,16,55,56]. The principal quantitative findings from these reviews are summarised in Table 5. These reviews addressed conceptually distinct outcomes and are therefore presented separately below: renal and biochemical markers [14,16,55,56], adverse events and tolerability [13], and thermoregulation and hydration status [11]. No pooled estimate combining these outcomes was computed; each review synthesised a single outcome, and this domain serves only to organise the presentation of the evidence. The principal quantitative findings from these reviews are summarised in Table 5. Across the available evidence, the most consistent finding was an increase in serum creatinine following creatine supplementation, whereas measures more directly intended to characterise renal function generally did not differ significantly between creatine and control groups.

In this line, de Souza et al. [14] identified significant increases in serum creatinine (SMD 0.48, 95% CI 0.24 to 0.73; I^2 = 22%) and plasma urea (SMD 1.10, 95% CI 0.34 to 1.85; I^2 = 28%), but no significant difference in creatinine clearance (SMD −12.25, 95% CI −25.75 to 1.44; I^2 = 0%), leading the review authors to conclude that the biochemical changes did not indicate renal damage. More recent meta-analyses reinforce this distinction between changes in serum creatinine and evidence of impaired renal filtration. Naeini et al. [16] reported a significant increase in serum creatinine (MD 0.07, 95% CI 0.01 to 0.12; I^2 = 69.73%), while GFR did not differ significantly between groups. Although funnel-plot asymmetry was observed for serum creatinine, trim-and-fill adjustment did not materially change the pooled estimate.

Tsiaras et al. [55], based on 19 randomised controlled trials and one randomised crossover study, similarly found an increase in serum creatinine (MD 0.13 mg/dL, 95% CI 0.07 to 0.18), without significant differences in serum urea or estimated GFR. Importantly, analyses according to supplementation duration did not identify significant differences between interventions lasting less than or more than one month. The most recent synthesis, by de Souza Almeida et al. [56], provides further evidence that the interpretation of creatinine-based renal outcomes requires caution. Across 26 studies involving 1036 participants, serum creatinine increased significantly (MD 0.14 mg/dL, 95% CI 0.05 to 0.22; I^2 = 93.9%), whereas the overall analysis of GFR showed no significant between-group difference (MD −2.19 mL/min, 95% CI −9.18 to 4.80; I^2 = 54.0%). However, an apparent reduction emerged when GFR was estimated using creatinine-based methods (MD −10.75 mL/min, 95% CI −17.48 to −4.02), whereas no significant difference was observed when GFR was assessed using Cr-EDTA (MD 5.89 mL/min, 95% CI −0.30 to 12.08; I^2 = 6.3%). Other renal-related outcomes, including serum urea, albuminuria, proteinuria, and urinary creatinine, also showed no significant differences between groups.

Taken together, these findings indicate a consistent biochemical signal in serum creatinine, observed across four independent meta-analyses (SMD 0.48, 95% CI 0.24 to 0.73 [14]; MD 0.07, 95% CI 0.01 to 0.12 [16]; MD 0.13 mg/dL, 95% CI 0.07 to 0.18 [55]; MD 0.14 mg/dL, 95% CI 0.05 to 0.22 [56]), without a corresponding and consistent signal of impaired renal function across the available measures (no significant between-group differences were observed in creatinine clearance [14] or estimated GFR [16,55,56], including GFR measured by the Cr-EDTA reference method: MD 5.89 mL/min, 95% CI −0.30 to 12.08 [56]). The discordance is particularly evident when creatinine-based estimates are contrasted with Cr-EDTA measurements, suggesting that changes in serum creatinine may complicate the interpretation of creatinine-derived estimates of filtration rather than necessarily reflecting a true decline in renal function. This discordance is physiologically expected: serum creatinine reflects not only glomerular filtration but also creatinine generation, which increases predictably with exogenous creatine intake, so creatinine-based GFR

equations lose biochemical validity during supplementation, and their estimates should be regarded as a metabolic artefact rather than evidence of renal stress. In contrast, measures independent of creatine metabolism, including Cr-EDTA-measured GFR and urinary markers of kidney injury, showed no evidence of functional deterioration. At the same time, the very high heterogeneity observed for serum creatinine in de Souza Almeida et al. [56] (I^2 = 93.9%) and the lower certainty assigned to some renal outcomes indicate that this evidence should not be interpreted as definitive proof of long-term renal safety.

Evidence concerning other physiological and adverse responses was comparatively reassuring. In females, de Guingand et al. [13], which included 29 studies involving 951 participants, found no statistically significant differences in total adverse events (RR 1.24, 95% CI 0.51 to 2.98) or gastrointestinal events (RR 1.09, 95% CI 0.53 to 2.24). No deaths or serious adverse outcomes were reported, and renal and hepatic measures, as well as body weight, did not differ significantly between groups. Regarding thermoregulation and hydration, Lopez et al. [11] found no statistically significant effect of creatine supplementation on body temperature during exercise in the heat (MD 0.03 °C, 95% CI −0.07 to 0.13; I^2 = 36%), and no consistent significant differences were observed for heart rate, sweat loss, or hydration-related outcomes. Across the included reviews, there were likewise no significant differences in total adverse events, gastrointestinal events, or creatinine clearance.

Table 5. Synthesis of the principal effects of creatine supplementation on dose–response and safety outcomes.

Review	Population	n Studies	Outcome	Measure	Effect Estimate (95% CI)	*p*	I^2	Direction
Lopez et al. [11]	Physically active individuals	10	Body temperature during exercise in the heat	MD (°C)	0.03 [−0.07, 0.13]	0.57	36%	Neutral
de Souza et al. [14]	General population	15	Serum creatinine	SMD	0.48 [0.24, 0.73]	<0.001	22%	Increased‡
		15	Creatinine clearance	SMD	−12.25 [−25.75, 1.44]	0.08	0%	Neutral
		15	Plasma urea	SMD	1.10 [0.34, 1.85]	0.004	28%	Increased ‡
de Guingand et al. [13]	Females	18	Total adverse events	RR	1.24 [0.51, 2.98]	NS	0%	Neutral
		8	Gastrointestinal events	RR	1.09 [0.53, 2.24]	NS	0%	Neutral
Naeini et al. [16]	General population	21	Serum creatinine	MD	0.07 [0.01, 0.12]	0.03	69.73%	Increased ‡
		21	GFR	MD (mL/min)	3.15 (−4.97 to 11.26)	0.45	33.17%	Neutral
de Souza Almeida et al. [56]	Healthy individuals and patients with CKD	26	Serum creatinine	MD (mg/dL)	0.14 [0.05, 0.22]	0.002	93.9%	Increased ‡
		5	Creatinine-based GFR	mL/min	−10.75 [−17.48, −4.02]	0.002	0.0%	Decreased ‡‡
		5	Cr-EDTA GFR	mL/min	5.89 [−0.30, 12.08]	0.06	6.3%	Neutral
		18	Serum urea	mg/dL	−0.52 (−2.97 to 1.93)	0.676	53.5%	Neutral
		5	Albuminuria	mg/L	0.41 (−2.09 to 2.90)	0.748	77.5%	Neutral
		6	Proteinuria	g/24 h	0.01 (−0.03 to 0.05)	0.633	0%	Neutral
		11	GFR	mL/min	−2.19 (−9.18 to 4.80)	0.539	54.0%	Neutral
		6	Urinary creatinine	g/24h)	−0.09 (−0.17 to 0.35)	0.484	67.5%	Neutral
Tsiaras et al. [55]	General population	19	Serum creatinine	MD (mg/dL)	0.13 [0.07, 0.18]	<0.01	76.3%	Increased ‡
		12	Serum urea	MD (mg/dL)	−0.60 [−2.15, 0.96]	0.45	2.09%	Neutral
		8	eGFR	MD (mL/min/1.73 m²)	−5.20 [−15.00, 4.60]	0.3	63.71%	Neutral

NS, not statistically significant; NR, not reported; RR, risk ratio; GFR, glomerular filtration rate. n studies refers to the number of studies included in the respective review; when the quantitative estimate was based on a subset of studies, this should be specified in the Supplementary Data S2. ‡ Statistically significant increase in serum creatinine; this direction is reported without inferring renal impairment. ‡‡ Statistically significant reduction in GFR estimated using creatinine-based methods; this finding was not observed when GFR was assessed using Cr-EDTA.

3.6. Muscle Recovery and Inflammation

Four systematic reviews and meta-analyses evaluated exercise-induced muscle damage (EIMD), muscle recovery, and inflammatory or oxidative stress markers [10,20,21,54]. The principal quantitative findings from these reviews are summarised in Table 6. Across this domain, the evidence indicates that creatine supplementation may attenuate selected biochemical responses to strenuous exercise, but there is considerably less evidence that these changes translate into faster functional recovery or a consistent reduction in systemic inflammation. The most recurrent finding was a reduction in CK concentrations following exercise, with significant effects reported particularly during the 48–96 h post-exercise period. However, this signal was not consistently reproduced across other markers of muscle damage, and effects on LDH were less robust. Similarly, reductions in indirect indices of muscle damage have been reported during the later phase of the acute response, whereas results during repeated or chronic training have been less consistent, including evidence of higher damage markers at 24 h in some analyses. Taken together, these findings suggest that the response of EIMD biomarkers to creatine is time- and protocol-dependent rather than uniformly attenuated.

