DOI: 10.1002/jpen.2607

REVIEW

Creatine supplementation for optimization of physical function in the patient at risk of functional disability: A systematic review and meta-analysis

Thomas W. Davies BMBS[1,2] | Naomi Watson BMBCh[1,2] | James J. Pilkington PhD[3] | Thomas J. McClelland BMBCh[1,2] | Giada Azzopardi MBBS[1,2] | Rupert M. Pearse MD[1,2] | John Prowle MD[1,2] | Zudin Puthucheary PhD[1,2]

[1]William Harvey Research Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, UK

[2]Adult Critical Care Unit, Royal London Hospital, London, UK

[3]Centre for Bioscience, Manchester Metropolitan University, John Dalton Building, Manchester, UK

Correspondence
Thomas W. Davies, BMBS, Critical Care and Perioperative Medicine Research Group, Adult Critical Care Unit, Royal London Hospital, London, E1 1BB, UK.
Email: thomas.davies6@nhs.net

Funding information
None

Abstract

Background: The efficacy of creatine replacement through supplementation for the optimization of physical function in the population at risk of functional disability is unclear.

Methods: We conducted a systematic literature search of MEDLINE, EMBASE, the Cochrane Library, and CINAHL from inception to November 2022. Studies included were randomized controlled trials (RCTs) comparing creatine supplementation with placebos in older adults and adults with chronic disease. The primary outcome was physical function measured by the sit-to-stand test after pooling data using random-effects modeling. We also performed a Bayesian meta-analysis to describe the treatment effect in probability terms. Secondary outcomes included other measures of physical function, muscle function, and body composition. The risk of bias was assessed using the Cochrane risk-of-bias tool.

Results: We identified 33 RCTs, comprising 1076 participants. From six trials reporting the primary outcome, the pooled standardized mean difference (SMD) was 0.51 (95% confidence interval [CI]: 0.01–1.00; $I^2 = 62\%$; $P = 0.04$); using weakly informative priors, the posterior probability that creatine supplementation improves physical function was 66.7%. Upper-body muscle strength (SMD: 0.25; 95% CI: 0.06–0.44; $I^2 = 0\%$; $P = 0.01$), handgrip strength (SMD 0.23; 95% CI: 0.01–0.45; $I^2 = 0\%$; $P = 0.04$), and lean tissue mass (MD 1.08 kg; 95% CI: 0.77–1.38; $I^2 = 26\%$; $P < 0.01$) improved with creatine supplementation. The quality of evidence for all outcomes was low or very low because of a high risk of bias.

Conclusion: Creatine supplementation improves sit-to-stand performance, muscle function, and lean tissue mass. It is crucial to conduct high-quality prospective RCTs to confirm these hypotheses (PROSPERO number, CRD42023354929).

KEYWORDS
creatine, functional disability, muscle, physical function, sarcopenia

INTRODUCTION

Half of the people aged ≥65 years in the United Kingdom are expected to live the remainder of their lives with a limiting physical or mental health condition, increasing their risk of functional disability and need for care and support.[1] Acquired functional disability, defined as a new inability to perform the tasks required for independent living, is because of physical impairments, including muscle weakness, reduced mobility, recurrent falls, and fatigue.[2] In England, this is projected to rise 67% by 2040, reflective of a global trend of the increasing burden of chronic disease and multimorbidity among the aging population of high-income countries.[3,4] Multimorbidity is also becoming more prevalent in the middle-aged population, with 30% of people with four or more conditions now <65 years old, adding to the concern of this growing public health issue.[5–7] Functional impairments and loss of independence are, therefore, appropriate, necessary, and urgent outcomes for research to target.

Populations at risk of acquired functional disability are more likely to have increased healthcare utilization and hospitalization with poor outcomes, including the need for care facilities.[8,9] Acute illness results in skeletal muscle wasting, a major determinant of this functional disability following hospitalization.[10,11] Sarcopenia, the age-related loss of muscle mass and function, is also a strong predictor of health outcomes, with high personal, social, and economic burdens when left untreated.[12,13] Muscle wasting in illness and aging results from decreased muscle protein synthesis underpinned by cellular bioenergetic failure and mitochondrial dysfunction characterized by a reduction in myocellular adenosine triphosphate (ATP) and phosphocreatine (PCr) levels.[10,14–17] Creatine (methyl-guanidine-acetic acid), a popular nutrition ergogenic dietary supplement for athletes, theoretically has the potential to correct this bioenergetic failure and muscle atrophy and has, therefore, generated considerable clinical interest.

Creatine is a naturally occurring nonprotein amino acid compound found primarily in meat and seafood that is stored mainly in skeletal muscle as PCr and free creatine.[18,19] Intramuscular creatine is degraded into creatinine and excreted in the urine, requiring the body to replenish 1–2 g/day through the diet to maintain normal stores.[19,20] Vegetarians, people with low meat intake, and older people are at risk of deficiency, and daily creatine intake has been observed to be 50% lower than required in large population studies, with 70% of >65-year-old adults consuming <1 g/day.[21–23] Reasons for lack of intake in the United Kingdom among older people include cultural factors (lower meat consumption especially among those of Asian descent), age-related factors (difficulties in meal planning and shopping), and structural factors (food poverty and social isolation), none of which are easily modifiable.[24,25] Creatine replacement may, therefore, have a role in those patients at risk of creatine malnutrition.

The primary metabolic role of creatine is to combine with a phosphoryl group to form PCr. The energy released from the hydrolysis of PCr can be used to resynthesize ATP (PCr and adenosine diphosphate ↔ Cr and ATP), helping to provide ATP availability during muscle contraction[26,27] (Figure 1). Dietary supplementation of creatine increases total muscle creatine, PCr, energy stores, and PCr resynthesis, increasing anaerobic energy capacity, decreasing protein breakdown, and increasing muscle mass and exercise performance.[19,20,28–30] The effects of creatine supplementation have been studied in a variety of chronic diseases in which muscle wasting is present, including diabetes, cancer, heart failure, and respiratory disease, with varying results.[31–34] In previous meta-analyses, creatine in combination with resistance training improves lean body mass and muscle strength in the older population, making it highly plausible that it may be effective in improving physical function in those at risk of functional disability.[35–38] This systematic review and meta-analysis will update and build on this previous work by including populations with chronic disease and studies that do not use resistance training. We investigated the effect of creatine supplementation on physical function in populations at risk of functional disability, namely the older population and those with chronic disease, using outcomes that are patient centered and relevant to normal daily activities.

METHODS

The study protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42023354929) and is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Outcomes were mapped to a recent core outcome set (COS) for trials of nutrition and metabolic interventions in critical illness, a population in which functional disability is common.[39] Physical function, muscle function, and nutrition status were all essential domains to be measured in future trials. The sit-to-stand (STS) test, a recommended measurement instrument in the COS, is a well-defined, validated functional performance test that has been extensively used and has had its properties examined across a spectrum of chronic diseases, with healthy age- and sex-matched data over normal ranges available.[40,41] This widespread use and patient acceptability stem from the fundamental role that the ability to stand from sitting unaided has in maintaining one's independence of function and activities of daily living (eg, getting out of bed, going to the toilet, or getting up from a chair).

Search strategy and selection criteria

The search process was carried out by two authors (Thomas W. Davies and Naomi Watson) who independently identified all relevant

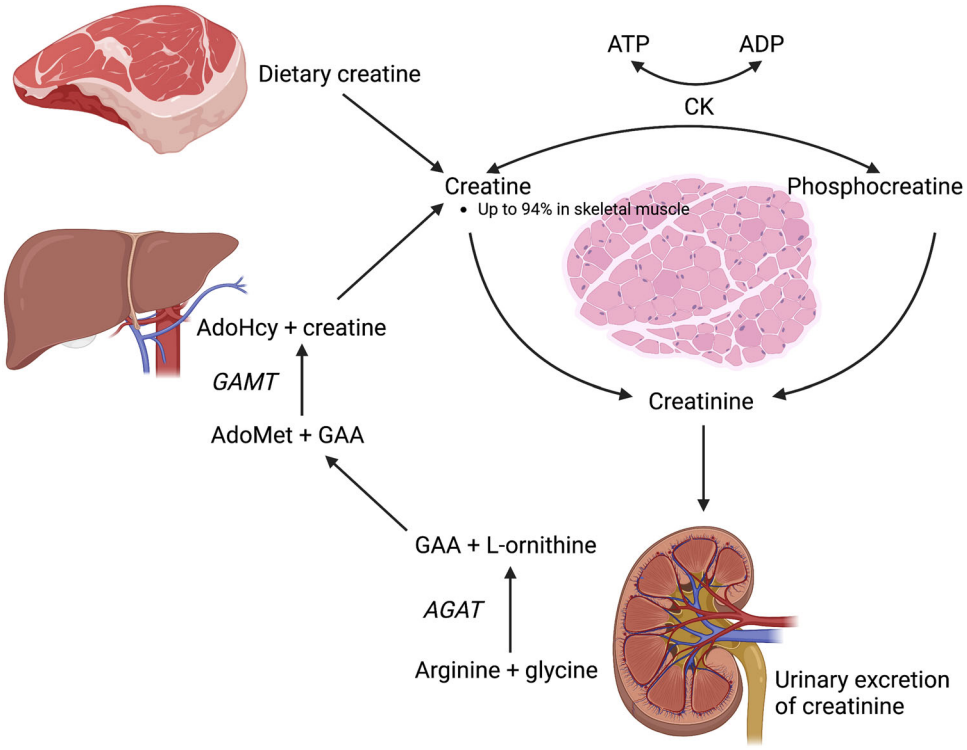

FIGURE 1 Diagrammatic representation of creatine metabolism. Creatine is taken up from the diet via intestinal absorption, or by creatine biosynthesis in the liver. This is initiated in the kidney where AGAT catalyzes the transfer of an amidino group from arginine to glycine resulting in GAA and L-ornithine. GAMT catalyzes the reaction which converts GAA to creatine. Creatine is taken up from the blood, into skeletal muscle. Creatine and phosphocreatine are converted nonenzymatically to creatine. AdoHcy, S-adenosyl-L-homocysteine; AdoMet, S-adenosyl methionine; ADP, adenosine diphosphate; AGAT, arginine:glycine aminotransferase; ATP, adenosine triphosphate; CK, creatine kinase; GAA, guanidinoacetate; GAMT, guanidinoacetate N-methyltransferase.

studies. The search was conducted on multiple electronic databases, including MEDLINE (via www.ovidsp.ovid.com), CENTRAL (via www.cochranelibrary.com), EMBASE (via www.ovidsp.ovid.com), and CINAHL (via Healthcare Databases Advanced Search). Each database was searched from inception to November 3, 2022, for original articles in peer-reviewed journals, excluding conference proceedings and publications in abstract form only. No limits for language, date, or geographical region were used. The full search strategies are available in the Supporting Information. The references of all included papers were reviewed against our inclusion criteria, and relevant review articles and editorials were reviewed to identify any other studies missed during the primary search.

