The Additive Effects of Creatine Supplementation and Exercise Training in an Aging Population: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Background and Purpose: The role of creatine supplementation in young athletes and bodybuilders is well established including ergogenic properties of muscular hypertrophy, strength, power, and endurance. Whether the benefits of creatine supplementation translate to an aging population with moderate training stimulus remains unclear especially in regard to gender, creatine dose, and duration. This systematic review assessed whether creatine supplementation combined with exercise results in additive improvements in indices of skeletal muscle, bone, and mental health over exercise alone in healthy older adults.

Methods: PubMed, CINAHL, and Web of Science databases were utilized to identify randomized controlled trials of creatine supplementation combined with exercise in an aging population with additional predetermined inclusion and exclusion criteria. Two reviewers independently screened the titles and abstracts, reviewed full-text articles, and performed quality assessments using the Physiotherapy Evidence Database scale.

Results and Discussion: Seventeen studies were comprehensively reviewed according to categories of strength, endurance, functional capacity, body composition, cognition, and safety. These studies suggest that any additive ergogenic creatine effects on upper and/or lower body strength, functional capacity, and lean mass in an older population would require a continuous and daily low-dose creatine supplementation combined with at least 12 weeks of resistance training. Potential creatine specific increases in regional bone mineral density of the femur are possible but may require at least 1 year of creatine supplementation combined with moderate resistance training, and additional long-term clinical trials are warranted. The limited data suggested no additive effects of creatine over exercise alone on indices of mental health. The beneficial effects of creatine supplementation are more consistent in older women than in men.

Conclusions: Creatine monohydrate is safe to use in older adults. While creatine in conjunction with moderate- to high-intensity exercise in an aging population may improve skeletal muscle health, additional studies are needed to determine the effective dosing and duration paradigm for potential combined creatine and exercise effects on bone and cognition in older adults.

Key Words: bone, exercise, nutritional supplement, older adults, skeletal muscle

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INTRODUCTION

Creatine has been a mainstay supplement in gyms across the globe, especially within the bodybuilding community since the early 1990s.[1] Boasting ergogenic properties including energy storage in the form of creatine phosphate, hydrating effects, and increased rate of protein synthesis, creatine supplementation accumulates muscular improvements in size, strength, and endurance.[1] These effects are all vital components of performance in activity and sports and as such have been investigated at large in young adults, especially athletes.[2] In the last decade, however, a number of studies have reported similar effects of creatine supplementation in older adults specifically on muscle function, bone remodeling, and central nervous system (CNS) processing.[3-6]

Creatine is naturally ingested through diet, is formed naturally in trace amounts from the liver, and can be ingested through various supplemental forms.[1] Once converted to phosphocreatine (PCr) and stored largely in skeletal muscle, it is available for the body to use preferentially over adenosine triphosphate as its primary energy source to replenish adenosine diphosphate after energy expenditure. Creatine allows for an increased fuel supply that is readily available throughout the body, leading to an increased rate of protein synthesis during activities with high-energy demand. Creatine monohydrate (CM) is the form of creatine supplementation that has been most widely used and

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investigated with an estimated $2.7 billion in annual sales of CM in 2009 worldwide.[1] Compared with other formulations of CM (creatine anhydrous, creatine ethyl ester, and creatine malate), the Food and Drug Administration has approved only CM for public consumption, and evidence shows that CM is safe to use and is most efficacious when compared with other novel forms of creatine.[1] Creatine monohydrate has well-established effects on muscle enhancement properties including effects on exercise capacity, endurance, muscle mass, bone mineral density (BMD), power, and strength.[1]

In 2003 and 2009, the American College of Sports Medicine[7] guidelines recommended the need for further CM studies to prove the safety of CM. The recreational use of CM was discouraged by the American College of Sports Medicine because of concerns of liver and kidney failure, dehydration, and cramping. All of these potential side effects were disproved and further studies verified that CM supplementation had no negative effects on liver and kidney function in healthy individuals. In fact, CM may prevent dehydration and muscle cramping when athletes exercise during extreme environmental conditions.[8] According to the majority of recent literature,[1,8] CM is a safe supplement to use and does not pose the aforementioned threats to health.

Although past creatine research was mainly focused on trained athlete performance, there is some available literature about its efficacy on muscle strength, bone and muscle mass, recovery enhancement, and cognitive function in older adults.[5,6,9] This is of interest considering the natural age-related decline that occurs with the musculoskeletal and central nervous systems and the subsequent increased risk of sarcopenia, osteoporosis, and cognitive decline. A number of published studies have looked at the combined effects of creatine and resistance training (RT) in the aging population with mixed results. While some report significant effects on muscle mass, strength, and functional performance with combined creatinine supplementation and RT compared with training alone,[6,10,11] others report no effects for the same measured outcomes.[6,12-16] Recently, research involving creatine supplements have stemmed away from ergogenic properties to focus on systematic effects, including but not limited to depression, neuroprotection, cardiac protection, cognition, and body composition, but the data in the aging population are limited. The uncertainty of the added benefits of creatine supplementation and RT becomes muddled when taking into account the heterogeneity of the available literature, which does not always distinguish between effects of creatine in men and women, presence of preexisting disease, dose and duration of creatine consumption, and intensity of RT protocol. An updated comprehensive review of the literature in the context of the aforementioned contributing factors in the aging population is lacking.