Importantly, the biochemical signal was not accompanied by a similarly consistent improvement in functional recovery. Across the available meta-analyses, creatine supplementation did not consistently improve post-exercise muscular strength, muscle soreness, or range of motion, despite reductions in CK under some conditions. Evidence for DOMS was also inconsistent, with a reduction reported at 24 h in one synthesis but not consistently across other time points or analyses. This divergence between biochemical markers and functional outcomes is relevant because CK and other circulating indicators primarily reflect aspects of muscle membrane disruption or cellular damage and should not be interpreted as direct measures of the restoration of force-generating capacity or readiness to perform. Thus, the available evidence supports a possible effect on biochemical manifestations of exercise-induced muscle stress but provides weaker evidence for accelerated recovery in a functional sense. A similar pattern emerged for oxidative and inflammatory responses. Some evidence suggests reduced oxidative stress markers during the acute response to muscle-damaging exercise, whereas the more recent synthesis of inflammatory biomarkers found no significant effects on either acute or chronic CRP or on chronic IL-6. These findings indicate that any modulation of inflammatory responses is unlikely to represent a broad systemic anti-inflammatory effect. Rather, the available evidence is compatible with a context-dependent response, in which creatine may have greater effects under conditions of acute and high-magnitude physiological stress than in chronic low-grade inflammatory states. The main quantitative findings from these reviews are summarised in Table 6.

Table 6. Synthesis of the principal effects of creatine supplementation on muscle recovery and inflammation outcomes.

Review	Population	n Studies	Outcome	Measure	Effect Estimate (95% CI)	*p*	I^2	Direction
Jiaming et al. [21]	Healthy young adults	9	CK (overall)	WMD	−30.94 [−53.19, −8.69]	0.006	99.7%	Reduced

		9	LDH (overall)	WMD	−5.99 [−14.49, 2.50]	0.167	47.2%	Neutral
Northeast et al. [20]	Adults	13	CK (48 h)	SMD	−1.06 [−1.97, −0.14]	0.02	>75%	Reduced
		13	Muscle strength, soreness, ROM and inflammation	—	No significant effect	>0.05	High †	Neutral
Doma et al. [10]	Adults undergoing muscle-damaging exercise	23	Indirect muscle damage markers—acute response (48–90 h)	SMD	−1.09 (−2.06 to −0.13)	0.03	83%	Reduced
		23	Indirect muscle damage markers—chronic response (24 h)	SMD	0.95 (0.04 to 1.86)	0.04	67%	Increased
		23	Oxidative stress—acute response (24–36 h)	SMD	−1.37 (−1.92 to −0.82)	<0.001	0%	Reduced
de Camargo et al. [54]	Healthy, athletic and clinical populations	8	CRP—acute effects	SMD	0.32 [−0.29, 0.94]	0.30	28%	Neutral
		8	CRP—chronic effects	SMD	−0.11 [−0.69, 0.48]	0.73	0%	Neutral
		8	IL-6—chronic effects	SMD	−0.06 [−0.64, 0.53]	0.84	0%	Neutral

CK, creatine kinase; LDH, lactate dehydrogenase; ROM, range of motion; CRP, *C*-reactive protein; IL-6, interleukin-6; NR, not reported. n studies refers to the total number of studies included in each systematic review/meta-analysis; individual quantitative outcomes may have been based on subsets of these studies. † High heterogeneity was reported across several follow-up-specific analyses; exact I^2 was not consistently reported for every outcome.

3.7. Endurance and VO₂max

Two systematic reviews and meta-analyses evaluated endurance-related outcomes and aerobic capacity [5,44]. The principal quantitative findings are summarised in Table 7. Overall, the evidence did not support a general ergogenic effect of creatine on endurance performance or aerobic capacity. Among trained and elite athletes, Fernández-Landa et al. [5], which included 13 studies and 277 participants, found no statistically significant effect of creatine monohydrate on composite endurance performance (SMD −0.07, 95% CI −0.32 to 0.18; $p = 0.47$; $I^2 = 34.75\%$), with the estimate remaining unchanged after exclusion of studies with funnel-plot asymmetry (SMD −0.07, 95% CI −0.27 to 0.13; $p = 0.49$; $I^2 = 0\%$). Similarly, the pooled analysis by Gras et al. [44], comprising 19 randomised controlled trials and 424 participants, found no evidence of improved aerobic capacity; although VO_2max increased in both groups, the increase was smaller with creatine than with placebo (ES −0.32, 95% CI −0.51 to −0.12; $p = 0.002$), a pattern that was also observed in the subgroup of young and healthy participants (ES −0.26, 95% CI −0.49 to −0.02; $p = 0.031$) and in post-intervention comparisons (ES −0.20, 95% CI −0.39 to −0.001; $p = 0.049$). However, notably, the young and healthy subgroup showed a higher ventilatory threshold with creatine supplementation (ES 0.66, 95% CI 0.23 to 1.10; $p = 0.003$). Thus, the available evidence suggests that creatine does not enhance endurance performance or VO_2max per se, although isolated improvements in ventilatory threshold may indicate more selective effects on physiological responses relevant to high-intensity aerobic exercise.

Table 7. Synthesis of the principal effects of creatine supplementation on endurance and VO_2max outcomes.

Review	Population	n Studies	Outcome	Measure	Effect Estimate (95% CI)	*p*	I^2	Direction
Fernández-Landa et al. [5]	Trained/elite athletes	13	Composite endurance performance	SMD	−0.07 [−0.32, 0.18]	0.47	34.75%	Neutral
Gras et al. [44]	Adults/overall population	19	VO_2max—change from baseline	ES	−0.32 [−0.51, −0.12]	0.002	0%	Lower
		19	VO_2max—post-intervention	ES	−0.20 [−0.39, −0.001]	0.049	NR	Lower
	Young healthy adults (subgroup)	14	VO_2max—change from baseline	ES	−0.26 [−0.49, −0.02]	0.031	0%	Lower
		6	Ventilatory threshold	ES	0.66 [0.23, 1.10]	0.003	42.2%	Higher

Note. NR, not reported; ES, effect size; SMD, standardised mean difference. n studies refers to the number of studies contributing to the corresponding quantitative outcome or subgroup analysis. Negative values for VO_2max represent a lower change or post-intervention value in the creatine group relative to the comparator; positive values for ventilatory threshold represent a higher threshold. The memory estimate for the subgroup of older adults (66–76 years) derives from only two primary studies with extreme heterogeneity (I^2 = 83%) and should be interpreted as a tentative, hypothesis-generating observation requiring replication.

3.8. Cognitive and Mental Health Outcomes

Three systematic reviews and meta-analyses evaluated cognitive and mental health outcomes associated with creatine supplementation, encompassing memory, broader cognitive domains, and depressive symptomatology [22,45,52]. The principal quantitative findings from these reviews are summarised in Table 8. Across the cognitive outcomes, the most consistent signal was observed for memory performance. Both quantitative syntheses that examined memory reported statistically significant improvements with creatine supplementation, with broadly similar effect estimates [SMD 0.29, 95% CI 0.04 to 0.53 in Prokopidis et al. [45]; SMD 0.31, 95% CI 0.18 to 0.44 in Xu et al. [22]]. However, the strength and generalizability of this finding were not uniform across populations. The earlier synthesis reported a larger effect estimate in adults aged 66–76 years (SMD 0.88, 95% CI 0.22 to 1.55), whereas no effect was observed in younger participants (SMD 0.03, 95% CI −0.14 to 0.20). However, this subgroup finding was based on only two primary studies and showed substantial statistical heterogeneity (I^2 = 83%). Furthermore, six of the ten RCTs included in the review were judged to be at high risk of bias. Therefore, this finding should be interpreted as tentative and hypothesis-generating rather than as evidence of a clinically meaningful age-specific effect. Confirmation in adequately powered trials is needed before drawing conclusions about differences in response according to age. By comparison, the larger synthesis by Xu et al. included 16 RCTs and 492 participants, reported lower heterogeneity for memory (I^2 = 21%), and rated the certainty of evidence as moderate. Taken together, these findings provide the clearest evidence within the cognitive domain for a potential beneficial effect on memory, although the extent to which this effect varies by age or other participant characteristics remains uncertain.

Likewise, evidence for broader cognitive performance was considerably less consistent. Neither overall cognitive function nor executive function differed significantly

between creatine and placebo groups, despite point estimates generally favouring creatine. Similarly, attention and processing-speed scores did not show clear between-group differences. Some improvements were nevertheless observed when outcomes were expressed as task-completion time rather than performance scores, with lower attention-task completion times (SMD −0.31, 95% CI −0.58 to −0.03) and processing-speed completion times (SMD −0.51, 95% CI −1.01 to −0.01) reported with creatine. These effects were not consistently generalizable across subgroups: the reduction in attention-task time was observed among participants with illness and those aged 18–60 years, but not in healthy participants or those older than 60 years, whereas the reduction in processing-speed time was observed in females but not males. The lack of concordance between faster task completion and corresponding performance scores, together with lower-to-very-low certainty for several of these outcomes, suggests that these findings should be regarded as domain- and measure-specific rather than evidence of a broad enhancement of cognitive function.

The evidence for mental health outcomes is similarly suggestive but substantially less certain. Creatine supplementation was associated with a modest reduction in depressive symptom scores (SMD −0.34, 95% CI −0.70 to −0.00), and a secondary analysis suggested greater odds of depression remission (OR 3.60, 95% CI 1.76 to 7.56). However, the certainty of evidence for depressive symptoms was rated as very low, and the apparent benefit was strongly influenced by study quality: the effect was not statistically significant in studies at lower risk of bias (SMD 0.06, 95% CI −0.38 to 0.49), whereas a larger effect was observed in studies at higher risk of bias (SMD −0.71, 95% CI −1.10 to −0.32; p for subgroup difference = 0.0016). Moreover, the analysis of treatment response did not show a statistically significant effect (OR 0.72, 95% CI 0.28 to 1.88).

Table 8. Synthesis of the principal effects of creatine supplementation on cognitive and mental health outcomes.