Trials were considered eligible if they (1) were a randomized or quasi-randomized controlled trial; (2) compared creatine at any dose with no creatine (defined as placebo or control); (3) used creatine as the sole metabolic intervention; (4) enrolled either healthy older adults or adults (age ≥18 years) with chronic disease, excluding neuromuscular disease; (5) had a treatment duration of <12 months; and (6) provided information on the prespecified primary (physical function) or secondary outcomes (muscle function; body composition). The primary outcome was physical function measured by STS. Secondary outcomes were physical function measured by other validated performance scales, muscle function (handgrip strength, leg press strength [1-rep maximum], and chest press strength [1-rep maximum]), and body composition (lean tissue mass).

The pathophysiology of muscle wasting in neuromuscular disease affecting the nervous system and neuromuscular junction was considered distinct from chronic disease and aging, and, therefore, trials of neuromuscular disease were not included to reduce heterogeneity. In addition, studies involving a treatment duration of ≥12 months were considered not relevant to the target population because extended supplementation might not be practical or feasible in a clinical setting. Previous work has demonstrated that an increased duration between a drug intervention and outcome decreases adherence by 1% a month, highlighting the need for a short-term goal.[42]

Study selection

After the removal of duplicates, two investigators (Thomas W. Davies and Naomi Watson) independently screened titles and abstracts for relevance. Full texts were reviewed against predetermined eligibility criteria by two authors (Thomas W. Davies and Naomi Watson) acting independently and blinded to each other. Interrater disagreements in the study selection were resolved by discussion and consensus or

with a third author (Zudin Puthucheary) when consensus could not be reached.

Data extraction

Data were extracted independently by four authors (Thomas W. Davies; Naomi Watson; James J. Pilkington; Thomas J. McClelland) and included study design, participant characteristics, inclusion criteria, study intervention, control treatment, cointervention, follow-up duration, and outcome data. The authors (Thomas W. Davies; Naomi Watson; James J. Pilkington; Thomas J. McClelland) independently assessed the risk of bias using the Cochrane risk-of-bias tool.[43] The quality of evidence was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.[44]

Data synthesis

Studies with common methodology for each outcome measure were grouped to facilitate comparability. Mean differences and SD change were extracted from each study. Mean differences were calculated as the preintervention mean subtracted from the postintervention mean. When SD change was not reported, it was estimated from preintervention and postintervention SDs (SD-pre and SD-post) according to the Cochrane Handbook for Systematic Reviews of Interventions.[45] We used 0.8 as the assumed correlation between prescores and postscores based on previous studies.[35] Because units of measurement differed across studies for measures of physical function and muscle function, the standardized mean difference (SMD) was used. Weighted MD was used to determine the group effect on body composition (lean tissue mass).

The primary and subgroup analysis used a random-effects DerSimonian–Laird method. Between-study heterogeneity was evaluated using the I^2 test, and we considered heterogeneity as I^2 >50%. Forest plots were generated for study-specific effect sizes, along with 95% CIs and pooled effects. A P value ≤0.05 was considered statistically significant. We assessed for publication bias by inspecting funnel plots in those outcomes with >10 studies.[45] We used a mixed-effects meta-regression model and a rank correction test to test the funnel plot asymmetry. Subgroup analysis was performed to examine the influence of exercise training in combination with creatine supplementation. A random-effects meta-regression with residual maximum likelihood analysis was conducted to assess evidence of an association between the primary outcome and study duration, participants' age, and creatine dose. Meta-analysis and meta-regression of data were performed using the statistical software package Review Manager 5.4 (RevMan 5.4.1) and JASP (Version 0.17.2).

A Bayesian hierarchical random-effects meta-analysis model was used to further explore the robustness of the results and calculate the probability of treatment effect. Posterior distributions of the estimates were obtained, with their uncertainty reported as a 95% credible interval (CrI). Between-study heterogeneity was represented by tau. Because of the limited data available, we used a weakly informative prior based on empirical work[46,47]: Inverse-Gamma (1, 0.15) for τ and the effect size prior was set as a Cauchy (0, 0.707). Meta-analyses were conducted on JASP (Version 0.17.2) based on the metaBMA package in R, version 4.0.4.[48]

RESULTS

A total of 4651 studies were identified by the search strategy. After the removal of duplicates, 3769 studies underwent screening, from which 74 full-text articles were assessed, with 33 studies meeting the inclusion criteria (Figure 2). Study characteristics are presented in Table 1. All studies were at a single center. Study populations included healthy older adults (n = 560) and those with chronic disease (n = 516); patient demographics are presented in Table S1. Creatine loading occurred in 21 of 33 (64%) of studies, and the maintenance dose ranged from 3 to 20 g or 0.07 to 0.3 g/kg/day, with the most common dosage being 5 g/day (17/33 studies [52%]). The duration of supplementation ranged from 5 days to 32 weeks. Seventeen (52%) studies involved resistance training, 2 (6%) involved pulmonary rehabilitation, 2 (6%) used mixed aerobic and resistance training, and 1 (3%) used whole-body vibration training. There were no significant adverse effects associated with creatine supplementation, but the most commonly reported side effects were gastrointestinal disturbance (n = 6) and muscle cramps (n = 3).

Quality of evidence and risk of bias

The GRADE quality assessment for each outcome is shown in the Supporting Information (Table S2). The quality of evidence for all outcomes was low or very low. Among the included studies, 2 (6%) had a low risk of bias, 20 (61%) had a high risk, and 11 (33%) had some concerns (Figure S1). There was no evidence of a publication bias on the effect of creatine supplementation on outcomes, with sufficient studies based on the funnel plots, mixed-effects meta-regression model, and rank correction test (Figure S2).

Primary outcome

Physical function: STS

Nine studies measured a variation of the STS test, six studies used comparable methodology, and data were available for meta-analysis.[31,49–56] Creatine supplementation, when compared with placebo, significantly increased STS performance (n = 188; SMD: 0.51; 95% CI: 0.01–1.00; I^2 = 62%; P = 0.04; Figure 3). The result of the Bayesian meta-analysis was consistent with the primary analysis (n = 188; SMD: 0.42; 95% CrI: 0.01–0.85; τ = 0.37; Figure S3), with a 66.7% probability that creatine supplementation was associated with improved physical function. In the studies not included

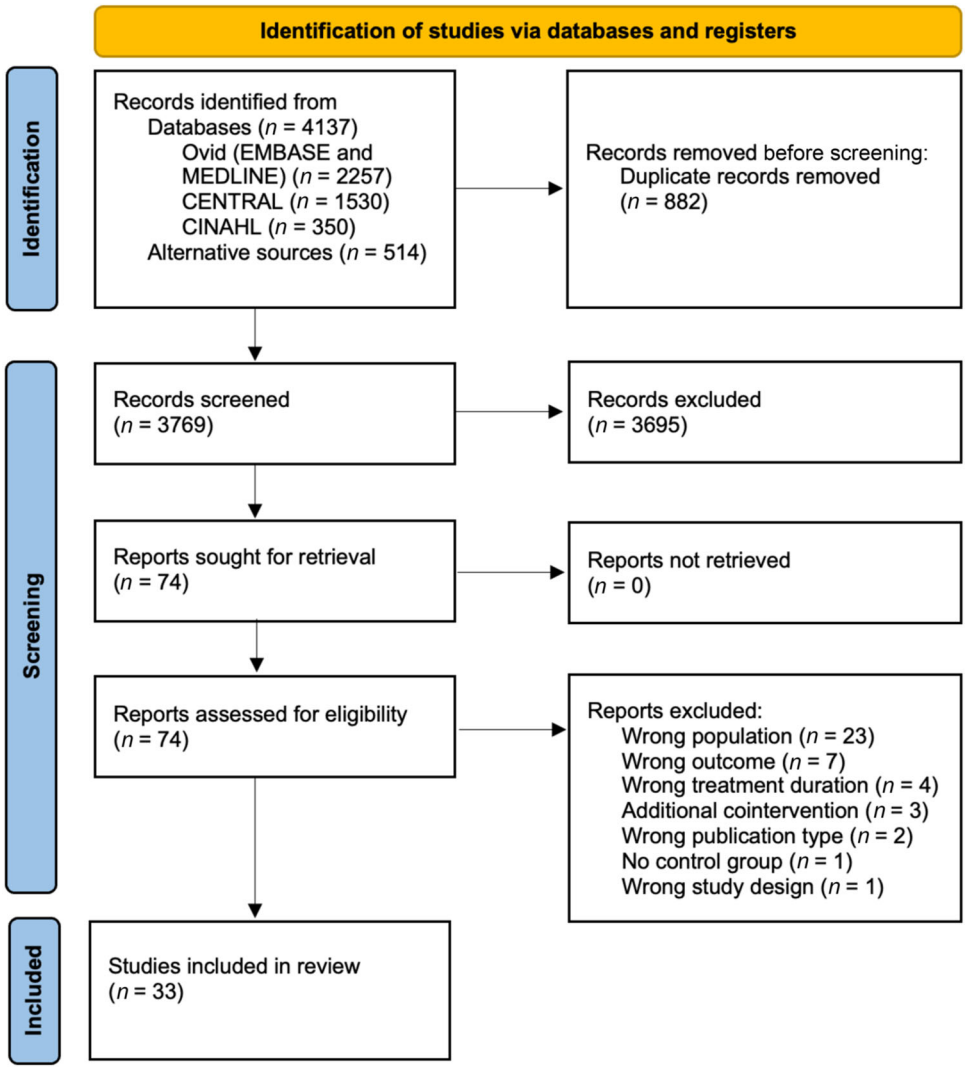

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

in the meta-analysis, there was no difference between the groups, but Gostshalk et al demonstrated an improvement in performance after creatine supplementation when compared with the baseline.[56]