This review specifically assessed the impact of creatine supplementation combined with physical exercise on age-related indices of muscle strength, functional tasks, endurance, body composition, and cognitive performance in healthy older adults, with a focus on gender and dose and duration of creatine supplementation. Results from this systematic literature review will provide further understanding of creatine supplementation and its potential therapeutic value in combination with exercise training to support healthy aging in an older population.

METHODS

Data Sources and Searches

A systematic literature search was conducted using the databases PubMed, CINAHL, and Web of Science to identify articles published in English between the time period 1998 through 2018 that specifically investigated the additive effects of creatine supplementation and exercise in older adults. Databases were searched for the terms "creatine supplementation" and "older adult." Additional terms that were searched with this MeSH heading include "rehabilitation," "resistance exercise" (and synonyms including "strength training"), "physical fitness," "aging," "recovery," "cognition," "muscle strength," and "body composition," Manual searches from the references of extracted articles were also performed to identify additional potential studies not identified through the databases. Initial database search results are available in Supplemental Digital Content Appendix 1, available at: http://links.lww.com/JGPT/A30.

Study Selection

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, including the 27-item checklist and flow diagram.[17] One reviewer (M.B.) independently screened the titles and abstracts of the search results for eligibility using the inclusion and exclusion criteria. Two reviewers (A.S. and M.B.) independently screened the collected full-text articles against the inclusion and exclusion criteria and any studies that did not meet the criteria were removed. The results of the remaining studies were discussed until a consensus on what studies to include in the study was achieved between the 2 reviewers.

The population of interest was healthy older adults, which is arbitrarily set at the age of 65 years; however, age-related decline in skeletal muscle mass, muscle strength, and BMD occurs steadily after the fourth decade. Thus, for study selection this review included participants aged 48 years and older. Additional inclusion criteria were creatine supplementation, inclusion of a true control (no creatine supplementation group), a physical training program, randomized controlled trials, and outcome measures in either of the following: strength, body composition, functional capacity, endurance, and cognition. Exclusion criterion included animal trials, athletic population, high-intensity exercise programs (ie, drop RT), mixed creatine formulations (ie, inclusion of protein, other dietary supplements, etc) and preexisting disease (cardiovascular, musculoskeletal, or other chronic conditions).

Quality Assessment

All articles were critically appraised by 2 reviewers, using the Physiotherapy Evidence Database (PEDro) scale, a validated and reliable 11-item tool that assesses the methodological quality of randomized controlled trials.[18] The maximum possible score is 10, with higher scores indicating greater methodological quality. Points were awarded for each criterion only if the study specifically reported that the criterion as described on the PEDro checklist had been met. Based on a previously published cutoff score, articles with PEDro scores of 6 or higher were considered to be of "high" methodological quality.[19] Both reviewers manually and independently scored the included studies and any disagreements were discussed until a consensus was reached. All 17 studies scored at least a 6 or higher on the PEDro scale and thus no articles were excluded from the review.

Data Extraction

Data extraction was performed by 1 reviewer (A.S.) and verified by the second reviewer (M.B.). Extracted information included authors, publication date, study design, sample size, participant age, RT protocol, creatine-dosing paradigm, intervention duration, adverse effects, and results of selected outcome measures (see Table 1). Results are reported as they were in the original study. For the studies primarily looking at strength, the outcome measures included 1-repetition maximum (1-RM) tests for bench press, bicep curl, chest press, and/or leg press,[3,10,12,13,15,20-22,29,31-33] isokinetic tests,[14,23] and isometric tests.[12,15] The outcome measures for the studies that analyzed functional capacity included the 30-second sit-to-stand test,[10,29] floor-to-stand test,[29] Timed Up and Go test,[10] 30-m walk test,[15] and 14-stair climb test.[15] Cycle ergometry and cardiorespiratory tests were used to assess endurance.[14,16] Extracted outcome measures for body composition included body mass, fat mass, lean tissue mass, fat-free mass, percentage of body fat, total and regional BMD, and bone mineral content (BMC).[3,10,12-16,20-23,25,29,31-33] Finally, the cognition-based study from Alves et al[9] utilized the Geriatric Depression Scale, Mini-Mental State Examination, Stroop Test, Trail-Making Test, Digit Span Test, and Delay Recall Test.