Review	Population	n Studies	Outcome	Measure	Effect Estimate (95% CI)	*p*	I^2	Direction
Prokopidis et al. [45]	Healthy adults	8	Memory	SMD	0.29 [0.04, 0.53]	0.02	66%	Higher
	Older adults, 66–76 y (subgroup)	2	Memory	SMD	0.88 [0.22, 1.55]	0.009	83%	Higher
Xu et al. [22]	Adults	6	Overall cognitive function	SMD	0.34 [−0.20, 0.88]	0.22	75%	Neutral
		24	Memory	SMD	0.31 [0.18, 0.44]	<0.00001	21%	Higher
		4	Executive function	SMD	0.32 [−0.08, 0.71]	0.12	0%	Neutral
		3	Executive function time	SMD	−0.03 [−0.47, 0.41]	0.89	0%	Neutral
		4	Attention scores	SMD	0.22 [−0.40, 0.84]	0.49	61%	Neutral
		8	Attention time	SMD	−0.31 [−0.58, −0.03]	0.03	18%	Lower time
		4	Processing speed scores	SMD	0.01 [−0.38, 0.40]	0.97	0%	Neutral
		8	Processing speed time	SMD	−0.51 [−1.01, −0.01]	0.04	63%	Lower time
Eckert et al. [52]	Adults with or without depression	11	Depressive symptoms	SMD	−0.34 [−0.70, −0.00]	NR	71.3%	Lower symptoms
		3	Depression remission	OR	3.60 [1.76, 7.56]	NR	NR	Higher odds
		2	Treatment response	OR	0.72 [0.28, 1.88]	NR	NR	Neutral

NR, not reported; SMD, standardised mean difference; OR, odds ratio. n studies refers to the number of trials contributing to the corresponding quantitative analysis.

3.9. Methodological Quality and Comparative Synthesis Across Clusters

The methodological quality of the 45 included systematic reviews and meta-analyses was assessed using AMSTAR-2. None of the included reviews achieved high confidence; three were classified as moderate, 21 as low, and 21 as critically low confidence (Supplementary Data S1). The confidence rating of each review is presented in Table 1. The ratings were driven mainly by reporting-related items: only three reviews provided a list of excluded full-text studies with justification (item 7, a critical item; absent in 89%), and 19 (42%) did not report a pre-registered protocol (item 2), whereas sources of funding of the primary studies were reported by only four reviews (item 10; 9%). In contrast, items directly related to the conduct of the meta-analyses were almost universally satisfied, including adequacy of the search strategy (item 4; 98%), risk-of-bias assessment (item 9; 96%), appropriateness of meta-analytical methods (item 11; 100%), consideration of risk of bias when interpreting the results (item 13; 100%), and assessment of publication bias (item 15; 98%). As a sensitivity analysis, all overlap analyses were repeated after excluding the 21 reviews rated critically low: the global CCA remained slight (3.92%; 24 reviews), and every domain retained at least three reviews rated moderate or low confidence, except endurance/VO_2max, for which only one review remained. Exclusion of critically low reviews was therefore not adopted as the primary approach; instead, interpretation was weighted by methodological confidence through the prioritisation framework described below.

Accordingly, the number of concordant systematic reviews was not considered a proxy for independent confirmation of an effect. Rather, when multiple reviews addressed the same or closely related outcome, findings were interpreted according to the methodological confidence of the reviews, the degree of primary-study overlap, the recency and comprehensiveness of the evidence base, and the relevance of the review to the specific population and outcome under consideration. For each major outcome domain, the review providing the most reliable synthesis according to these criteria was considered the prioritised review, and its findings were used as the principal basis for interpretation. Other reviews addressing the same outcome were retained as corroborative evidence and were considered in relation to their consistency, methodological confidence, and overlap with the prioritised review. Thus, concordant findings from reviews based largely on the same primary trials were not interpreted as independent replications. Conversely, consistent findings across reviews with limited overlap were considered more informative regarding the robustness of the observed effect. The prioritisation process was applied to guide interpretation rather than to exclude evidence; all eligible reviews remained part of the evidence map and contributed to the overall assessment of consistency across outcomes.

In the strength and power domain, Kazeminasab et al. [48] was prioritised because it was the only review addressing strength outcomes in general, healthy and resistance-trained populations that was classified as moderate confidence according to AMSTAR-2, having satisfied all seven critical items of the instrument, including a prospective protocol (item 2), a complete list of excluded studies with justification (item 7), and risk-of-bias assessment using a validated tool (item 9). The other reviews addressing overlapping strength and power outcomes in these populations were classified as low or critically low confidence, most commonly because no prospective protocol (item 2) or list of excluded studies (item 7) was reported; in addition, the older foundational syntheses appraised trial quality using reporting checklists rather than validated risk-of-bias instruments (item 9). These reporting practices became widespread only after the publication of PRISMA 2020,

which postdates most of the earlier reviews in this domain. The findings of Lanhers et al. [37], Lanhers et al. [38], Wang et al. [46], Zhang et al. [49] and Gu et al. [18] were therefore interpreted as corroborative rather than independent confirmations, particularly where substantial reuse of primary trials was present. Accordingly, apparent consistency across these reviews was interpreted as convergence of evidence syntheses rather than as evidence of multiple independent replications. In sport-specific populations, Luo et al. [6] and Luo et al. [51] were also classified as moderate confidence and were considered the principal reviews for combat-sport and football outcomes, respectively. These analyses consistently supported benefits for selected power- and performance-related outcomes, while the magnitude and direction of effects remained outcome- and sport-specific.

For body composition, no included review achieved moderate or high AMSTAR-2 confidence. Ashtary-Larky et al. [1] was therefore prioritised among the relevant reviews because of its relatively recent search and broader evidence base, while Delpino et al. [41], Burke et al. [2], Desai et al. [3], and Pashayee-Khamene et al. [17] were considered corroborative evidence. Across these reviews, increases in lean or fat-free mass were generally consistent, whereas evidence for reductions in fat mass or body-fat percentage was less consistent. Importantly, the prioritisation of the more methodologically robust review does not imply that the remaining reviews represent independent replications when they contain overlapping primary trials. Thus, the apparent breadth of support for changes in lean or fat-free mass was interpreted in light of both the consistency of findings and the degree of reuse of underlying primary studies.

For physical function and outcomes in older adults, Davies et al. [19] was prioritised among the relevant reviews because it provided a relatively broad synthesis of 33 primary studies and was classified as low rather than critically low confidence. Choi et al. [40], Devries et al. [9], Dos Santos et al. [4], Sharifian et al. [50], and Yao et al. [58] were interpreted as corroborative evidence. The overall direction of findings was favourable for selected measures of physical function and strength, but the confidence in these effects remained limited by methodological quality and variation in populations and interventions. For recovery and muscle-damage outcomes, Doma et al. [10] was prioritised among the relevant reviews because it was classified as low confidence and incorporated a comparatively broad evidence base. Jiaming et al. [21], Northeast et al. [20], and de Camargo et al. [54] were treated as corroborative evidence. Collectively, these reviews suggested outcome- and time-specific effects, particularly for creatine kinase, but did not provide consistent evidence for broader improvements in soreness, muscle damage, or inflammatory outcomes.

For endurance and aerobic outcomes, Fernández-Landa et al. [5] was prioritised because it was classified as low confidence, whereas Gras et al. [44] was classified as critically low confidence. The available evidence did not support a consistent enhancement of endurance performance, and findings varied according to the specific physiological outcome assessed and the population studied. For cognitive outcomes, Xu et al. [22] was prioritised because it included a broader evidence base than Prokopidis et al. [45] and was classified as low confidence. Prokopidis et al. [45] was considered corroborative evidence. The most consistent signal concerned memory, whereas evidence for overall cognition, executive function, attention, and processing speed remained less certain. For depressive symptoms, Eckert et al. [52] represented the relevant evidence synthesis; however, its findings were interpreted cautiously given the limited methodological confidence and the uncertainty surrounding the clinical generalizability of the evidence.

For renal outcomes, Tsiaras et al. [55] was prioritised because it was the most recent review addressing kidney function in healthy and physically active adults and was classified as low confidence. The reviews by de Souza Almeida et al. [56], Naeini et al. [16], and de Souza et al. [14] were considered as corroborative evidence. Across these analyses,

the increase in serum creatinine was relatively consistent, whereas changes in estimated or measured glomerular filtration and urinary markers of kidney injury were not consistently observed. These findings were therefore interpreted as evidence of a biochemical change rather than definitive evidence of renal impairment, while recognising the limited duration of controlled studies. Figure 2 provides an overview of the distribution of quantitative findings across thematic clusters and outcomes, together with the methodological confidence of the contributing reviews. Because 21 of the 45 included reviews (47%) were rated as critically low confidence, the map should be read as a depiction of an evidence base with pervasive methodological weaknesses, in which apparently favourable outcomes rest largely on low- or critically low-confidence syntheses, rather than as an endorsement of broad therapeutic benefit.