Secondary outcomes

Physical function: Other measures

Meta-analysis of pooled studies showed no difference between creatine supplementation and the placebo for timed up-and-go, walking time, and aerobic capacity (Figure 3; Figure S3). One study conducted the 6-minute walk test, with no difference between creatine supplementation and the placebo.[51] Two studies measured the incremental shuttle walk test, and two studies measured the endurance shuttle walk test, with no differences between groups.[32,57,58] The physical component of the SF-36 was measured in one study, with no difference between the two groups.[59]

Muscle function: Bench press strength

Sixteen studies measured bench press strength, with data available from 15 studies for meta-analysis, including 450 participants.[31,49,50,52,53,56,60–69] When compared with the placebo, creatine supplementation significantly increased bench press strength when analyzed by frequentist meta-analysis ($n = 450$; SMD: 0.25; 95% CI: 0.06–0.44; $I^2 = 0\%$; $P = 0.01$; Figure 4). The results were similar using Bayesian methods ($n = 450$; SMD: 0.24; 95% CrI: 0.04–0.43; $\tau = 0.14$; Figure S4), with a probability of 66.2% that creatine supplementation improved bench press strength.

Muscle function: Leg press strength

Fifteen studies measured leg press strength, including 463 participants.[31,50,52,54,56,60–67,69,70] Creatine supplementation, when compared with the placebo, did not affect leg press strength when

TABLE 1 Study characteristics.

Author (year)	Population (*n*)	Mean age ± SD, years	Baseline creatine measured (technique), Y/N	Loading protocol and duration	Maintenance dosage	Protocol duration, days	Exercise program	Outcomes	Adverse effects
Aguiar et al (2013)	Older women (18)	Cr: 64 ± 4 (*n* = 9) Pla: 65 ± 6	N	None	5 g/day	84	RT 3 days/week	↑ STS; ↑ bench press; ↑ LTM (DEXA)	None reported
Alves et al (2013)	Older women (22)	Cr: 66.4 ± 5.6; Pla: 63.9 ± 3.8	N	20 g/day for 5 days	5 g/day	168	RT 2 days/week	↑ Bench press; ↔ leg press	None reported
Bemben et al (2010)	Older men (42)	Cr: 56.1 ± 5.7; Cr and protein: 57.2 ± 2.2; Pla: 56.1 ± 1.4; Pla and protein: 58.2 ± 2.0	N	7 g/day for 3days per week (2 weeks)	5 g on 3 days per week	98	RT 3 days/week	↔ Bench and leg press; ↔ LTM (DEXA)	None reported
Bermon et al (1998)	Older adults (32 [16 men; 16 women])	Cr: 71.8 ± 2.2; Cr and RT: 71.0 ± 5.4; Pla: 69.3 ± 1.4; Pla + RT: 69.3 ± 1.1	N	20 g/day for 5 days	3 g/day	52	RT 3 days/week	↔ Bench and leg press; ↔ LTM (DEXA)	None reported
Bernat et al (2019)	Older men (24)	Cr: 59.0 ± 7.1; Pla: 58.2 ± 5.9	N	None	0.1 g/kg/day	56	RT 2 days/week	↔ 80 m walking time; ↔ bench and leg press; ↔ LTM (ultrasound)	None reported
Brose et al (2003)	Older adults (28 [15 men; 13 women])	Cr (men): 68.7 ± 4.8; Cr (women): 70.8 ± 6.1; Pla (men): 68.3 ± 3.2; Pla (women): 69.9 ± 5.6	Y (muscle biopsy)	None	5 g/day	98	RT 3 days/week	↑ STS; ↑ 30 m walking time; ↔ bench and leg press; ↔ handgrip strength; ↑ LTM (DEXA)	Cr: GI disturbance x1; Pla: GI disturbance x1
Candow et al (2015)	Older adults (39 [17 men; 22 women])	Cr before exercise: 53.2 ± 2.5; Cr after exercise: 55.5 ± 3.5; Pla: 57.2 ± 6.5	N	None	0.1 g/kg on training days	224	RT 3 days/week	Cr before: ↑ bench and leg press; Cr after: ↑ bench and leg press; ↑ LTM (DEXA)	None reported

TABLE 1 (Continued)

Author (year)	Population (*n*)	Mean age ± SD, years	Baseline creatine measured (technique), Y/N	Loading protocol and duration	Maintenance dosage	Protocol duration, days	Exercise program	Outcomes	Adverse effects
Chami and Candow (2019)	Older adults (31 [14 men; 17 women])	Cr high dose: 59.3 ± 3.2; Cr moderate dose: 58.8 ± 5; Pla: 57.3 ± 4.6	N	None	Cr high: 0.3 g/kg/day Cr moderate: 0.1 g/kg/day	10	None	Cr high and moderate: ↔ bench and leg press; ↔ handgrip strength	Cr high: knee pain x1; constipation x1; muscle cramps x1; bloating x1; Cr moderate: cold x1; pulled groin muscle x1; GI gas x1; Pla: cold x1; knee pain x1
Chrusch et al (2001)	Older men (30)	Cr: 70.4 ± 6.4; Pla: 71.1 ± 6.7	N	0.3 g/kg/day	0.07 g/kg/day	84	RT 3 days/week	↔ Bench press; ↑ leg press; ↑ LTM (DEXA)	Cr: loose stools x1; muscle cramping x1; muscle strain x1
Cooke et al (2014)	Older men (20)	Cr: 61.4 ± 5.0; Pla: 60.7 ± 5.4	N	20 g/day for 5 days	0.1 g/kg on training days	84	RT 3 days/week	↔ Bench and leg press; ↔ LTM (DEXA)	None reported
Cornelissen et al (2010)	Cardiac disease (70 [66 men; 4 women])	Cr: 55.0 ± 9.5; Pla: 59.7 ± 6.7	N	15 g/day for 7 days	5 g/day	84	RT 3 days/week	↔ Peak VO_2; ↔ PCS of SF36	None reported
Deacon et al (2008)	COPD (80 [50 men; 30 women])	Cr: 67.6 ± 7.4; Pla: 68.3 ± 8.2	Y (muscle biopsy)	22 g/day for 5 days	3.76 g/day	49	Pulmonary rehab 3 days/week	↔ ISWT; ↔ LTM (BIA)	Cr: hair loss x1; Pla: stomach upset x1
Domingues et al (2021)	Peripheral arterial disease (29 [15 men; 14 women])	Cr: 64 ± 8; Pla: 64 ± 10	Y (plasma)	20 g/day for 7 days	5 g/day	49	None	↔ STS; ↔ 6MWT; ↔ handgrip strength	Cr: GI discomfort x1
Eijnde et al (2003)	Older men (46)	Cr: 62.2 ± 6.2; Pla: 63.9 ± 5.3	Y (muscle biopsy)	None	5 g/day	182 (6 months)	Endurance and RT 10 days in 4 weeks	↔ Peak VO_2; ↔ LTM (hydrostatic weighing)	Cr: ST depression during exercise x4; Pla: ST depression during exercise x1
Eliot et al (2008)	Older men (42)	Range: 48–72 (no mean given)	N	7 g/day for 7 days	5 g/day	98	RT 3 days/week	↔ LTM (DEXA)	None reported

(Continues)

TABLE 1 (Continued)