RESULTS

Study Characteristics

A total of 480 potentially relevant studies were identified out of the initial PubMed, CINAHL and Web of Science database searches, of which duplicates were removed and studies were further excluded from title and abstract reviews. The remaining 28 studies proceeded to full-text review and were assessed for eligibility. The study selection process, which was in accordance with the PRISMA statement,[17] is presented in the Figure. The mean PEDro score was 7.5, with most studies failing to report whether the allocation of participants was concealed and/or whether there was inclusion of an intention-to-treat analysis where appropriate. Results of the qualitative review are found in Supplemental Digital Content Appendix 2, available at: http://links.lww.com/JGPT/A33. A total of 17 studies were included for qualitative synthesis. Characteristics of the 17 studies including the detailed intervention (RT protocol and creatine dosing) and reviewed outcome measures are shown in Table 1, organized alphabetically and divided by gender. All participants were reported as healthy and cleared for participation and most studies[3,9,10,12,13,15,20-22,25,29,31-33] reported a required dietary record from participants to monitor nourishment status. With the exception of a few studies,[15,21,23,25,31,32] participants were reported as being previously untrained as defined by the following: lacking regular physical fitness or RT for a period of 4 months to 2 years prior to the study,[3,9,10,13,14,20,29] being sedentary to active exercise,[12,33] moderately active,[3,16,20,33] or having no prior experience with RT.[12,16,22] The compiled extracted results were organized into the following 6 sections: (1) strength, (2) functional capacity, (3) endurance, (4) body composition, (5) cognition, and (6) adverse effects. The results were organized into separate tables, divided by gender, and are further described later.

Strength

All studies measuring strength in female participants demonstrated significant creatine effects on the 1-RM bench press. In addition, Aguiar et al[29] demonstrated improvements in the 1-RM biceps curl and knee extension compared with the RT placebo group ($P < .05$). In each of these studies, creatine supplementation was considered long term (>12 weeks), with a daily 5-g, low-dose ingestion.

Of the 7 all male participant studies, 2 reported significant strength effects in the 1-RM leg press over the RT placebo group.[32,33] Chrusch et al[33] also demonstrated significant increases in average isokinetic knee extension/flexion power in the trained creatine group compared with trained placebo ($P < .02$). Both studies utilized a creatine-loading dosage of 0.3 g/kg/d for 5 days, followed by a low daily maintenance dose for 11 weeks. Despite significant increases in strength overall, the remaining 5 studies conducted in men failed to demonstrate any significant strength increases in the RT creatine group over the RT placebo group.[13,14,20,23,31] With the exception of Eijnde et al,[14] the 5 studies that did not demonstrate significant strength effects in the RT creatine group utilized creatine supplementation on training days only in replace of daily ingestion.[13,20,23,31] Eijnde et al[14] utilized a 6-month, 5-g daily creatine ingestion protocol.

Four studies investigated the effects of creatine and RT in combined older men and women. Brose et al[15] demonstrated significant creatine effects in isometric dorsiflexion and knee extension strength over the equivalent RT placebo group ($P < .05$). Creatine supplementation followed a daily 5-g dose for 14 weeks.[15] Candow et al[3] showed that creatine supplementation, on training days only, when combined with 32 weeks of RT significantly increased

Table 1. Details of Included Studies Organized by Gender[a]