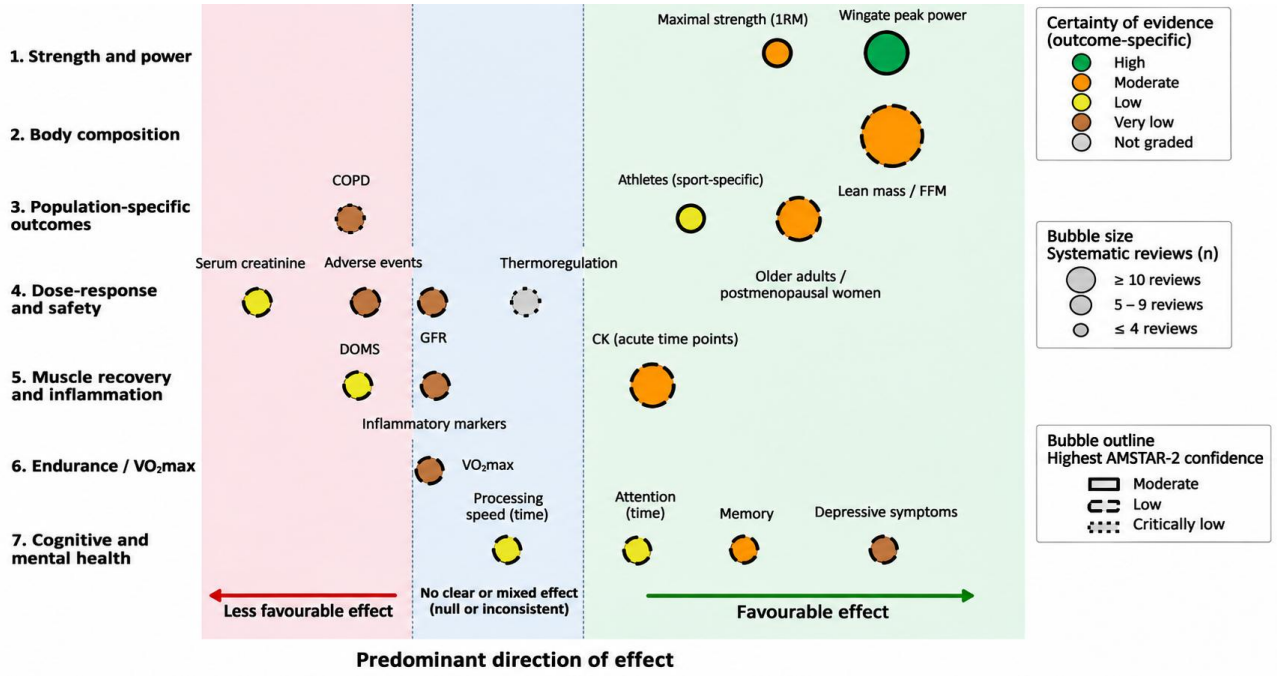


Figure 2. Evidence map of the effects of creatine supplementation across seven thematic domains. Each bubble represents a key outcome. Horizontal position indicates the predominant direction of the reported effect, ranging from less favourable (**left**) to favourable (**right**), with the central region representing null, mixed, or inconsistent findings. This positioning is qualitative and does not represent effect magnitude or numerical cut-offs. Bubble size reflects the number of systematic reviews contributing to each outcome. Bubble colour indicates the outcome-specific certainty of evidence reported in the original reviews, based on GRADE or an equivalent framework. Bubble outline indicates the highest AMSTAR-2 confidence rating among the reviews contributing to each outcome.

3.10. Overlap of Primary Studies Across Reviews

Primary-study overlap was assessed across the 45 included systematic reviews using the citation matrix and the Corrected Covered Area (CCA) index. The citation matrix comprised 1001 study–review inclusions corresponding to 395 unique primary studies across 45 systematic reviews, after consolidation of multiple reports, follow-up publications, and intervention arms originating from the same underlying trials. The resulting global CCA was 3.49%. The global CCA provided a summary measure of overlap across the complete evidence base but did not fully capture variation in primary-study reuse across individual reviews or outcome domains. Pairwise and study-level inspection identified substantial reuse of primary trials within specific evidence syntheses, indicating that the degree of independence varied across the literature. Thus, some findings were supported by multiple systematic reviews drawing extensively on the same underlying primary studies,

whereas other findings were supported by reviews with more limited overlap. Accordingly, concordance across systematic reviews was not interpreted as evidence of independent replication. Rather, the extent of primary-study overlap was considered when evaluating the robustness and apparent consistency of findings, particularly for outcomes addressed by multiple overlapping evidence syntheses. The complete citation matrix and detailed pairwise overlap estimates are provided in the Supplementary Data S2.

3.11. Supplementation Protocols and Dosing Patterns Across Clusters

Supplementation protocols were examined as cross-cutting intervention characteristics across the seven thematic domains (Supplementary Table S1). Across the included reviews, the most commonly reported loading regimen consisted of approximately 20 g/day (typically four 5 g doses) for 5–7 days, followed by a maintenance dose of approximately 3–5 g/day. However, substantial variation was observed, with fixed daily doses ranging from approximately 1 to 40 g/day and body mass-adjusted doses from 0.03 to 0.3 g/kg/day.

Supplementation duration also varied across domains. Strength and power reviews covered protocols lasting 3–180 days, including both short loading-only interventions and longer supplementation regimens. One review reported 49 trials lasting less than 8 weeks compared with 21 lasting 8 weeks or longer, illustrating the substantial representation of shorter interventions. Body-composition reviews predominantly examined chronic supplementation, generally combined with resistance training, with durations ranging from 4 to 365 days. Population-specific reviews showed two distinct patterns: interventions in older adults and clinical populations generally lasted 7–104 weeks, whereas sport-specific reviews predominantly examined shorter protocols (5–63 days). Recovery and inflammation reviews focused mainly on short-term interventions (5–168 days), reflecting their use in exercise-induced muscle damage models. Safety and physiological-response reviews covered the widest duration range, from 4 days to 5.6 years, including loading-only protocols and longer-term supplementation or observational follow-up. Endurance reviews covered interventions lasting 4–180 days, with a mean duration of approximately 42 days. Cognitive and mental health reviews included interventions ranging from 5 days to 5 years, with fixed daily doses of 2.2–20 g/day (median approximately 5 g/day). Loading protocols, typically involving 20 g/day for 5–7 days, were largely restricted to shorter interventions.

Several reviews investigated potential dose- or protocol-related differences, but the criteria used varied considerably across domains. Examples included comparisons of daily doses of ≤5 versus >5 g/day, ≤8 versus >8 g/day, lower versus higher cumulative doses, and loading versus maintenance regimens. Other analyses examined supplementation duration or participant-related moderators rather than dose itself. These differences in subgroup definitions and analytical approaches limit direct comparisons of dose–response patterns across domains.

Regarding the possibility that cognitive benefits may be attributable to acute dosing, the available evidence does not support this conclusion. Of the 16 trials included in Xu et al. [22], nine lasted less than 4 weeks. Prokopidis et al. [45] included interventions lasting 5 days to 24 weeks, whereas Eckert et al. [52] included interventions ranging from 4 weeks to 5 years. Loading-type protocols (approximately 20 g/day for 5–7 days) were reported mainly in shorter interventions, while longer trials generally used fixed daily doses. Importantly, all three reviews examined dose or duration as potential effect modifiers, but none identified significant moderation. Xu et al. [22] found no difference between interventions lasting less than or more than 4 weeks; Prokopidis et al. [45] found no significant moderation by daily dose (≤5 vs. >5 g/day) or duration (<2 vs. ≥2 weeks); and Eckert et al. [52] found no association between effect size and daily dose (p = 0.83) or treatment

duration (p = 0.36). Although the largest numerical effect estimate in Xu et al. [22] was observed for interventions shorter than 4 weeks (attention time: SMD −0.62, 95% CI −1.25 to 0.01), this finding was not statistically significant. Therefore, current evidence does not establish that cognitive benefits are preferentially associated with either short-term loading or chronic supplementation.

Overall, supplementation periods of at least 28 days predominated in the evidence concerning body composition and older or clinical populations, whereas shorter protocols were more frequent in recovery and sport-specific studies. Strength and power, safety, endurance, and cognitive domains included a broader range of supplementation durations. These differences in intervention exposure should be considered when interpreting findings across domains, as variation in dose and duration may partly contribute to differences in observed effects and should not necessarily be interpreted as evidence of domain-specific responsiveness.

3.12. Sensitivity Analyses

Leave-one-out sensitivity analyses confirmed the robustness of the overlap estimate: excluding any single review yielded CCA values between 3.13% and 3.66%, and excluding the three largest reviews yielded 2.80%, all within the 'slight' range. Domain-stratified analyses showed slight-to-moderate overlap in the largest domains (strength, 8.48%; population-specific, 6.46%; safety, 9.86%), high overlap in body composition (12.93%) and cognitive/mental health (12.50%), and very high overlap in recovery/inflammation (25.56%) and endurance/VO_2max (18.52%). These latter two domains comprise few reviews covering largely the same primary studies, which tempers the independence of their conclusions (Supplementary Table S2).

4. Discussion

The present umbrella review synthesised 45 systematic reviews with quantitative meta-analysis examining creatine supplementation across performance, body composition, recovery, cognitive, functional, and safety outcomes [48,60]. Overall, the evidence does not support a uniform effect of creatine across all domains. Rather, the findings indicate a differentiated pattern in which the most consistent evidence concerns selected measures of muscular strength, power, lean mass, and physical function, whereas evidence for endurance, recovery, inflammation, cognition, mental health, and renal outcomes is more outcome- and population-specific [22,48]. This interpretation is consistent with the overall evidence map generated in the present review, which showed a greater concentration of favourable quantitative findings for strength, power, body composition, and selected outcomes in population-specific analyses, while other domains contained a larger proportion of null or heterogeneous estimates. However, the apparent convergence of findings across reviews should be interpreted in light of the methodological confidence of the contributing reviews and the extent of primary-study overlap, as multiple meta-analyses may draw on substantially overlapping sets of primary trials.