Author (year)	Population (*n*)	Mean age ± SD, years	Baseline creatine measured (technique), Y/N	Loading protocol and duration	Maintenance dosage	Protocol duration, days	Exercise program	Outcomes	Adverse effects
Faager et al (2006)	COPD (23 [10 men; 13 women])	Cr: 67 ± 6; Pla: 64 ± 6	N	0.3 g/kg/day for 7 days	0.07 g/kg	56	Pulmonary rehab 2 days/week	↔ ESWT; ↔ handgrip strength	None reported
Fuld et al (2005)	COPD (38 [23 men; 15 women])	Cr: 61.7 ± 8.0; Pla: 63.9 ± 9.7	N	17.1 g/day for 14 days	5 g/day	112	Mobility and strength training 2 days/week	↔ ISWT; ↔ ESWT; ↑ LTM (air displacement plethysmography)	None reported
Gotshalk et al (2002)	Older men (18)	Cr: 65.4 ± 4.7; Pla: 65.7 ± 5.7	N	None	0.9 g/kg/day	14	None	↑ LTM (hydrostatic weighing)	None reported
Gotshalk et al (2008)	Older women (27)	Cr: 63.3 ± 4.6; Pla: 63.0 ± 3.8	N	None	0.9 g/kg/day	14	None	↔ STS; ↑ bench and leg press; ↔ handgrip strength; ↑ LTM (skinfold measurement)	None reported
Goudarzian et al (2017)	Older women (22 [nursing home residents])	Cr and exercise: 64.9 ± 3.4; Pla and exercise: 66.0 ± 4.6; control: 68.0 ± 9.2	N	20 g/day for 7 days	5 g/day	10	Whole-body vibration training5 consecutive days	↑ 30 m walking time; ↔ TUG; ↔ handgrip strength	None reported
Gualano et al (2011)	T2DM (25 [9 men; 16 women])	Cr: 57.5 ± 5.0; Pla: 56.4 ± 8.2	Y (^{31}P MRS)	None	5 g/day	84	RT 3 days/week	↔ STS; ↔ TUG; ↔ peak VO_2; ↔ bench and leg press; ↔ handgrip strength; ↔ LTM (DEXA)	None reported
Gualano et al (2014)	Women with osteoporosis (60)	Cr: 66.1 ± 4.8; Cr and RT: 67.1 ± 5.6; Pla: 66.3 ± 6.9; Pla and RT: 63.6 ± 3.6	N	20 g/day for 5 days	5 g/day	168	RT 2 days/week	Cr and RT vs Pla and RT: ↔ STS; ↔ TUG; ↑ bench press; ↔ leg press; CR vs Pla: ↔ STS; ↔ TUG; ↔ bench and leg press	None reported

TABLE 1 (Continued)

Author (year)	Population (*n*)	Mean age ± SD, years	Baseline creatine measured (technique), Y/N	Loading protocol and duration	Maintenance dosage	Protocol duration, days	Exercise program	Outcomes	Adverse effects
Hass (2007)	Parkinson disease (20 [10 men; 10 women])	Cr: 62.2 ± 8.2; Pla: 62.8 ± 8.2	N	20 g/day for 5 days	5 g/day	84	None	↔ STS; ↔ bench press; ↔ LTM (skinfold measurement)	None reported
Johannsmeyer et al (2016)	Older adults (31 [17 men; 14 women])	Cr: 58.0 ± 3.0; Pla: 57.6 ± 5.0	N	None	0.1 g/kg/day	84	RT 3 days/week	↔ 80 m walking time; ↔ bench and leg press; ↔ handgrip strength; ↔ LTM (DEXA)	Pla: GI disturbance x2
Marini et al (2020)	Chronic kidney disease on hemodialysis (28 [19 men; 9 women])	Cr: 41.9 ± 12.3; Pla: 41.8 ± 10.1	N	20 g/day for 7 days	5 g/day	42	None	↑ LTM (DEXA)	None reported
Neves et al (2011)	Women with osteoarthritis (24)	Cr: 58 ± 3; Pla: 56 ± 3	N	20 g/day for 7 days	5 g/day	84	RT 3 days/week	↑ STS; ↔ leg press; ↔ LTM (DEXA)	None reported
Norman et al (2006)	Colorectal cancer (31 [20 men; 11 women])	Cr: 65.1 ± 12.6; Pla: 61.6 ± 13.8	N	20 g/day for 7 days	5 g/day	56	None	↑ Handgrip strength	None reported
Pinto et al (2016)	Older adults (27)	Cr: 67.4 ± 4.7; Pla: 67.1 ± 6.3	N	None	5 g/day	84	RT 3 days/week	↔ Bench and leg press; ↑ LTM (DEXA)	None reported
Rawson et al (1999)	Older men (20)	Cr: 66.7 ± 6.0; Pla: 66.9 ± 7.0	N	20 g/day for 10 days	4 g/day	30	None	↔ LTM (hydrostatic weighing)	Cr: GI discomfort x1; skin rash x1; muscle cramping x1
Rawson and Clarkson (2000)	Older men (17)	Cr: 65.0 ± 6.3; Pla: 65.8 ± 4.0	N	None	20 g/day	5	None	↔ LTM (skinfold measurement)	None reported
Roy et al (2005)	Osteoarthritis undergoing TKA (37 [17 men; 20 women])	Cr: 63.7 ± 10.0; Pla: 63.3 ± 10.2	Y (muscle biopsy)	10 g/day for 10 days	5 g/day	42	None	↔ 9 m walking time; ↔ handgrip strength; ↔ LTM (DEXA)	None reported

(Continues)

TABLE 1 (Continued)

Author (year)	Population (*n*)	Mean age ± SD, years	Baseline creatine measured (technique), Y/N	Loading protocol and duration	Maintenance dosage	Protocol duration, days	Exercise program	Outcomes	Adverse effects
Sakkas et al (2009)	HIV positive men (40)	Cr: 44 ± 9; Pla: 44 ± 8	Y (^{31}P MRS)	20 g/day for 5 days	4.8 g/day	98	RT 3 days/week	↔ Leg press; ↑ LTM (DEXA)	Cr: hypersensitivity reaction x1
Wilkinson et al (2016)	Rheumatoid arthritis (35 [9 men; 24 women])	Cr: 63.0 ± 10.0; Pla: 57.2 ± 10.4	N	5 g/day for 5 days	3 g/day	84	None	↔ STS; ↔ TUG; ↔ 15 m walking time; ↔ handgrip strength; ↔ LTM (DEXA)	None reported

Abbreviations: 6MWT, 6-min walk test; BIA, bioelectrical impedance; COPD, chronic obstructive pulmonary disease; Cr, creatine; DEXA, dual-energy X-ray absorptiometry; ESWT, endurance shuttle walk test; GI, gastrointestinal; ISWT, incremental shuttle walk test; LTM, lean tissue mass; MRS, magnetic resonance spectroscopy; N, no; Pla, placebo; RT, resistance training; STS, sit-to-stand; T2DM, type 2 diabetes mellitus; TKA, total knee arthroplasty; TUG, timed up-and-go; Y, yes.

analyzed by frequentist ($n = 463$; SMD: 0.07; 95% CI: −0.18 to 0.31; $I^2 = 43\%$; $P = 0.61$; Figure 4) and Bayesian methods ($n = 463$; SMD: 0.06; 95% CrI: −0.16 to 0.28; $\tau = 0.26$; Figure S4).

Muscle function: Handgrip strength

Eleven studies measured handgrip strength, including 325 participants.[31,32,50,51,55,56,61,65,71–73] Using frequentist meta-analysis, creatine supplementation improved handgrip strength compared with the placebo ($n = 325$; SMD: 0.23; 95% CI: 0.01–0.45; $I^2 = 0\%$; $P = 0.04$; Figure 4). The Bayesian analysis yielded consistent results but with wider confidence intervals ($n = 325$; SMD: 0.22; 95% CrI, −0.02 to 0.45; $\tau = 0.12$; Figure S4).

Body composition: Lean tissue mass

Data were available for meta-analysis from 23 studies including 683 participants.[31,49,50,53–58,60,61,64,66–68,70,72,74–79] Creatine supplementation, when compared with the placebo, significantly increased lean tissue mass by 1.08 kg ($n = 683$; 95% CI: 0.77–1.38; $I^2 = 26\%$; $P < 0.01$; Figure 5) when analyzed by frequentist meta-analysis and 1.03 kg ($n = 645$; 95% CrI: 0.69–1.40; $\tau = 0.39$; Figure S5) using Bayesian meta-analysis, with a probability of >99.99% that lean tissue mass increases with creatine supplementation.

Subgroup analysis

Studies of creatine supplementation in combination with exercise training produced greater improvements vs placebo in STS performance ($n = 123$; SMD: 0.76; 95% CI: 0.23–1.28; $I^2 = 48\%$; $P < 0.01$; Figure S6), bench press strength ($n = 334$; SMD: 0.35; 95% CI: 0.13–0.57; $I^2 = 0\%$; $P < 0.01$; Figure S7), and lean tissue mass ($n = 546$; MD: 1.25; 95% CI: 0.83–1.67; $I^2 = 26\%$; $P < 0.01$; Figure S10). There was no difference when compared with placebo in leg press strength ($n = 379$; SMD: 0.22; 95% CI: −0.03 to 0.47; $I^2 = 31\%$; $P = 0.08$; Figure S8) or handgrip strength ($n = 122$; SMD: 0.07; 95% CI: −0.29 to 0.43; $I^2 = 0\%$; $P = 0.71$; Figure S9). Meta-regression analysis found a significant negative association between the duration of supplementation and the effect size of creatine supplementation on the primary outcome ($z = -2.64$; $P < 0.01$). There was no association with creatine dosage ($z = 1.55$; $P = 0.12$) or age ($z = -1.38$; $P = 0.17$).