Author	Age (Sample Size)	Intervention (RT Protocol, Groups, Creatine Dose)	Outcome Measures *(Italics Indicates No Reported Significant Creatine Effects)*
Female subjects only			
Aguiar et al (2013)[29]	60-80 y (n = 18)	RT: 3 d/wk, 2 sets of 10-15 reps, 60- and 120-s rest between sets and exercises, respectively (8 whole-body exercises). Completed 12 wk of RT prior to supplementation, then an additional 12 wk of RT ± supplements Groups: Pl or Cr Cr dose: 5 g/d, 7 d/wk, immediately posttraining on training days	S: 1-RM tests (bench press, biceps curl, and knee extension) F: 30-s chair-stand test, floor-to-stand test BC: total fat-free mass, muscle mass, *fat mass, percentage body fat, body mass*
Alves et al (2013)[9]	60-80 y (n = 47)	RT: 2 d/wk, 3 sets of 12-15 reps, 1-min interval between sets (7 exercises) Groups: Cr, Cr + RT, Pl, Pl + RT Cr dose: loading: 20 g/d, in 4 divided doses per day, for 5 d; Cr maintenance: 5 g/d for remaining weeks	Cog: *Geriatric Depression Scale, Mini-Mental State Examination, Stroop Test, Trail-Making Test, Digit Span Test, Delay Recall Test*
Canete et al (2006)[16]	60-80 y (n = 16)	Physical activity: 4-5 d/wk; walking for 30-60 min/d Groups: Cr or Pl Cr dose: 0.3 g/kg of body weight, in 3 divided doses per day with each meal, 7 d/wk.	F: sit-stand test E*: 1-mile walk, ventilatory threshold, and peak oxygen intake during cycle ergometry* BC*: body mass*
Chilibeck et al (2015)[21]	57 y (n = 37)	RT: 3 d/wk, 3 sets of 10 reps, 80% of 1 RM (15 exercises) Groups: Cr, Pl Cr dose: .1 g/kg body weight, in 2 equal doses with meals, 4 d/wk on nontraining days; 0.1 g/kg body weight, in 2 equal doses immediately before and after RT sessions, 3 d/wk, on training days	S: 1-RM tests (*hack squat*, bench press) BC: *total* and regional BMD (*lumbar spine*, femoral neck), *whole-body lean tissue mass* AE: Documented during the study
Gualano et al (2014)[10]	>60 y (n = 60)	RT: 2 d/wk, 2 sets of 15-20 reps on week 1; 3 sets of 8-12 reps thereafter Groups: Cr, Cr + RT, Pl, Pl + RT Cr dose: Cr loading: 20 g/d, in 4 divided doses per day at meals, for 5 d; Cr maintenance: 5 g/d, 7 d/wk, with lunch	S: 1-RM test (*leg press* and bench press) F: 30-s chair-stand test; *Timed Up and Go* (*TUG*) BC: appendicular lean mass, *total body and regional* (*lumbar spine, femoral neck, total femur*) *measures of BMD*, *fat mass*
Male subjects only			
Bemben et al (2010)[13]	48-72 y (n = 40)	RT: 3 d/wk, 3 sets of 8 reps, 80 % 1-RM. Groups: Pl, Cr, Pr, or Pr + Cr Cr dose: loading: 7 g/d, 3 d/wk on training days; Cr maintenance: 5 g/d, 3 d/wk on training days	S: *1-RM tests* (*knee extensions; knee flexion; bicep curls; tricep extension; military press; lat pull downs; seated leg press and bench press*) BC: *lean body mass*
Candow et al (2008)[31]	59-77 y (n = 35)	RT: 3 d/wk; 3 sets of 10 reps, 70% of 1-RM, 2-min rest between sets Groups: Pl, Cr, Cr + Pr Cr dose: Cr: 0.1 g/kg body weight in 3 divided doses per day, 3 d/wk posttraining	S: *1-RM tests* (*leg press and bench press*) BC: body mass, *lean tissue mass*
Carter et al (2005)[23]	48-72 y (n = 37)	RT: 3 d/wk, 3 sets of 8 reps, 80% of 1-RM, (8 exercises) Groups: Pl, Cr, Cr + Pr Cr dose: loading: 7 g/d, for 3 d/wk, immediately post-training; Cr maintenance: 5 g/d, for 3 d/wk	S: *isokinetic tests for knee extensors and flexors* (*peak torque, time to torque, average power*) *at three testing velocities* (*60°/s, 180°/s, 240°/s*) BC: *total and regional fat-free mass*
Chilibeck et al (2005)[32]	64-77 y (n = 29)	RT: 3 d/wk, 3 sets of 10 reps, 50% of 1-RM (12 exercises) Groups: Cr, Pl Cr dose: loading: 0.3 g/kg body weight for 5 d, followed by 0.07 g/kg body weight for remaining 11 wk	S: 1-RM tests (leg press and *bench press*) BC: *BMD* and BMC in arms, *legs, trunk, whole body*

(*continues*)

Table 1. Details of Included Studies Organized by Gender[a] (*Continued*)