An important finding of the present umbrella review is that the apparent size of the literature should not be equated with high confidence in its conclusions [29]. Although 45 systematic reviews were identified, none achieved high confidence according to AMSTAR-2; only three were classified as moderate confidence, whereas 21 were classified as low and 21 as critically low confidence [28,29]. This distinction is methodologically important because AMSTAR-2 evaluates confidence in the methodological conduct of systematic reviews rather than the certainty of individual effect estimates. The observed consistency of findings across reviews should therefore be interpreted in conjunction with methodological confidence, the extent of primary-study overlap, and the characteristics of the populations, interventions, and outcomes evaluated. Consequently, the expanding

number of systematic reviews in the creatine literature represents substantial research activity, but not necessarily a proportional increase in certainty [61]. Thirty-seven of the 45 included reviews were published from 2021 onwards, illustrating the rapid expansion and increasing specialisation of creatine research across athletic, ageing, clinical, cognitive, and safety-related populations [5,12,13]. This growth is scientifically valuable, but it also introduces an increasingly fragmented literature in which populations, supplementation protocols, exercise exposure, outcomes, follow-up periods, and analytical strategies differ substantially between studies and reviews. Thus, a central implication of the present synthesis is that the relevant question is no longer simply whether creatine "works", but rather for which outcomes, in which populations, under which conditions, and with what magnitude and certainty of effect.

4.1. Strength and Power: The Most Consistent Convergence of Findings

Among the domains examined, muscular strength and power provide the clearest convergence across evidence syntheses. Multiple meta-analyses consistently reported favourable effects for lower- and upper-body strength, including squat, leg press, bench press, and chest-press performance [37,38,48,49]. In the present umbrella review, Lanhers et al. [37] reported significant improvements in squat and leg-press strength, while Lanhers et al. [38] identified improvements in bench-press and chest-press strength. More recent analyses reported increases in maximal upper- and lower-body strength in adults undertaking resistance training, with effects remaining evident in larger and more contemporary datasets [46]. These findings are also compatible with earlier meta-analytic evidence showing that creatine combined with resistance training increases maximal weight lifted in young adults, particularly in resistance-trained men [4,24,46]. The consistency of these findings across successive generations of meta-analyses is noteworthy. However, this consistency should be interpreted in light of the methodological confidence of the contributing reviews: none of the reviews addressing strength and power achieved high AMSTAR-2 confidence, and only three were rated as moderate, while the remainder were classified as low or critically low confidence.

A recent analysis restricted to healthy men aged 18–30 years reported moderate-certainty evidence for greater squat 1RM and high-certainty evidence for Wingate peak power, with additional moderate-certainty evidence for fat-free mass, lean body mass, and Wingate mean power [18]. However, this apparent consistency should not be interpreted as evidence of multiple independent replications, because several reviews addressing strength and power outcomes incorporated overlapping primary studies. Within the present synthesis, Kazeminasab et al. [48] was considered the principal evidence synthesis for broadly defined strength and power outcomes on the basis of its higher AMSTAR-2 confidence, whereas other reviews were interpreted as corroborative evidence. Taken together, these findings suggest that the strength- and power-enhancing effects of creatine are not driven solely by a small number of historical studies, as they remain evident in more recent evidence syntheses. However, confidence in these effects remains limited by the moderate-to-critically-low methodological confidence of the underlying reviews.

Nevertheless, the magnitude of the effect is not uniform across populations or outcomes. Zhang et al. [49], for example, reported a substantially larger pooled effect in untrained participants than in trained participants, while the high-dose subgroup did not show a statistically significant effect. This pattern may be compatible with the hypothesis that baseline training status and muscle creatine availability modify responsiveness, but subgroup comparisons should be interpreted cautiously because they are based on smaller numbers of studies and may be affected by confounding, between-study differences, and multiple testing [62,63]. Some apparently differential effects may reflect study design or baseline fitness rather than true physiology, as seen in the null findings from

high-dose short-term supplementation in professional cyclists and in reviews noting counterintuitive subgroup patterns [48,64]. The present evidence therefore supports a relatively consistent ergogenic effect for selected strength- and power-related outcomes, while the magnitude and determinants of individual responsiveness remain less certain.

The evidence for power similarly favours a task-specific interpretation rather than a universal enhancement of performance. Improvements have been reported for repeated-sprint mean power, jumping performance, Wingate peak power, and repeated-sprint ability, while other measures such as repeated-sprint peak power and leg-press strength have been non-significant in some analyses [42,53,65]. Sport-specific analyses also demonstrate that the magnitude of the effect may vary according to the demands of the sport, with relatively large effects for power-related outcomes in elite combat-sport athletes but less consistent effects in football players [6,51]. Accordingly, the most defensible interpretation is that creatine preferentially benefits high-intensity and repeated-bout performance, rather than all forms of exercise performance equally.

4.2. Body Composition: Consistent Increases in Fat-Free Mass, but a More Nuanced Interpretation of Hypertrophy

The largest included meta-analysis, involving 143 studies, reported an increase in fat-free mass of 0.82 kg, with no statistical heterogeneity for this outcome, while studies involving resistance training generally reported larger effects [17]. Similar findings were reported by Desai et al. [3], who observed an increase in lean body mass of approximately 1.14 kg, and by Ashtary-Larky et al. [1], whose pooled estimate indicated an increase of approximately 1.39 kg in fat-free mass among adults undertaking resistance training. Recent evidence increasingly suggests that the body-composition response depends on the interaction between creatine and resistance training rather than creatine alone [17,18]. Pashayee-Khamene et al. [17] reported that the effects on lean tissue were more pronounced when creatine supplementation was combined with resistance training, while the 2026 analysis by Gu et al. [18] identified significant gains in fat-free and lean body mass under resistance-training conditions but not in non-resistance-training conditions. This pattern is also evident in older adults, in whom several reviews evaluated creatine primarily in conjunction with resistance training, making it difficult to separate the contribution of supplementation from that of the exercise stimulus [9,19,39]. The same pattern extends to postmenopausal women: lean-mass gains were more pronounced in the resistance-training trials, whereas the non-training trials were non-significant and the subgroup difference was significant [15]. This pattern supports the interpretation that creatine acts primarily as an adjunct to training-induced adaptation, not as an independent hypertrophic stimulus [15,18].

An important conceptual distinction is that fat-free mass and lean body mass are composite measures and cannot be assumed to equal contractile skeletal muscle accretion [2,43]. This matters for creatine because it can increase total body water and shift water intracellularly, which can inflate lean-mass estimates without equivalent protein accretion [2,17]. Direct clinical evidence also supports this caution: in haemodialysis patients, creatine increased fat-free mass and skeletal muscle mass index alongside higher total body water, mainly from intracellular water [66]. Burke et al. [2] reported a very small pooled effect favouring creatine supplementation combined with resistance training on regional skeletal muscle hypertrophy (SMD 0.11, 95% CrI −0.02 to 0.25), with a 96.1% posterior probability of a positive effect. However, the credible interval included zero, and the estimated magnitude was small, indicating that the evidence for an additional hypertrophic benefit remains uncertain. This contrasts with findings from previous meta-analyses, which reported increases of approximately 1.1–1.4 kg in whole-body lean mass. Such differences may be partly explained by the fact that whole-body lean mass reflects not only

changes in muscle tissue but also alterations in body water, including the water retention associated with creatine supplementation. A randomised trial is directionally consistent with that concern: a 7-day creatine wash-in increased lean body mass before training, but creatine did not augment lean-body-mass growth over the subsequent 12-week resistance-training phase [3].

Adiposity findings are weaker and more mixed than the evidence for lean mass. The largest GRADE-assessed analysis found a small reduction in body-fat percentage but no clear reduction in fat mass [17]. Resistance-training meta-analyses in adults under 50 and over 50 years likewise found small decreases in body-fat percentage, but no statistically significant reduction in absolute fat mass [39,43]. Desai et al. [3] did report reductions in both body-fat percentage and body-fat mass during resistance training. By contrast, other studies found no significant effects on fat mass or body-fat percentage overall, and a recent older-adult synthesis lost significance after removal of a high-weight study [1,50]. Therefore, the current evidence is considerably stronger for increasing lean or fat-free mass than for directly reducing adiposity. Across older-adult and resistance-training meta-analyses, several resistance-training meta-analyses reported increases in lean or fat-free mass in the approximate range of 1.2–1.4 kg, whereas fat-loss effects remain small, inconsistent, or absent in absolute terms [9,15,39]. Therefore, creatine should not be conceptualised primarily as a fat-loss intervention [43,67]. The same caution applies to the lean-mass estimates. The increases of approximately 1.1 to 1.4 kg reported across reviews are based on syntheses rated as low or critically low confidence according to AMSTAR-2 and partly involve overlapping primary studies. Therefore, these findings indicate a consistent pattern, but not one supported by high methodological confidence.

4.3. Population-Specific Outcomes: Translational Relevance and Remaining Uncertainty

A major advance in the literature is the expansion of creatine research beyond young male athletes. The present umbrella review identified 13 reviews addressing population-specific outcomes across older adults, postmenopausal women, females engaged in exercise, clinical populations, and sport-specific cohorts. In older adults, several meta-analyses reported improvements in lean mass, strength and selected measures of physical function [9,39,43,68]. Devries et al. [9] reported increases in fat-free mass, leg-press strength and chair-stand performance, while Forbes et al. [39] similarly identified greater lean mass and small improvements in upper- and lower-body strength. More recent evidence further supports this direction. Davies, et al. [19] reported improvements in sit-to-stand performance and lean tissue mass among older adults and adults with chronic disease at risk of functional disability. Similarly, reviews focusing on adults aged ≥55 years and ≥60 years have reported benefits for resistance-training performance, muscle mass and selected functional outcomes [50,58]. These findings are potentially important because they extend the relevance of creatine from sport performance to preservation of physical capacity during ageing. Nevertheless, the magnitude and certainty of these effects remain less secure than those observed for strength and power in younger adults [18,39,69].