DISCUSSION

In this systematic review, we pooled results from 33 studies, aiming to investigate the effects of creatine supplementation on physical function, muscle function, and body composition in a population at risk of functional disability. Our main finding is that creatine

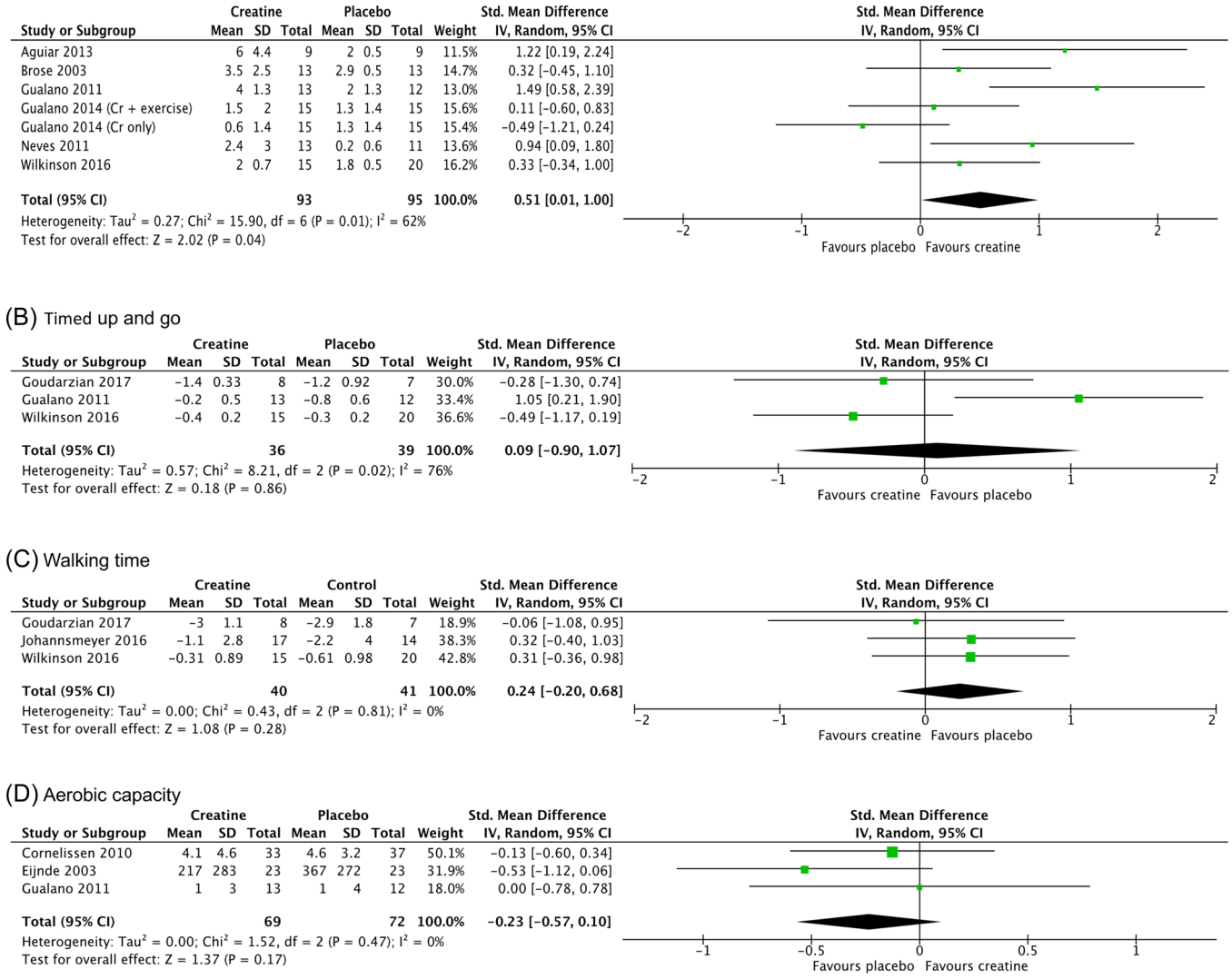

FIGURE 3 Forest plots of studies reporting physical function outcomes demonstrated as a standardized mean difference using frequentist meta-analysis. The mean change was calculated as the difference between the end point mean and the baseline mean. The SD for the mean change was calculated using a correlation coefficient of 0.8. CI, confidence interval; df, degrees of freedom; IV, inverse variance.

improves physical function, as measured by the STS test. Based on our primary analysis, upper body muscle strength, handgrip strength, and lean tissue mass are also improved with creatine supplementation. Pooled results for other outcomes of physical and muscle function were not significant. These findings may have important clinical implications in patients at risk of muscle wasting and loss of functional independence. Importantly, creatine appears to be safe without increased incidence of adverse events when compared with placebo. We performed frequentist and Bayesian analyses to comprehensively assess treatment effects. Evidence for all outcomes in the review was graded low or very low quality, and there were significant differences between the studies, including the duration of intervention and cointerventions such as exercise.

The ability to stand from sitting unaided is central to ensuring independence of function.[80–82] This movement is a high-intensity short-term task, a form of exercise for which oral creatine supplementation has been used successfully to improve performance.[19] Our findings support those of two previous meta-analyses of older adults demonstrating creatine supplementation in conjunction with resistance training resulted in greater improvements in STS performance than that of resistance training and placebo.[37,38] This must be interpreted cautiously because wide confidence intervals and a low posterior probability suggest some uncertainty regarding the true effect size. Our additional inclusion of studies using creatine supplementation as a sole intervention investigating a heterogeneous population with chronic disease enhances the clinical relevance of creatine use.

Creatine did not affect other measures of physical function, including timed up-and-go, walking time, and aerobic capacity. This is perhaps unsurprising, because these measures are predominantly of

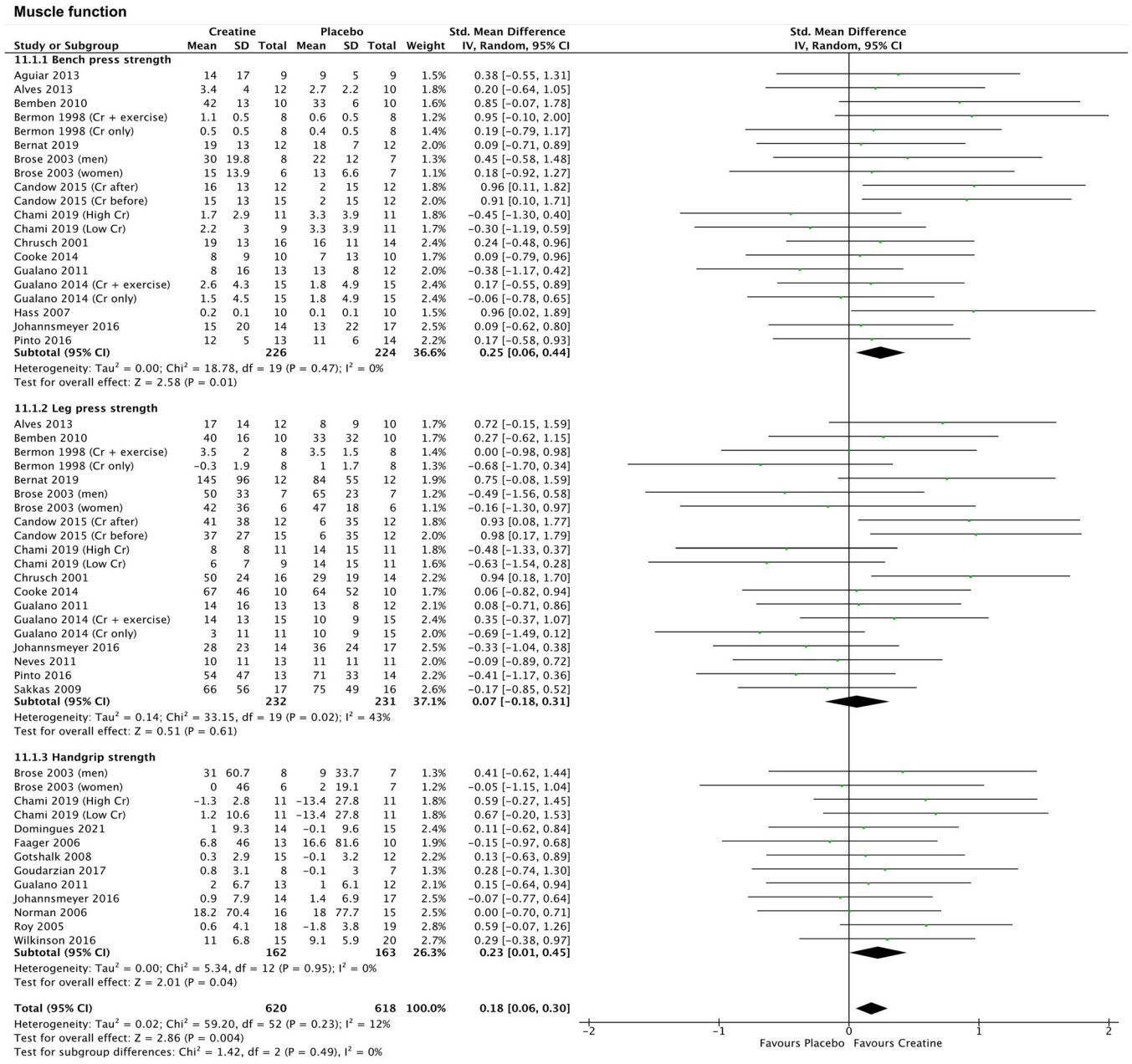

FIGURE 4 Forest plots of studies reporting muscle function outcomes demonstrated as a standardized mean difference using frequentist meta-analysis. The mean change was calculated as the difference between the end point mean and the baseline mean. The SD for the mean change was calculated using a correlation coefficient of 0.8. CI, confidence interval; Cr, creatine, df, degrees of freedom; IV, inverse variance.

endurance capacity and lack the intense nature of exercise that creatine has been shown to improve.[19] STS, in comparison, is explosive, a more patient-relevant outcome with greater acceptability, and more consistent clinimetric properties.[39,83] This highlights the importance of the choice of outcome measure in future trials of creatine.