Author	Age (Sample Size)	Intervention (RT Protocol, Groups, Creatine Dose)	Outcome Measures *(Italics Indicates No Reported Significant Creatine Effects)*
Chrusch et al (2001)[33]	60-84 y (n = 30)	RT: 3 d/wk, 3 sets of 10 reps, 50% of 1-RM, 1-min rest between sets (12 exercises) Groups: Cr, Pl Cr dose: loading: 0.3 g/kg body weight, in 3 divided does with meals, for 5 d; Cr maintenance: 0.07 g/kg body weight, in 3 divided does with meals for remaining 11 wk	S: 1-RM tests (leg press, *knee extension, and bench press*), average power for the knee extensors/flexors test BC: body mass, lean tissue mass, *fat mass, and % body fat* AE: Retrospective creatine side effect assessment
Cooke et al (2014)[20]	50-70 y (n = 20)	RT: 3 d/wk, 3 sets of 10 reps, 75% of 1-RM, 1 min rest between sets (7 exercises) Groups: Cr, Pl Cr dose: loading: 20 g/d, in 4 divided doses per day, for 7 d; Cr maintenance: 0.1 g/kg of body weight, 3 d/wk, on training days	S: *1-RM tests* (*leg press and bench press*) BC: *body mass, % body fat, fat-free mass, fat mass*
Eijnde et al (2003)[14]	55-75 y (n = 46)	Cardiorespiratory endurance and RT 2-3 d/wk: cycle ergometry for 12 min, followed by treadmill walking/jogging or rowing ergometry for 12 min, set at 65% of the individual heart rate reserve; RT: 2 sets of 30 reps, set at 30-repetition maximum workload Groups: Cr, Pl Cr dose: 5 g/d, in 3 divided doses per day (1-g breakfast, 3-g lunch, 1-g dinner), on nontraining days; with the 3-g dose taken immediately following training on training days	S: *isometric strength of the knee-extensor muscles via an isokinetic dynamometer* E: *maximal cycle-ergometer test* (*anaerobic threshold* (*VT*)*; heart rate and respiratory gas exchange ratio* (VCO_2/VO_2) *at VT; peak oxygen uptake; diastolic blood pressure*) BC: *fat-free mass, % body fat* AE: Blood and urine analysis
Eliot et al (2008)[25]	48-72 y (n = 42)	RT, 3 d/wk, 3 sets of 8 reps, 80% 1-RM (8 exercises) Groups: Pl, Cr, Pr, Cr + Pr Cr dose: loading: 7.0 g/d, 3 d/wk; Cr maintenance: 5 g/d, 3 d/wk, immediately posttraining	BC: *body mass and body fat mass; total body and regional* (*arms, legs, and trunk*) *measures of bone free-fat free mass and % body fat*
Combined male and female subjects			
Bermon et al (1998)[12]	67-80 y (n = 32)	RT: 3 d/wk, 3 sets of 8 reps, 80% of 1 RM (3 exercises) Groups: Cr, Cr+ RT, Pl, Pl + RT Cr dose: loading: 20 g/d, in 4 divided doses per day, for 5 d; Cr maintenance: 3 g/d, 7 d/wk	S: *1-RM, 12-RM tests* (*chest press, horizontal leg press, leg extension*) *isometric intermittent endurance* (*IIE*) *of 1 upper and 2 lower body muscle groups* BC: body mass, body mass index, and body fat
Brose et al (2003)[15]	>65 y (n = 28) 15 men, (67.8 ± 4.0 y) 15 women (69.3 ± 6.3 y)	RT: 3 d/wk, 1 set of 10-12 reps, 50% of 1-RM (12 exercises); progressing to 3 sets at 80% of 1 RM Groups: Cr, Pl Cr dose: 5.0 g/d, 7 d/wk	S: *1-RM* (*chest press, leg press, arm flexion, and knee extension*); isometric tests (knee extension, handgrip, ankle dorsiflexion) F: *30-s chair-stand test, 30-m walk test, 14-stair climb test* BC: total body mass, *fat mass*, fat-free mass, *% body fat, BMC*
Candow et al (2015)[3]	50-71 y (n = 39)	RT: 3 d/wk, 3 sets of 10 reps, 1- to 2-min rest between sets (11 exercises) Groups: Pl, Cr before (CrB), and Cr after (CrA) training Cr dose: .1 g/kg body weight, either immediately before or after training, on training days only	S: 1-RM tests (leg press and chest press) BC: lean tissue, *fat mass*
Pinto et al (2016)[22]	60-80 y (n = 27)	RT: 3 d/wk, 3 sets of 13-15 reps for abdominal and lumbar regions, 3 sets of 10-13 reps for all other muscles, 1-min rest between sets, alternate days between upper limbs/abdomen (7 exercises) and lower limbs/lumbar (7 exercises) exercises Groups: Cr, Pl Cr dose: 5 g/d, 4 d/wk, with lunch on nontraining days; 5/g/d, 3 d/wk, immediately after RT	S: *10-RM tests* (*bench press and leg press exercises*) BC: lean mass; *total and regional* (*lumbar spine, femoral neck, femur*) *BMC and BMD*

Abbreviations: AE, adverse effects; BC, body composition; BMC, bone mineral composition; BMD, bone mineral density; Cog, cognition; Cr, creatine; E, endurance; F, functional tasks; Pl, placebo; RM, repetition maximum; RT, resistance training; S, strength; VT, ventilatory threshold.
[a]Italicized outcome measures indicate no significance between Cr and Pl groups.