Population-specific meta-analyses often involve relatively few trials, and exercise programmes, nutritional conditions and functional outcomes vary considerably. The contrast between the favourable findings in older adults and the predominantly null findings in individuals with COPD is informative: creatine should not be assumed to produce equivalent benefits in every condition characterised by muscle weakness or physical limitation [12]. This heterogeneity indicates that the response may depend not simply on the presence of low physical function, but on the underlying pathophysiology, training stimulus, and capacity for adaptation [15,70]. Evidence in postmenopausal women is similarly promising but still relatively limited. Naddafha et al. [15] reported a modest increase in lean mass and a larger improvement in leg-press 1RM, but no statistically significant effect

on bone mineral density. Overall, current evidence suggests that creatine may complement exercise in ageing and menopause. However, evidence for outcomes such as bone health remains insufficient. The consistency across reviews should also be interpreted cautiously because several reviews included the same primary studies, and the methodological quality of the evidence syntheses was limited.

4.4. Recovery and Inflammation: Promising Biochemical Signals Without Consistent Functional Translation

Recovery is one of the clearest examples in which biological signals have not yet translated into consistent functional benefits [20,21]. Jiaming et al. [21] reported a significant reduction in creatine kinase (CK) following exercise, including at 48, 72, and 96 h, while Northeast et al. [20] similarly identified reductions in CK at selected post-exercise time points. However, neither review demonstrated consistent improvements across the broader spectrum of recovery outcomes, with evidence for muscle strength recovery, delayed-onset muscle soreness, range of motion, lactate dehydrogenase (LDH), and inflammatory outcomes remaining inconsistent [20,21]. The latter review included 13 trials involving 278 participants and evaluated muscle function recovery, soreness, inflammation, oxidative stress, and biochemical markers of exercise-induced muscle damage [20]. More recent evidence further supports the heterogeneous nature of this response. In a 2026 systematic review and meta-analysis of eight randomised controlled trials, de Camarg, et al. [54] found no significant effects of creatine supplementation on acute or chronic CRP, or on chronic IL-6, despite reports of favourable effects on other inflammatory mediators in individual studies conducted under conditions of extreme endurance exercise. This apparent discrepancy between biochemical markers and functional recovery is important when interpreting the effects of creatine. Creatine kinase is a marker of myocellular membrane disruption and enzyme efflux rather than a direct measure of functional recovery [71,72].

Thus, a reduction in CK cannot necessarily be interpreted as evidence of faster recovery or improved subsequent exercise performance [71]. Similarly, the absence of consistent effects on CRP and IL-6 suggests that reductions in selected biochemical markers should not be interpreted as evidence of a broad anti-inflammatory or recovery-enhancing effect. Rather, the dissociation between reductions in CK and the absence of consistent improvements in soreness, muscle function, or conventional systemic inflammatory markers suggests that creatine may modify specific biochemical manifestations of exercise-induced muscle stress without necessarily producing a clinically meaningful acceleration of recovery [10,20]. This interpretation is further reinforced by the context-dependent pattern reported by de Camarg, et al. [54], whereby potentially favourable inflammatory responses were largely confined to acute, high-magnitude physiological stress, whereas chronic low-grade inflammatory conditions showed predominantly null findings. Accordingly, future research should move beyond isolated biochemical markers and place greater emphasis on ecologically valid and clinically meaningful outcomes, including restoration of force production, subsequent training performance, perceived recovery, and time to return to baseline function. Standardisation of exercise protocols, supplementation strategies, outcome definitions, and biomarker sampling times will also be essential to determine whether the apparent biochemical effects of creatine translate into reproducible functional benefits [10,54].

4.5. Endurance Performance: Absence of Clear Benefit Rather than Evidence of Meaningful Impairment

The evidence for endurance performance differs substantially from that for strength and power [60]. Fernández-Landa et al. [5] found no statistically significant overall effect

on composite endurance performance in trained or elite athletes, while Gras et al. [44] reported lower VO_2max values but a higher ventilatory threshold in selected populations. These findings suggest that creatine should not currently be considered a general endurance ergogenic aid. The apparently paradoxical observation of lower VO_2max but higher ventilatory threshold warrants particular caution. VO_2max represents maximal oxygen consumption, whereas ventilatory threshold captures a distinct physiological transition related to sustainable exercise intensity [44,73]. Changes in one variable should therefore not automatically be interpreted as equivalent changes in functional endurance performance. Moreover, creatine-induced changes in body mass could influence relative measures of aerobic capacity without necessarily indicating impairment of exercise capacity [44]. This interpretation is consistent with the physiological rationale for creatine. The phosphocreatine system is particularly important for rapid ATP resynthesis during high-intensity exercise, whereas prolonged steady-state endurance depends predominantly on oxidative metabolism [2]. This distinction is reinforced by endurance reviews noting improved ventilatory threshold with no parallel effect on time to exhaustion, maximal power output, or relative VO_2max [74].

Accordingly, the absence of a meaningful effect of creatine supplementation on conventional endurance performance is consistent with the current evidence, as athlete-focused reviews generally report no clear improvements in aerobic performance or overall endurance outcomes [5,8]. This is further supported by a recent randomised trial in professional cyclists, which found no consistent benefits for critical power, time-trial or sprint performance, recovery, or body composition during a strenuous training camp [64]. However, potential benefits may be more relevant to endurance sports involving repeated high-intensity efforts, surges, or finishing sprints. Reviews suggest more favourable effects on repeated-sprint and intermittent power-endurance tasks than on steady-state aerobic performance, consistent with evidence that creatine can improve high-intensity repeatability and mean power [42,60]. Nevertheless, evidence in endurance athletes remains limited and heterogeneous, and these context-specific benefits cannot yet be considered consistently established across sports or protocols [39].

4.6. Cognition and Mental Health: Promising Signals, but Substantially Less Mature Evidence

The cognitive literature represents one of the most rapidly expanding and potentially consequential areas of creatine research, yet it remains considerably less mature than the evidence supporting its effects on muscular performance. Of the 45 included reviews, only two quantitatively synthesised memory performance; both reported improvements in memory, with standardised effect sizes of approximately 0.29–0.31 [22,45], whereas the remaining cognitive review addressed depressive symptoms and is discussed below [52]. Xu et al. [22] also observed shorter completion times in tasks assessing attention and processing speed; however, these findings were not accompanied by significant between-group differences in overall cognitive function, executive function, or attention outcomes. The consistency of the findings for memory is therefore noteworthy, although this convergence should not be interpreted as independent replication because the underlying primary-study populations may overlap across reviews. This interpretation is further constrained by important methodological limitations. Prokopidis et al. [45] included only eight studies in the quantitative meta-analysis, while six of the ten included trials were judged to be at high risk of bias. Moreover, the apparent benefit observed in older adults was derived from only two studies and was characterised by substantial heterogeneity. Similarly, Xu et al. [22] rated the certainty of the evidence for processing speed, overall cognitive function, executive function, and attention as low. Taken together, these findings indicate that the current evidence base is suggestive but remains insufficiently robust to support broad claims regarding cognitive enhancement.

This cautious interpretation is consistent with the broader literature. McMorris et al. [75] concluded that evidence for cognitive effects remains equivocal, despite evidence that creatine supplementation can increase brain creatine content, and highlighted methodological concerns regarding supplementation protocols and the importance of directly assessing brain creatine availability where feasible. Accordingly, the most defensible interpretation at present is that creatine may exert domain-specific cognitive effects under particular physiological or demographic conditions, rather than acting as a universal cognitive enhancer. Evidence regarding mental-health outcomes is even less established. Eckert et al. [52] reported reductions in depressive symptom scores and greater odds of remission; however, the overall treatment response did not reach statistical significance, and the certainty of the evidence was rated as very low. These findings should therefore be considered hypothesis-generating rather than sufficient to support a therapeutic recommendation for depression. Establishing the clinical relevance of creatine in mental-health treatment will require larger, prospectively registered trials involving clinically diagnosed populations, standardised antidepressant co-interventions, and clinically meaningful outcomes. Until such evidence becomes available, the potential role of creatine in the management of depression should be regarded as promising but preliminary.

4.7. Renal Safety: The Creatinine Signal Must Be Interpreted Within the Biology of Creatine Metabolism

The renal findings provide perhaps the clearest illustration of why biomarker interpretation is critical when evaluating the safety of creatine supplementation. Across several meta-analyses, creatine supplementation has been consistently associated with increases in serum creatinine, whereas most analyses have not identified significant changes in GFR, eGFR, creatinine clearance, albuminuria, or proteinuria [14,16,55,56]. The most recent evidence further reinforces this distinction. Tsiaras et al. [55] reported an increase in serum creatinine of 0.13 mg/dL without a significant change in eGFR, while Naeini et al. [16] similarly found a significant increase in serum creatinine but no significant difference in GFR. The analysis by de Souza Almeida et al. [56] is particularly informative because the apparent reduction in GFR occurred only when GFR was estimated using creatinine-based methods; no significant reduction was observed when GFR was assessed using Cr-EDTA. In addition, albuminuria and proteinuria were unchanged.

Within the present evidence hierarchy, Tsiaras et al. [55] provided the principal synthesis for this outcome, while the remaining reviews were interpreted as corroborative evidence. Importantly, serum creatinine reflects not only glomerular filtration but also creatinine generation, which may be altered by creatine supplementation and muscle mass. Thus, an increase in serum creatinine following supplementation should not, in isolation, be interpreted as evidence of renal injury. Consistent with this interpretation, recent renal meta-analyses have characterised the observed increase in creatinine as compatible with altered creatinine metabolism in the absence of parallel changes in GFR or urinary markers of kidney damage [16,55,56]. However, these findings should be interpreted within the populations and follow-up durations represented in the available controlled evidence, and do not support an unconditional assertion of long-term renal safety across all populations. Notably, Tsiaras et al. [55]. highlighted the need for randomised trials extending beyond one year, given the relative paucity of long-term controlled data. Accordingly, the most defensible conclusion is that current controlled evidence does not demonstrate clinically meaningful deterioration of renal filtration in the studied populations, although longer-duration studies incorporating biomarkers less dependent on creatine metabolism remain warranted.