Within sarcopenia research, muscle strength has been recognized as the best predictor of health outcomes.[84] Lean tissue mass, commonly used as a surrogate for muscle mass, is a nondefining parameter and, therefore, holds less clinical significance.[84] Previous meta-analyses have consistently found that the combination of creatine supplementation and resistance training augments lean tissue mass (0.9–1.3 kg) and upper-body strength in older adults when compared with the placebo and resistance training.[35–37,85] The effect on lower body strength is more heterogeneous. We found no difference between the groups in lower body strength, similar to a previous meta-analysis of older adults.[85] Improvements in leg press strength after creatine were seen in other meta-analyses, specifically in those in which higher doses were used.[35–37] These inconsistencies may be attributed to the variable levels of intramuscular PCr in different muscle groups.[35] With aging, PCr stores tend to decrease, particularly in lower limb muscles, which also exhibit more

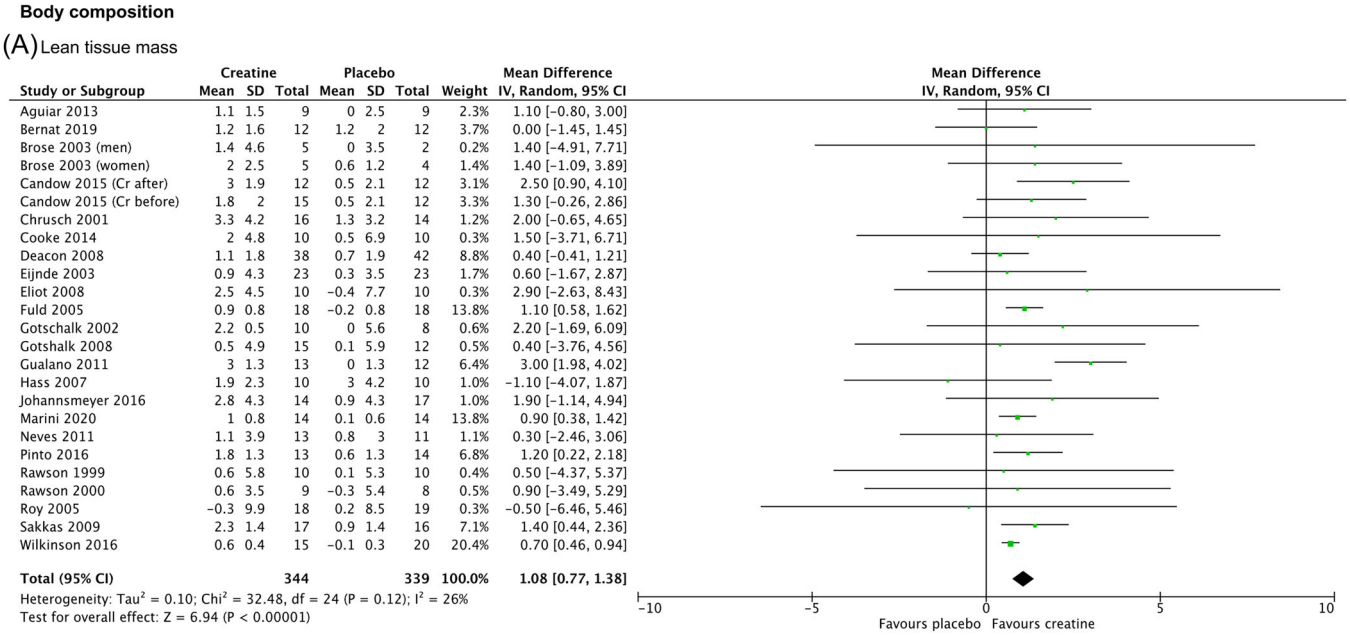

FIGURE 5 Forest plot of studies reporting body composition outcomes demonstrated as a standardized mean difference using frequentist meta-analysis. The mean change was calculated as the difference between the end point mean and the baseline mean. The SD for the mean change was calculated using a correlation coefficient of 0.8. CI, confidence interval; df, degrees of freedom; IV, inverse variance.

pronounced declines in strength compared with that of upper-body muscle groups.[86,87] It is plausible that higher dosages of creatine may be required to improve lower-body muscle strength, potentially accounting for the more frequent instances of negative trials.

Our findings in lower limb strength could also be because of the inclusion of studies investigating creatine supplementation without exercise training, adding to the significant heterogeneity seen in this analysis. Our subgroup analysis demonstrated greater improvements in physical function, upper and lower body strength, and lean tissue mass in studies using a combination of creatine supplementation and exercise training, compared with that of creatine alone. Exercise may have a synergistic effect with creatine supplementation on stimulating muscle protein synthesis but is difficult to deliver as an intervention in the clinical environment.[19]

In addition to previous works, handgrip strength was seen to increase with creatine in our primary analysis, a finding replicated in athletes in the sports science literature.[88] Handgrip strength is routinely used to measure strength and is an indicator of general health status, specifically for early all-cause and cardiovascular mortality and disability.[89,90] This finding is, therefore, of clinical importance, although it must be interpreted cautiously because the lower CRi in the Bayesian analysis was below zero. Interestingly in our subgroup analysis handgrip strength did not improve when only trials of creatine supplementation and exercise training were included. This may be because of the small number of studies and because studies used specific exercises that did not target grip strength.

Many of the studies included in the meta-analysis show divergent results, with the majority not reporting a between-group difference in muscle function or lean tissue mass. Individual studies may lack the necessary statistical power and additionally, the responsiveness of creatine in older adults is likely influenced by baseline PCr levels determined by muscle mass and dietary intake of creatine. This is highlighted by research in vegetarians who have lower baseline muscle creatine and PCr content.[91] Creatine supplementation improves muscle creatine and PCr content to a much greater extent in vegetarians when compared with omnivores, resulting in functional improvements.[91,92] The variability seen in individual studies may be because patients with creatine malnutrition benefit more from creatine replenishment, rather than supplementation to supranormal levels, which could have important clinical implications.

The studies we examined were highly heterogeneous, and there was inadequate reporting on key determinants, such as baseline muscle creatine measurement, dietary data, baseline risk of malnutrition, or socioeconomic status, limiting the potential for subgroup analysis to identify those patients most at risk of creatine deficiency. The cost-of-living crisis is driving food insecurity among older and vulnerable people, with one in four people >60 years of age saying they are unable to eat healthy or nutritious food.[93] Because of the complexity of long-term dietary interventions in this population, it is vital that future work identifies those at high risk of malnutrition and low creatine intake. Short-term nutrition supplements like creatine introduced at the time of healthcare interventions, such as surgery or discharge from the hospital, benefit from defined timescales and are likely to improve adherence, ultimately driving potential longer-term behavioral change and improving outcomes. Interestingly our subgroup analysis indicated a signal of benefit for short-term durations of creatine supplementation; however, it is important to note that this finding is at high risk of bias because of the small number of heterogeneous studies.

Multimorbidity and aging are associated with functional disability because of muscle wasting.[11,13] The shared common pathway is an

imbalance between muscle protein synthesis and breakdown, due, in part, to reduced muscle ATP concentrations.[10,15–17] Anabolic resistance limits the effectiveness of interventions, such as resistance training and amino acid supplementation.[94,95] These data suggest creatine may counteract these metabolic effects by addressing bioenergetic failure enhancing muscle protein synthesis and improving functional outcomes. This evidence synthesis supports the need for large hypothesis-testing trials of creatine treatment to optimize clinical nutrition therapy in patients at risk of functional disability.

Limitations

Limitations of this meta-analysis mainly relate to the quality of study design and heterogeneity of included studies with a lack of standardization of the intervention and outcomes. Heterogeneity of outcomes is common in retrospective data synthesis, and future trials should map outcomes to published standardized COSs helping to guide future trial development and implementation.[39] The quality of evidence for the primary outcome was poor, and the analysis included a relatively small number of trials with high heterogeneity resulting in wide confidence intervals. As a result, subgroup analyses considering treatment duration, age, and creatine dosage are difficult to interpret. The risk of bias in many of the included studies was high because of per-protocol analysis in the context of missing data limiting external validity. We did not report on the source of funding for individual studies and, therefore, cannot rule out the possibility of bias because of the competing interests of funders. Inconsistent reporting of data required some SDs to be imputed.[45] The population included in the analysis were all outpatients, limiting the generalizability to the hospitalized patient at risk of acquired functional disability, and, therefore, the findings should be regarded as hypothesis generating for only the inpatient population.

CONCLUSION

Creatine supplementation improves STS performance, muscle function, and lean tissue mass. Oral creatine supplementation may counteract muscle bioenergetic failure in those at risk of functional disability, optimizing their ability to perform functional tasks independently and improving their quality of life. Given the bias in many of the included studies, conducting high-quality prospective randomized controlled trials in the appropriate population is crucial to confirm these hypotheses.

AUTHOR CONTRIBUTIONS

Protocol development: Thomas W. Davies and Zudin Puthucheary. *Electronic searches*: Thomas W. Davies and Naomi Watson. *Selection and data extraction*: Thomas W. Davies, Naomi Watson, Thomas J. McClelland, and John Prowle. *Data analysis*: Thomas W. Davies, Naomi Watson, and Zudin Puthucheary. *Drafting manuscript*: Thomas W. Davies and Zudin Puthucheary. All authors developed the study concept and design, interpreted the data, provided critical revisions for important intellectual content, read, and approved the final manuscript and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

Zudin Puthucheary has received honoraria for consultancy from Nestlé, Nutriticia, Faraday Pharmaceuticals, and Fresenius-Kabi and speaker fees from Baxter, Fresenius-Kabi, Nutriticia, and Nestlé. Rupert M. Pearse has received research grants and/or honoraria from Edwards Lifesciences and Intersurgical UK. John Prowle has Consultancy agreements with Jaffron Biomedical, Paion Ltd, Nephrolyx GmbH, Medibeacon Inc, Baxter Inc and Nikkiso Europe GmbH, has received research support from Astute Medical a Biomerieux company and Jafron Biomedical Co Ltd and speaker's fees and hospitality from Baxter Inc, BBraun, Nikkiso Europe GmbH and Fresenius Medical Care.