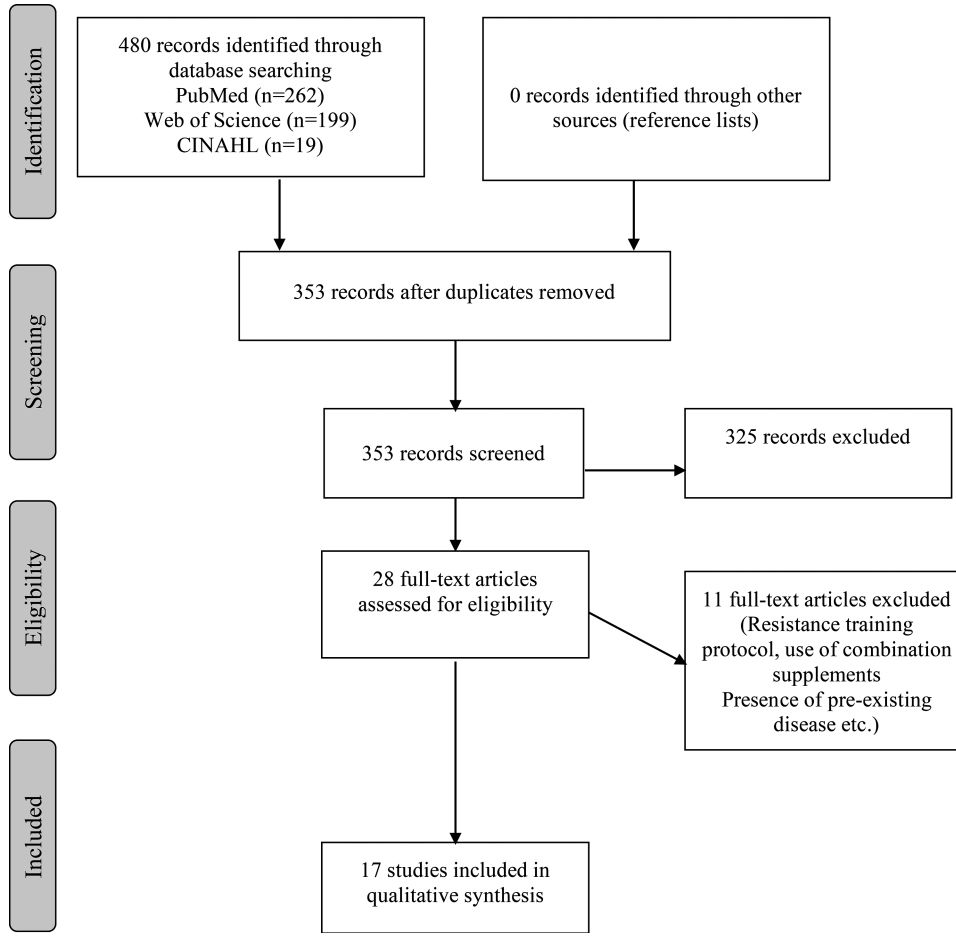

Figure. PRISMA flow diagram outlining the search and screening process.

upper and lower body strength as measured by chest press and leg press, respectively, compared with RT alone ($P <$ .025). Conversely, Bermon et al[12] and Pinto et al[22] both utilized a low-dose daily creatine ingestion protocol combined with RT for 7 and 12 weeks, respectively, and reported significant training effects in strength overall with no differences between RT creatine and placebo groups. See Table 2 for details of significant creatine effects found for strength and Table 1 for a list of all strength measures assessed.

Functional Capacity

All 3 studies conducted in older (>60 years) healthy women demonstrated significant effects of creatine on functional capacity following daily ingestion of creatine. Aguiar et al[29] reported significantly greater posttest improvements for both the 30-second chair-stand test and the floor-to-stand test in the creatine supplementation group over the placebo group ($P < .01$). Gualano et al[10] also reported significant effects on the 30-second chair-stand posttest in the RT creatine group over the RT placebo group ($P = .02$). Finally, Canete et al[16] demonstrated a significant reduction in the posttreatment time to complete the sit-to-stand test compared with baseline measurements in the creatine RT group ($P < .05$) but not in the RT only group. Brose et al[15] conducted a study in both healthy men and women (>65 years), which also utilized a similar daily creatine ingestion and RT protocol for 14 weeks. Significant increases in all 3 functional tasks (30-second chair-stand test, 30-m walk test, or 14-stair climb) were found following RT in all groups ($P < .05$), with no between-group differences. See Table 3 for details of significant creatine effects found for functional capacity and Table 1 for a list of all functional tests assessed.

Endurance

Canete et al[16] assessed the short-term effects of 1-week daily creatine supplementation combined with exercise in healthy older females (>60 years) on endurance capacity as measured by a 1-mile walk test and ventilatory threshold and peak oxygen intake ($\dot{V}o_{2peak}$) measured during cycle ergometry. No significant group, time, or interaction effects were found between creatine and placebo groups for all measured indices of endurance capacity. Eijnde et al[14] assessed the long-term effects of 6-month daily creatine supplementation combined with RT in healthy older males (>55 years) on markers of cardiorespiratory endurance

Table 2. Strength

Author	Duration	Creatine Versus Placebo Supplementation Results
Strength measurements in female subjects		
Aguiar et al (2013)[29]	24-wk RT (12-wk without and with supplementation) 12-wk Cr, daily ingestion, and immediately posttraining	Significant Cr gains in 1-RM bench press, biceps curl, and knee extension compared to Pl group ($P < .05$)
Gualano et al (2014)[10]	24-wk RT 1-wk Cr loading; 23-wk maintenance daily ingestion	Significant Cr gains in 1-RM bench press compared to all groups ($P < .05$)
Chilibeck et al (2015)[21]	12-mo RT 12-mo low-dose Cr daily ingestion	Significant Cr training gains in 1-RM bench press compared to Pl training group ($P < .05$)
Strength measurements in male subjects		
Bemben et al (2010)[13]	14-wk RT 2-wk Cr loading, 10-wk Cr posttraining days only	None
Candow et al (2008)[31]	10-wk RT 10-wk Cr: 1× pre-, and 2× posttraining days only	None
Carter et al (2005)[23]	16-wk RT 1-wk Cr loading; 15-wk Cr posttraining days only	None
Chilibeck (2005)[32]	12-wk RT 5-d Cr loading; 79 d Cr daily ingestion	Significant Cr gains in 1-RM leg press compared to Pl group ($P < .05$)
Cooke et al (2014)[20]	12-wk RT 1-wk Cr loading; 11-wk Cr posttraining days only	None
Chrusch et al (2001)[33]	12-wk RT 11-wk Cr daily ingestion, with 5-d initial loading dose	Significant Cr strength gains in leg press over Pl group ($P < .05$) Significant Cr isokinetic knee extension/flexion power compared to Pl group ($P < .02$)
Eijnde et al (2003)[14]	6-mo strength and endurance training 6-mo low-dose Cr daily ingestion	None
Strength measurements in combined male and female subjects		
Bermon et al (1998)[12]	7-wk RT 5-d Cr loading; 47-d Cr once daily ingestion	None
Brose et al (2003)[15]	14-wk RT 14-wk Cr daily ingestion	Significant Cr isometric dorsiflexion strength in men compared to Pl group ($P < .05$) Significant Cr isometric knee extension strength in men and women compared to Pl group ($P < .05$)
Candow et al (2015)[3]	32-wk RT 32-wk Cr, immediately before or after training days only	Significant Cr gains in leg press and chest press strength for both CrA and Cr B groups compared to Pl ($P < .025$)
Pinto et al (2016)[22]	12-wk RT 12-wk low-dose Cr daily ingestion	None