4.8. Methodological Fragility of the Evidence Base: Why Quantity Should Not Be Mistaken for Certainty

A key contribution of the present umbrella review is its demonstration that the apparent consensus surrounding creatine supplementation coexists with substantial methodological fragility in the evidence-synthesis literature. None of the 45 included reviews achieved high confidence according to AMSTAR-2, and 42 were classified as having low or critically low confidence [61,76]. This finding is important because the validity of systematic review conclusions depends not only on the underlying primary studies but also on the rigour with which evidence is identified, appraised, synthesised, and interpreted [29,76]. Accordingly, consistency across systematic reviews should not be equated with high certainty when the methodological foundations of those reviews are limited.

Moreover, agreement across systematic reviews does not necessarily represent independent replication of the underlying evidence. The present umbrella review identified 1001 study–review inclusions corresponding to 395 unique primary studies across 45 systematic reviews, resulting in a global Corrected Covered Area (CCA) of 3.49%. Although this global estimate provides a summary of overlap across the evidence base, it should not be interpreted as indicating negligible redundancy across all outcomes or review pairs. Primary-study reuse varied across the evidence base, and some systematic reviews addressing similar questions were based substantially on the same underlying primary trials. Accordingly, concordant findings were interpreted in light of the degree of primary-study overlap, with greater overlap reducing the extent to which apparently consistent findings could be considered independent evidence [26]. This issue is particularly relevant for extensively studied outcomes such as muscle strength, lean mass, and physical function in older adults, for which influential trials may be repeatedly incorporated into different reviews and meta-analyses. To account for this dependence, the present umbrella review did not treat all systematic reviews as equally informative. When multiple reviews addressed the same or closely related outcomes, greater interpretive weight was assigned to those with higher methodological confidence and greater relevance, whereas overlapping reviews were retained primarily as corroborative evidence. This approach helps distinguish the consistency of findings across reviews from the extent to which those findings are supported by independent primary evidence. Importantly, the relatively low global CCA does not preclude substantial local redundancy within specific outcome domains; therefore, overlap should be interpreted in relation to the distribution of primary studies across individual evidence syntheses rather than solely through the overall CCA.

Finally, convergence was not defined by statistical significance alone. The interpretation incorporated effect magnitude, heterogeneity, certainty of evidence, and methodological quality, thereby avoiding a simplistic classification of the literature as either "effective" or "ineffective" [19,54]. This broader perspective is particularly relevant to creatine research, in which statistically significant effects may coexist with substantial heterogeneity, methodological limitations, or low certainty of evidence. Thus, the apparent convergence of the literature should be interpreted in light of three complementary dimensions: the consistency and magnitude of observed effects, the methodological robustness of the reviews reporting them, and the independence of the underlying primary evidence. Taken together, these considerations suggest that the volume and apparent agreement of the evidence base should not be mistaken for a corresponding level of certainty.

4.9. Strengths and Limitations of the Present Umbrella Review

Several features strengthen the present synthesis. The literature search covered PubMed, Scopus, and Web of Science and was designed to identify systematic reviews with meta-analysis addressing a broad range of performance, body composition, recovery, cognitive, mental health, functional, and safety outcomes. A total of 684 records were

retrieved, and 45 systematic reviews with quantitative meta-analysis were ultimately included. Restricting eligibility to reviews that provided a quantitative estimate specifically attributable to creatine also reduced the potential for attributing effects from multi-ingredient interventions to creatine itself. The explicit assessment of primary-study overlap represents an additional methodological strength. The 1001 study–meta-analysis inclusions were harmonised into 395 unique primary studies, with duplicate publications and multiple reports originating from the same underlying trials consolidated before calculation of the Corrected Covered Area. This approach provides information on the structure and independence of the evidence base that would be overlooked by simply counting the number of systematic reviews available. In addition, the comparative synthesis explicitly considered methodological confidence, primary-study overlap, recency, comprehensiveness, and clinical relevance when multiple reviews addressed the same or closely related outcomes, thereby reducing the risk of interpreting concordant but substantially overlapping reviews as independent replications.

Nevertheless, several limitations should be considered when interpreting the findings. First, as is inherent to umbrella reviews, the present synthesis remains dependent on the methodological quality, reporting, and analytical decisions of the underlying systematic reviews, because the primary studies were not independently re-analysed or reassessed in their entirety. Second, certainty-of-evidence assessments were extracted from the original reviews rather than recalculated de novo and may therefore reflect differences in the frameworks, criteria, and assumptions applied across reviews and outcome domains. A similar limitation applies to the assessment of risk of bias in the primary studies. The included reviews used different instruments, including PEDro, the Cochrane RoB 2 tool, the Jadad scale, and the Newcastle–Ottawa Scale, which address distinct methodological aspects. As these instruments are based on different criteria, their risk-of-bias judgments are not directly comparable across reviews. Therefore, conclusions based on these assessments should be interpreted with caution. Similarly, the AMSTAR-2 assessment evaluates the methodological confidence of the systematic reviews rather than the certainty of individual effect estimates, and a higher AMSTAR-2 rating was therefore used to guide the relative interpretive weight of overlapping reviews rather than to establish clinical certainty. Third, the substantial variation in participant characteristics, supplementation protocols, exercise exposure, outcome definitions, and follow-up duration limits the extent to which effect estimates can be directly compared across reviews.

The search strategy may also have introduced retrieval limitations. Eligibility was restricted to English-language publications and reviews published within the predefined 20-year window (September 2006 to September 2026). In addition, only three bibliographic databases were searched, and the electronic search incorporated meta-analysis-related terminology and predefined outcome terms. Consequently, relevant systematic reviews may have been missed because of language restrictions, limited database coverage, differences in indexing practices, or the absence of explicit meta-analysis terminology in their titles or abstracts. Nevertheless, despite the temporal restriction, earlier primary studies remained substantially represented in the included reviews: 138 of the 395 unique primary studies (35%) were published in 2005 or earlier, accounting for 389 of the 1001 study–review inclusions and appearing in 40 of the 45 included reviews. The global CCA should also be interpreted cautiously, as this summary measure does not fully capture the extent and distribution of redundancy within specific outcome domains or between individual pairs of reviews. Finally, despite the increasing number of available reviews, some domains remain comparatively underdeveloped, particularly cognition, female-specific outcomes, and renal safety in clinical populations. Further well-designed and adequately powered primary studies, together with more methodologically rigorous and

prospectively planned evidence syntheses, are therefore needed to establish the robustness, reproducibility, and generalizability of emerging findings.

4.10. Implications for Future Research

The findings suggest that the next phase of creatine research should prioritise precision, methodological quality and clinical relevance rather than simply increasing the number of trials. For strength and power, future studies should prospectively examine potential effect modifiers such as training status, baseline dietary creatine intake, habitual resistance-training exposure, supplementation dose and duration. The subgroup differences reported by Zhang et al. [49] illustrate the importance of this approach, but also demonstrate that existing evidence is insufficient to establish definitive dose–response relationships.

For body composition, future trials should distinguish changes in total fat-free mass from direct measures of skeletal muscle hypertrophy, as these endpoints are not interchangeable [2]. For cognition, harmonised neuropsychological batteries, direct assessment of brain creatine availability, and better targeting of theoretically responsive populations may help resolve the current uncertainty [22,75]. For renal safety, future studies should incorporate measured GFR or biomarkers that are less dependent on creatine metabolism and should extend substantially beyond the follow-up periods of most existing trials [55].

More broadly, the field would benefit from adequately powered, prospectively registered randomised controlled trials with standardised supplementation protocols, transparent outcome reporting, clinically meaningful endpoints and prespecified effect modifiers. Improvements are also needed at the level of evidence synthesis, particularly in the critical methodological domains identified by AMSTAR-2 [29]. The principal knowledge gap is therefore no longer simply whether creatine produces measurable physiological effects, but which individuals benefit, from which protocol, for which outcome, and whether the observed magnitude is sufficiently large to be clinically or practically meaningful. Future evidence syntheses should also minimise unnecessary duplication of systematic reviews addressing identical PICO questions and should report primary-study overlaps transparently when multiple reviews coexist within the same outcome domain.

5. Conclusions

This umbrella review indicates that creatine supplementation is associated with beneficial effects on selected measures of muscular strength, power, and lean or fat-free mass, particularly when combined with resistance training. However, these effects should not be regarded as universally established, as confidence in the findings is constrained by substantial methodological limitations in the available systematic-review literature. None of the 45 included reviews achieved high confidence according to AMSTAR-2, and 42 were classified as having low or critically low confidence, limiting the robustness of the available conclusions. In addition, considerable variation in populations, supplementation protocols, exercise exposure, outcome definitions, and follow-up periods limits the generalizability and direct comparability of findings across domains.

Evidence for physical function in older adults is encouraging but remains less mature, whereas findings for endurance, exercise recovery, inflammation, cognition, mental health, and disease-specific outcomes are more heterogeneous and should not be interpreted as established effects. Renal analyses consistently show increases in serum creatinine, which should be interpreted as an expected consequence of increased creatine turnover rather than as an indicator of renal stress or functional decline. Current evidence does not demonstrate corresponding reductions in glomerular filtration, including when assessed using the reference Cr-EDTA method, or increases in urinary markers of kidney injury. Nevertheless, evidence regarding long-term renal safety remains limited. Overall,

the evidence supports outcome-specific rather than universal effects of creatine supplementation. The most consistent findings concern strength, high-intensity power, and lean or fat-free mass, but these conclusions should be interpreted in light of the limited methodological confidence of the underlying evidence syntheses. Future research should prioritise well-designed, prospectively registered randomised controlled trials with standardised supplementation protocols, clinically meaningful outcomes, longer follow-up, and prespecified effect modifiers, together with more rigorous and consistent evidence-synthesis methods.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/nu18223776/s1, Supplementary Data S1—AMSTAR2 analysis; Supplementary Data S2—CCA analysis; Supplementary Table S1. Supplementation dose and duration across the 45 included meta-analyses; Supplementary Table S2—Sensitivity analyses of primary-study overlap domain-stratified and leave-one-out Corrected Covered Area.