ORCID

Thomas W. Davies http://orcid.org/0000-0002-1934-9443
Thomas J. McClelland http://orcid.org/0000-0001-6662-9176
Giada Azzopardi http://orcid.org/0000-0002-4598-6526

REFERENCES

1. Office for National Statistics. Health state life expectancies, UK, 2018 to 2020. Accessed May 18, 2023. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/healthstatelifeexpectanciesuk/2018to2020
2. Rodrigues MAP, Facchini LA, Thumé E, Maia F. Gender and incidence of functional disability in the elderly: a systematic review. *Cad Saúde Pública*. 2009;25(suppl 3):S464-S476.
3. Wittenberg R, Hu B, Hancock R. Projections of demand and expenditure on adult social care 2015 to 2040. Accessed May 18, 2023. http://eprints.lse.ac.uk/88376/
4. Garin N, Koyanagi A, Chatterji S, et al. Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study. *J Gerontol A Biol Sci Med Sci*. 2016;71(2):205-214.
5. Stafford M, Steventon A, Thorlby R, Fisher R, Turton C, Deeny S. Briefing: Understanding the Health Care Needs of People with Multiple Health Conditions. The Health Foundation; 2018.
6. Kingston A, Robinson L, Booth H, Knapp M, Jagger C, for the MODEM project. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. *Age Ageing*. 2018;47(3):374-380.
7. Kingston A, Comas-Herrera A, Jagger C, MODEM project. Forecasting the care needs of the older population in England over the next 20 years: estimates from the Population Ageing and Care Simulation (PACSim) modelling study. *Lancet Public Health*. 2018;3(9):e447-e455.
8. Zekry D, Loures Valle BH, Graf C, et al. Prospective comparison of 6 comorbidity indices as predictors of 1-year post-hospital discharge institutionalization, readmission, and mortality in elderly individuals. *J Am Med Dir Assoc*. 2012;13(3):272-278.
9. Palladino R, Tayu Lee J, Ashworth M, Triassi M, Millett C. Associations between multimorbidity, healthcare utilisation and health status: evidence from 16 European countries. *Age Ageing*. 2016;45(3):431-435.
10. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA*. 2013;310(15):1591-1600.
11. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-1304.

12. Mijnarends DM, Luiking YC, Halfens RJG, et al. Muscle, health and costs: a glance at their relationship. *J Nutr Health Aging*. 2018;22(7):766-773.
13. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48(1):16-31.
14. Puthucheary ZA, Astin R, McPhail MJW, et al. Metabolic phenotype of skeletal muscle in early critical illness. *Thorax*. 2018;73(10):926-935.
15. Marzetti E, Calvani R, Cesari M, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. *Int J Biochem Cell Biol*. 2013;45(10):2288-2301.
16. Hinkley JM, Cornnell HH, Standley RA, et al. Older adults with sarcopenia have distinct skeletal muscle phosphodiester, phosphocreatine, and phospholipid profiles. *Aging Cell*. 2020;19(6):e13135.
17. Short KR, Bigelow ML, Kahl J, et al. Decline in skeletal muscle mitochondrial function with aging in humans. *Proc National Acad Sci USA*. 2005;102(15):5618-5623.
18. Riesberg LA, Weed SA, McDonald TL, Eckerson JM, Drescher KM. Beyond muscles: the untapped potential of creatine. *Int Immunopharmacol*. 2016;37:31-42.
19. Kreider RB, Kalman DS, Antonio J, et al. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *J Int Soc Sports Nutr*. 2017;14:18.
20. Harris RC, Söderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. *Clin Sci (Lond)*. 1992;83(3):367-374.
21. Bakian AV, Huber RS, Scholl L, Renshaw PF, Kondo D. Dietary creatine intake and depression risk among U.S. adults. *Transl Psychiatr*. 2020;10(1):52.
22. Ostojic SM. Dietary creatine intake in U.S. population: NHANES 2017-2018. *Nutrition*. 2021;87-88:111207.
23. Ostojic SM, Korovljev D, Stajer V. Dietary intake of creatine and risk of medical conditions in U.S. older men and women: Data from the 2017–2018 National Health and Nutrition Examination Survey. *Food Sci Nutr*. 2021;9(10):5746-5754.
24. Stewart C, Piernas C, Cook B, Jebb SA. Trends in UK meat consumption: analysis of data from years 1-11 (2008-09 to 2018-19) of the National Diet and Nutrition Survey rolling programme. *Lancet Planet Health*. 2021;5(10):e699-e708.
25. Leslie WS. Improving the dietary intake of frail older people. *Proc Nutr Soc*. 2011;70(2):263-267.
26. Schlattner U, Klaus A, Ramirez Rios S, Guzun R, Kay L, Tokarska-Schlattner M. Cellular compartmentation of energy metabolism: creatine kinase microcompartments and recruitment of B-type creatine kinase to specific subcellular sites. *Amino Acids*. 2016;48(8):1751-1774.
27. Ydfors M, Hughes MC, Laham R, Schlattner U, Norrbom J, Perry CGR. Modelling in vivo creatine/phosphocreatine in vitro reveals divergent adaptations in human muscle mitochondrial respiratory control by ADP after acute and chronic exercise. *J Physiol*. 2016;594(11):3127-3140.
28. Hultman E, Soderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in men. *J Appl Physiol*. 1996;81(1):232-237.
29. Febbraio MA, Flanagan TR, Snow RJ, Zhao S, Carey MF. Effect of creatine supplementation on intramuscular TCr, metabolism and performance during intermittent, supramaximal exercise in humans. *Acta Physiol Scand*. 1995;155(4):387-395.
30. Yquel RJ, Arsac LM, Thiaudiere E, Canioni P, Manier G. Effect of creatine supplementation on phosphocreatine resynthesis, inorganic phosphate accumulation and pH during intermittent maximal exercise. *J Sports Sci*. 2002;20(5):427-437.
31. Gualano B, DE Salles Painneli V, Roschel H, et al. Creatine in type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Med Sci Sports Exerc*. 2011;43(5):770-778.
32. Faager G, Söderlund K, Sköld CM, Rundgren S, Tollbäck A, Jakobsson P. Creatine supplementation and physical training in patients with COPD: a double blind, placebo-controlled study. *Int J Chron Obstruct Pulmon Dis*. 2006;1(4):445-453.
33. Gordon A, Hultman E, Kaijser L, et al. Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance. *Cardiovasc Res*. 1995;30(3):413-418.
34. Lønbro S, Dalgas U, Primdahl H, Overgaard J, Overgaard K. Feasibility and efficacy of progressive resistance training and dietary supplements in radiotherapy treated head and neck cancer patients-the DAHANCA 25A study. *Acta Oncol*. 2013;52(2):310-318.
35. Chilibeck P, Kaviani M, Candow D, Zello GA. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. *Open Access J Sports Med*. 2017;8:213-226.
36. Forbes SC, Candow DG, Ostojic SM, Roberts MD, Chilibeck PD. Meta-analysis examining the importance of creatine ingestion strategies on lean tissue mass and strength in older adults. *Nutrients*. 2021;13(6):1912.
37. Devries MC, Phillips SM. Creatine supplementation during resistance training in older adults--a meta-analysis. *Med Sci Sports Exerc*. 2014;46(6):1194-1203.
38. Candow DG, Forbes SC, Chilibeck PD, Cornish SM, Antonio J, Kreider RB. Effectiveness of creatine supplementation on aging muscle and bone: focus on falls prevention and inflammation. *J Clin Med*. 2019;8(4):488.
39. Davies TW, van Gassel RJJ, van de Poll M, et al. Core outcome measures for clinical effectiveness trials of nutritional and metabolic interventions in critical illness: an international modified Delphi consensus study evaluation (CONCISE. *Crit Care*. 2022;26(1):240.
40. Ozalevli S, Ozden A, Itil O, Akkoclu A. Comparison of the Sit-to-Stand Test with 6 min walk test in patients with chronic obstructive pulmonary disease. *Respir Med*. 2007;101(2):286-293.
41. Strassmann A, Steurer-Stey C, Lana KD, et al. Population-based reference values for the 1-min sit-to-stand test. *Int J Public Health*. 2013;58(6):949-953.
42. Demonceau J, Ruppar T, Kristanto P, et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. *Drugs*. 2013;73(6):545-562.
43. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
44. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
45. Higgins J, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.3. Cochrane; 2022. Accessed May 22, 2023. www.training.cochrane.org/handbook
46. Gronau QF, Van Erp S, Heck DW, Cesario J, Jonas KJ, Wagenmakers EJ. A Bayesian model-averaged meta-analysis of the power pose effect with informed and default priors: the case of felt power. *Compr Results Soc Psychol*. 2017;2(1):123-138.
47. Van Erp S, Verhagen J, Grasman RPPP, Wagenmakers E-J. Estimates of between-study heterogeneity for 705 meta-analyses reported in *Psychological Bulletin* from 1990–2013. *J Open Psychol Data*. 2017;5(1):4.
48. Heck D, Gronau Q, Wagenmakers E. metaBMA: Bayesian model averaging for random and fixed effects meta-analysis. Accessed May 25, 2023. https://CRAN.R-project.org/package=metaBMA
49. Aguiar AF, Januário RSB, Junior RP, et al. Long-term creatine supplementation improves muscular performance during resistance training in older women. *Eur J Appl Physiol*. 2013;113(4):987-996.
50. Brose A, Parise G, Tarnopolsky MA. Creatine supplementation enhances isometric strength and body composition improvements following strength exercise training in older adults. *J Gerontol A Biol Sci Med Sci*. 2003;58(1):11-19.