Abbreviations: Cr, creatine; Pl, placebo; RM, repetition maximum; RT, resistance training.

capacity (heart rate, $\dot{V}o_2$, workload, and diastolic blood pressure measured at ventilatory threshold), which were collected during a maximal incremental cycle ergometer test. Similar to the study by Canete et al,[16] all cardiorespiratory endurance measurements were not significantly different between placebo and creatine groups at any measured time point across the study (data not shown). See Table 1 for a list of endurance measurements assessed.

Body Composition

Three of the 4 studies conducted in older females reported significant body composition effects with creatine supplementation during RT compared with placebo (see Table 4). Following 12 weeks of daily creatine ingestion, Aguiar et al[29] showed significant creatine-specific improvements in fat-free mass and muscle mass compared with RT alone ($P < .01$). Chilibeck et al[21] investigated the effects of daily creatine ingestion on lean tissue mass as well as total and regional BMD of the lumbar spine and femoral neck and showed significantly reduced rate of femoral neck BMD loss with the RT creatine group compared with RT placebo ($P < .05$). An increase in femoral shaft subperiosteal width was also observed with the RT creatine group at 12 months compared with baseline ($P < .05$) but not

Table 3. Functional Capacity

Author	Duration	Creatine Versus Placebo Supplementation Results
Functionality measurements in female subjects		
Aguiar et al (2013)[29]	24-wk RT (12-wk without and with supplementation) 12-wk Cr, daily ingestion, and immediately posttraining	Cr significantly more efficient by 18.7% and 10.7% in the 30-s chair-stand test and floor-to-stand test at posttest than Pl group ($P < .01$)
Canete et al (2006)[16]	1-wk physical exercise 1-wk Cr daily ingestion	Significant decrease (12%) in sit-to-stand test time from the pre- to posttreatment conditions in Cr group ($P < .05$).
Gualano et al (2014)[10]	24-wk RT 1-wk Cr 23-wk daily ingestion	Significant Cr difference in 30-s chair-stand test compared to Pl + RT ($P = .02$)
Functionality measurements in female and male subjects		
Brose et al (2003)[15]	14-wk RT 14-wk Cr daily ingestion	None

Abbreviations: Cr, creatine; Pl, placebo; RT, resistance training.

in the RT placebo group. Gualano et al[10] reported similar effects of daily creatine supplementation combined with RT on significantly greater appendicular lean mass accrual at 24 months postcreatine supplementation compared with placebo ($P < .05$). The shortest supplementation period of 1-week daily creatine ingestion combined with exercise in healthy older females (>60 years) as assessed by Canete et al[16] showed no significant differences in posttest body mass values compared with baseline for either the RT creatine group or the RT placebo group.

All 8 studies conducted in men assessed body composition to varying degrees with 3 demonstrating creatine-specific effects. Candow et al[31] demonstrated significant creatine effects on body mass with creatinine supplementation ($P < .05$) over placebo following 10 weeks of RT and creatine supplementation ingested on training days only. Chrusch et al[33] utilized a similar 12-week RT program combined with daily creatine ingestion and showed increases in both body mass ($P < .05$) and lean tissue mass ($P < .05$) compared with the RT placebo group. In a 12-week RT study utilizing daily creatine ingestion, Chilibeck et al[32] showed significant creatine effects in arm BMC (3.2% greater, $P = .0009$) compared with placebo.[32] The remaining 5 studies in older males failed to demonstrate any added creatine-specific body composition differences over RT alone.

The studies assessing body composition that were conducted in both older males and females combined demonstrated significant creatine effects on lean mass[3,22] or total body mass and fat-free mass[15] when compared with the RT placebo group. The RT training programs ranged from 12 to 32 weeks and included both daily supplementation of creatine[15,22] and supplementation on training days only.[3] Pinto et al[22] also measured BMC and BMD from total body and lumbar spine, femoral neck, and femur similar to both Gualano et al[10] and Chilibeck et al[21] described previously; however, there were no significant differences between the creatine and placebo RT groups. See Table 4 for details of significant creatine effects for body composition and Table 1 for a list of all body composition indices assessed.

Cognition

One study investigated potential additive effects of daily creatine ingestion combined with 24 weeks of RT on a battery of cognitive and mental outcomes.[9] Although both creatine and placebo RT groups demonstrated decreases in the Geriatric Depression Scale scores when compared with their respective non-RT controls ($P < .0001$ and $P < .01$, respectively), there was no added effect of creatine supplementation on mental state over RT alone.[9] Cognitive performance remained unchanged for all groups across all cognitive tests (Data not shown). See Table 1 for a list of cognitive measurements assessed.