Author Contributions: M.A.F.S., C.J.B. and N.R.A. were responsible for the conceptualisation and design of the study, data collection and analysis, statistical modelling and interpretation, and manuscript preparation. M.A.F.S., N.R.A., M.A.d.B., C.J.B., F.J.A., K.F.C. and L.B.M.B. contributed to manuscript preparation. C.J.B., L.B.M.B., D.V.P., D.A.S.S., E.A.-M., O.T.N. and J.R.F. contributed to the critical review and approval of the final manuscript. All authors assume full responsibility for all aspects of the research and for the integrity and accuracy of the reported results. All authors have read and agreed to the published version of the manuscript.

Funding: M.A.F.S. and K.F.C. gratefully acknowledge the scholarships awarded by the Coordination for the Improvement of Higher Education Personnel (CAPES), under Grant No. 88887.389913/2026-00 (M.A.F.S.) and Grant No. 88887.389820/2026-00 (K.F.C.).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting the findings of this study are publicly available in Figshare: 10.6084/m9.figshare.33893737.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

1RM	One-repetition maximum
AMSTAR-2	A MeaSurement Tool to Assess systematic Reviews 2
ATP	Adenosine triphosphate
BMD	Bone mineral density
BMI	Body mass index
CCA	Corrected Covered Area
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
CMJ	Countermovement jump
COPD	Chronic obstructive pulmonary disease
CONSORT	Consolidated Standards of Reporting Trials
CrI	95% Bayesian credible interval
CRP	C-reactive protein
DOMS	Delayed-onset muscle soreness
EDTA	Ethylenediaminetetraacetic acid
EIMD	Exercise-induced muscle damage

ES	Effect size
FFM	Fat-free mass
FM	Fat mass
GFR	Glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IL-6	Interleukin-6
JBI	Joanna Briggs Institute
LBM	Lean body mass
LDH	Lactate dehydrogenase
MD	Mean difference
NMA	Network meta-analysis
NOS	Newcastle–Ottawa Scale
NR	Not reported
NS	Not statistically significant
OR	Odds ratio
PEDro	Physiotherapy Evidence Database
PICO	Population, Intervention, Comparator, Outcome
PRIOR	Preferred Reporting Items for Overviews of Reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomised controlled trial
RoB	Risk of bias
RoB 2	Cochrane Risk of Bias 2
ROM	Range of motion
RR	Risk ratio
RSA	Repeated-sprint ability
RT	Resistance training
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardised mean difference
VO_2max	Maximal oxygen uptake
WMD	Weighted mean difference

Appendix A

Database-Specific Search Strategies and Retrieval Counts

Search period: 2–8 September 2026. Searches were conducted in PubMed, Scopus, and Web of Science. The searches were limited to records published within the preceding 20 years, English-language publications, and human studies.

PubMed—Search string:
("creatine"[tiab] OR "creatine monohydrate"[tiab]) AND ("meta-analysis"[tiab] OR "metaanalysis"[tiab]) AND ("muscular strength"[tiab] OR strength[tiab] OR power[tiab] OR performance[tiab] OR "exercise performance"[tiab] OR "body composition"[tiab] OR "lean mass"[tiab] OR "lean body mass"[tiab] OR "fat-free mass"[tiab] OR "muscle mass"[tiab] OR endurance[tiab] OR "endurance performance"[tiab] OR VO2max[tiab] OR "VO2 max"[tiab] OR "maximal oxygen uptake"[tiab] OR "aerobic capacity"[tiab] OR recovery[tiab] OR "muscle recovery"[tiab] OR inflammation[tiab] OR inflammatory[tiab] OR "oxidative stress"[tiab] OR "exercise-induced muscle damage"[tiab] OR cognition[tiab] OR cognitive[tiab] OR memory[tiab] OR attention[tiab] OR "executive function"[tiab] OR "processing speed"[tiab] OR "mental health"[tiab] OR depression[tiab] OR safety[tiab] OR "adverse events"[tiab] OR tolerability[tiab] OR renal[tiab] OR kidney[tiab] OR creatinine[tiab] OR "glomerular filtration rate"[tiab] OR GFR[tiab] OR urea[tiab] OR proteinuria[tiab] OR albuminuria[tiab]) AND Humans[MeSH Terms] AND English[lang] AND ("2006/09/02"[Date—Publication]: "6 September 2026"[Date—Publication]).

https://doi.org/10.3390/nu18223776

Scopus—Search string:
TITLE-ABS-KEY(creatine OR "creatine monohydrate") AND TITLE-ABS-KEY("meta-analysis" OR metaanalysis) AND TITLE-ABS-KEY(strength OR "muscular strength" OR power OR performance OR "exercise performance" OR "body composition" OR "lean mass" OR "lean body mass" OR "fat-free mass" OR "muscle mass" OR endurance OR "endurance performance" OR VO2max OR "VO2 max" OR "maximal oxygen uptake" OR "aerobic capacity" OR recovery OR "muscle recovery" OR inflammation OR inflammatory OR "oxidative stress" OR "exercise-induced muscle damage" OR cognition OR cognitive OR memory OR attention OR "executive function" OR "processing speed" OR "mental health" OR depression OR safety OR "adverse events" OR tolerability OR renal OR kidney OR creatinine OR "glomerular filtration rate" OR GFR OR urea OR proteinuria OR albuminuria) AND PUBYEAR > 2005 AND PUBYEAR < 2027 AND LANGUAGE(English).

Web of Science Core Collection—Search string:
TS=("creatine" OR "creatine monohydrate") AND TS=("meta-analysis" OR metaanalysis) AND TS=(strength OR "muscular strength" OR power OR performance OR "exercise performance" OR "body composition" OR "lean mass" OR "lean body mass" OR "fat-free mass" OR "muscle mass" OR endurance OR "endurance performance" OR VO2max OR "VO2 max" OR "maximal oxygen uptake" OR "aerobic capacity" OR recovery OR "muscle recovery" OR inflammation OR inflammatory OR "oxidative stress" OR "exercise-induced muscle damage" OR cognition OR cognitive OR memory OR attention OR "executive function" OR "processing speed" OR "mental health" OR depression OR safety OR "adverse events" OR tolerability OR renal OR kidney OR creatinine OR "glomerular filtration rate" OR GFR OR urea OR proteinuria OR albuminuria).

Appendix B

Annual Distribution of Included Meta-Analysis

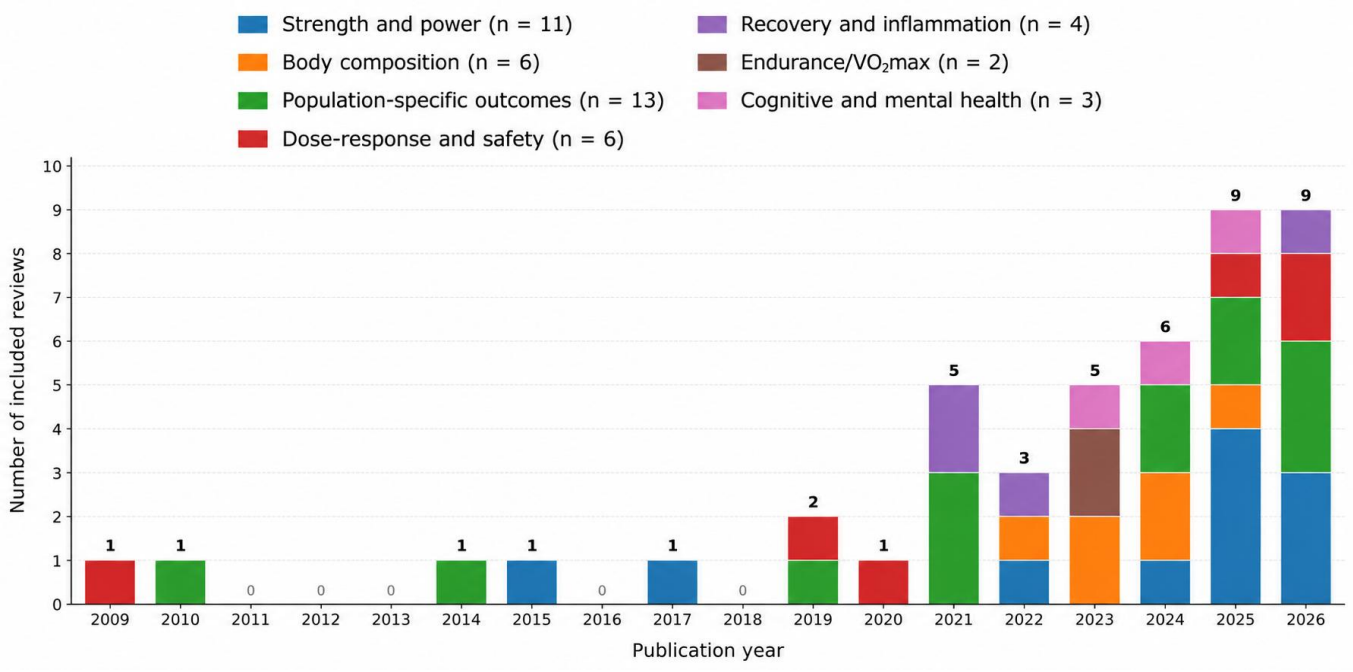


Figure A1. Annual distribution of the 45 included systematic reviews and meta-analyses, stratified by thematic domain.

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