51. Domingues WJR, Ritti-Dias RM, Cucato GG, et al. Effect of creatine supplementation on functional capacity and muscle oxygen saturation in patients with symptomatic peripheral arterial disease: a pilot study of a randomized, double-blind placebo-controlled clinical trial. *Nutrients*. 2021;13(1):149.
52. Gualano B, Macedo AR, Alves CRR, et al. Creatine supplementation and resistance training in vulnerable older women: a randomized double-blind placebo-controlled clinical trial. *Exp Gerontol*. 2014;53(7):7-15.
53. Hass CJ, Collins MA, Juncos JL. Resistance training with creatine monohydrate improves upper-body strength in patients with Parkinson disease: a randomized trial. *Neurorehabil Neural Repair*. 2007;21(2):107-115.
54. Neves M Jr, Gualano B, Roschel H, et al. Beneficial effect of creatine supplementation in knee osteoarthritis. *Med Sci Sports Exerc*. 2011;43(8):1538-1543.
55. Wilkinson TJ, Lemmey AB, Jones JG, et al. Can creatine supplementation improve body composition and objective physical function in rheumatoid arthritis patients? A randomized controlled trial. *Arthritis Care Res*. 2016;68(6):729-737.
56. Gotshalk LA, Kraemer WJ, Mendonca MAG, et al. Creatine supplementation improves muscular performance in older women. *Eur J Appl Physiol*. 2008;102(2):223-231.
57. Deacon SJ, Vincent EE, Greenhaff PL, et al. Randomized controlled trial of dietary creatine as an adjunct therapy to physical training in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008;178(3):233-239.
58. Fuld JP, Kilduff LP, Neder JA, et al. Creatine supplementation during pulmonary rehabilitation in chronic obstructive pulmonary disease. *Thorax*. 2005;60(7):531-537.
59. Cornelissen V, Defoor J, Stevens A, et al. Effect of creatine supplementation as a potential adjuvant therapy to exercise training in cardiac patients: a randomized controlled trial. *Clin Rehabil*. 2010;24(11):988-999.
60. Bernat P, Candow DG, Gryzb K, Butchart S, Schoenfeld BJ, Bruno P. Effects of high-velocity resistance training and creatine supplementation in untrained healthy aging males. *Appl Physiol Nutr Metab*. 2019;44(11):1246-1253.
61. Johannsmeyer S, Candow DG, Brahms CM, Michel D, Zello GA. Effect of creatine supplementation and drop-set resistance training in untrained aging adults. *Exp Gerontol*. 2016;83:112-119.
62. Alves CRR, Merege Filho CAA, Benatti FB, et al. Creatine supplementation associated or not with strength training upon emotional and cognitive measures in older women: a randomized double-blind study. *PloS one*. 2013;8(10):e76301.
63. Bemben MG, Witten MS, Carter JM, Eliot KA, Knehans AW, Bemben DA. The effects of supplementation with creatine and protein on muscle strength following a traditional resistance training program in middle-aged and older men. *J Nutr Health Aging*. 2010;14(2):155-159.
64. Candow DG, Vogt E, Johannsmeyer S, Forbes SC, Farthing JP. Strategic creatine supplementation and resistance training in healthy older adults. *Appl Physiol Nutr Metab*. 2015;40(7):689-694.
65. Chami J, Candow DG. Effect of creatine supplementation dosing strategies on aging muscle performance. *J Nutr Health Aging*. 2019;23(3):281-285.
66. Chrusch MJ, Chilibeck PD, Chad KE, Davison KS, Burke DG. Creatine supplementation combined with resistance training in older men. *Med Sci Sports Exerc*. 2001;33(12):2111-2117.
67. Cooke MB, Brabham B, Buford TW, et al. Creatine supplementation post-exercise does not enhance training-induced adaptations in middle to older aged males. *Eur J Appl Physiol*. 2014;114(6):1321-1332.
68. Pinto CL, Botelho PB, Carneiro JA, Mota JF. Impact of creatine supplementation in combination with resistance training on lean mass in the elderly. *J Cachexia Sarcopenia Muscle*. 2016;7(4):413-421.
69. Bermon S, Venembre P, Sachet C, Valour S, Dolisi C. Effects of creatine monohydrate ingestion in sedentary and weight-trained older adults. *Acta Physiol Scand*. 1998;164(2):147-155.
70. Sakkas GK, Mulligan K, Dasilva M, et al. Creatine fails to augment the benefits from resistance training in patients with HIV infection: a randomized, double-blind, placebo-controlled study. *PloS one*. 2009;4(2):e4605.
71. Goudarzian M, Rahimi M, Karimi N, et al. Mobility, balance, and muscle strength adaptations to short-term whole body vibration training plus oral creatine supplementation in elderly women. *Asian J Sports Med*. 2017;8:e36793.
72. Roy BD, de Beer J, Harvey D, Tarnopolsky MA. Creatine monohydrate supplementation does not improve functional recovery after total knee arthroplasty. *Arch Phys Med Rehabil*. 2005;86(7):1293-1298.
73. Norman K, Stübler D, Baier P, et al. Effects of creatine supplementation on nutritional status, muscle function and quality of life in patients with colorectal cancer--a double blind randomised controlled trial. *Clin Nutr*. 2006;25(4):596-605.
74. Eijnde BO, Van Leemputte M, Goris M, et al. Effects of creatine supplementation and exercise training on fitness in men 55-75 yr old. *J Appl Physiol*. 2003;95(2):818-828.
75. Eliot KA, Knehans AW, Bemben DA, Witten MS, Carter J, Bemben MG. The effects of creatine and whey protein supplementation on body composition in men aged 48 to 72 years during resistance training. *J Nutr Health Aging*. 2008;12(3):208-212.
76. Gotshalk LA, Volek JS, Staron RS, Denegar CR, Hagerman FC, Kraemer WJ. Creatine supplementation improves muscular performance in older men. *Med Sci Sports Exerc*. 2002;34(3):537-543.
77. Marini ACB, Motobu RD, Freitas ATV, et al. Short-term creatine supplementation may alleviate the malnutrition-inflammation score and lean body mass loss in hemodialysis patients: a pilot randomized placebo-controlled trial. *JPEN J Parenter Enteral Nutr*. 2020;44(5):815-822.
78. Rawson ES, Clarkson PM. Acute creatine supplementation in older men. *Int J Sports Med*. 2000;21(1):71-75.
79. Rawson ES, Wehnert ML, Clarkson PM. Effects of 30 days of creatine ingestion in older men. *Eur J Appl Physiol Occup Physiol*. 1999;80(2):139-144.
80. Applebaum EV, Breton D, Feng ZW, et al. Modified 30-second Sit to Stand test predicts falls in a cohort of institutionalized older veterans. *PloS one*. 2017;12(5):e0176946.
81. Dall PM, Kerr A. Frequency of the sit to stand task: an observational study of free-living adults. *Appl Ergon*. 2010;41(1):58-61.
82. Grant PM, Dall PM, Kerr A. Daily and hourly frequency of the sit to stand movement in older adults: a comparison of day hospital, rehabilitation ward and community living groups. *Aging Clin Exp Res*. 2011;23(5-6):437-444.
83. O'Grady HK, Edbrooke L, Farley C, et al. The sit-to-stand test as a patient-centered functional outcome for critical care research: a pooled analysis of five international rehabilitation studies. *Crit Care*. 2022;26(1):175.
84. Sanchez-Rodriguez D, Marco E, Cruz-Jentoft AJ. Defining sarcopenia: some caveats and challenges. *Curr Opin Clin Nutr Metab Care*. 2020;23(2):127-132.
85. Candow DG, Chilibeck PD, Forbes SC. Creatine supplementation and aging musculoskeletal health. *Endocrine*. 2014;45(3):354-361.
86. Candow DG, Chilibeck PD. Differences in size, strength, and power of upper and lower body muscle groups in young and older men. *J Gerontol A Biol Sci Med Sci*. 2005;60(2):148-156.

87. Candow DG, Forbes SC, Chilibeck PD, Cornish SM, Antonio J, Kreider RB. Variables influencing the effectiveness of creatine supplementation as a therapeutic intervention for sarcopenia. *Front Nutr*. 2019;6:124.
88. Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. *J Strength Cond Res*. 2003;17(4):822-831.
89. Bohannon RW. Grip strength: an indispensable biomarker for older adults. *Clin Interv Aging*. 2019;14:1681-1691.
90. Soysal P, Hurst C, Demurtas J, et al. Handgrip strength and health outcomes: umbrella review of systematic reviews with meta-analyses of observational studies. *J Sport Health Sci*. 2021;10(3):290-295.
91. Kaviani M, Shaw K, Chilibeck PD. Benefits of creatine supplementation for vegetarians compared to omnivorous athletes: a systematic review. *Int J Environ Res Public Health*. 2020;17(9):3041.
92. Burke DG, Chilibeck PD, Parise G, Candow DG, Mahoney D, Tarnopolsky M. Effect of creatine and weight training on muscle creatine and performance in vegetarians. *Med Sci Sports Exerc*. 2003;35(11):1946-1955.
93. Age UK. 1 in 4 (1.4 M) aged 60+ have been eating less since the start of the pandemic. Accessed June 20, 2023. https://www.ageuk.org.uk/latest-press/articles/2021/1-in-10-1.4-million-aged-60-have-been-eating-less-since-the-start-of-the-pandemic/
94. Smeuninx B, Mckendry J, Wilson D, Martin U, Breen L. Age-related anabolic resistance of myofibrillar Protein Synthesis Is Exacerbated in Obese Inactive Individuals. *J Clin Endocrinol Metab*. 2017;102(9):3535-3545.
95. Phillips BE, Williams JP, Greenhaff PL, Smith K, Atherton PJ. Physiological adaptations to resistance exercise as a function of age. *JCI Insight*. 2017;2(17):e95581.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Davies TW, Watson N, Pilkington JJ, et al. Creatine supplementation for optimization of physical function in the patient at risk of functional disability: a systematic review and meta-analysis. *J Parenter Enteral Nutr*. 2024;48:389-405. doi:10.1002/jpen.2607