Adverse Effects

Several studies[14,21,33] reported adverse effects that occurred during the course of their investigation (see Table 5). All 3 studies utilized a daily, low dose of creatine. Chrusch et al[33] also utilized an initial 5-day creatine loading period. During the poststudy follow-up, participants self-reported varied mild to moderate gastrointestinal disturbances,[21,33] muscle cramping,[21,33] and muscle strain.[33] The 6-month combined creatine and RT study by Eijnde et al[14] reported 5 cardiovascular adverse events of ST-segment depression during the 3- or 6-month exercise tests, which included 4 RT creatine participants and 1 RT placebo participant (no significance detected between the 2 groups). Two of these participants were instructed to leave the study and entered a cardiovascular rehabilitation program, while the other participants were cleared to continue with the remainder of the study. Liver enzymes and blood and urine markers were not significantly altered in participants supplementing with creatine in these studies.[14,21,33] See Table 5 for a summary of reported creatine adverse effects.

DISCUSSION

This systematic review assessed whether creatine supplementation combined with exercise results in additive effects on indices of skeletal muscle, bone, and mental health over exercise alone in older adults. Additional attention was also

Table 4. Body Composition

Author	Duration	Creatine Versus Placebo Supplementation Results
Body composition measurements in female subjects		
Aguiar et al (2013)[29]	24-wk RT (12-wk without and with supplementation) 12-wk Cr, daily ingestion, and immediately posttraining	Significant Cr gains in fat-free mass (+3.2) and muscle mass (+2.8) than Pl group ($P < .01$)
Canete et al (2006)[16]	1-wk physical exercise 1-wk Cr daily ingestion	None
Chilibeck et al (2015)[21]	12-mo RT 12-mo low-dose Cr daily ingestion	Significant decrease in the rate of femoral neck BMD loss in Cr compared to Pl group ($P < .05$) Significant increase in femoral shaft subperiosteal width in Cr compared to Pl group ($P < .05$)
Gualano et al (2014)[10]	24-wk RT 1-wk Cr; 23-wk daily ingestion	Significant Cr gains in appendicular lean mass accrual compared to Pl + RT ($P < .05$)
Body composition measurements in male subjects		
Bemben et al (2010)[13]	14-wk RT 2-wk Cr loading, 10-wk Cr posttraining days only	None
Candow et al (2008)[31]	10-wk RT 10-wk Cr: 1× pre- and 2× posttraining days only	Significant Cr increase in body mass and total muscle thickness compared to Pl ($P < .05$)
Carter et al (2005)[23]	16-wk RT 1-wk Cr loading; 15-wk Cr posttraining days only	None
Chilibeck et al (2005)[32]	12-wk RT 5-d Cr loading; 79 d Cr daily ingestion	Significant Cr gains in arm BMC by 3.2% compared to Pl ($P = .0009$)
Chrusch et al (2001)[33]	12-wk RT 11-wk Cr daily ingestion, with 5-d initial loading dose	Significant Cr increases in body mass compared with the Pl group ($P < .05$) Significant Cr gains in lean tissue mass compared with Pl group ($P < .05$)
Cooke et al (2014)[20]	12-wk RT 1-wk Cr loading; 11-wk Cr posttraining days only	None
Eijnde et al (2003)[14]	6-mo strength and endurance training 6-mo low-dose Cr daily ingestion	None
Eliot et al (2008)[25]	14 wk 1-wk Cr loading, 13-wk maintenance posttraining days only	None
Body composition measurements in combined female and male subjects		
Bermon et al (1998)[12]	7-wk RT 5-d Cr loading; 47-d Cr once daily ingestion	None
Brose et al (2003)[15]	14 wk 14-wk Cr daily ingestion	Significant Cr gains in fat-free mass and total body mass compared with placebo ($P < .05$); differences between men and women not indicated
Candow et al (2015)[3]	32-wk RT 32-wk Cr, immediately before or after training days only	Significant Cr gains in lean mass compared to Pl ($P < .025$)
Pinto et al (2016)[22]	12-wk RT 12-wk low-dose Cr daily ingestion	Significant Cr gains in lean mass compared to Pl ($P = .02$)

Abbreviations: BMC, bone mineral composition; BMD, bone mineral density; Cr, creatine; Pl, placebo; RT, resistance training.

given to potential gender differences and differences attributed to the dose and duration of creatine supplementation. A discussion of each reviewed category follows.

Strength and Functional Capacity

Creatine when administered daily for 6 months[10,29] and up to 1 year[21] and combined with at least 2 to 3 days of RT a week can lead to beneficial effects on upper body strength in women aged 57 years and older. The ability to increase maximal strength tests with greater training volume also translated to increased functional capacity.[10,29] An acute RT program combined with creatine supplementation for 1 week also improved functional performance, thus supporting creatine as an effective strategy to improve functional capacity as it relates to activities of daily living in older adults.[16] These studies support

Table 5. Reported Adverse Effects

Author	Duration	Creatine Versus Placebo Supplementation Results
Adverse effects reported in studies with female subjects		
Chilibeck et al (2015)[21]	12-mo RT 12-mo low-dose Cr daily ingestion	Five creatine group subjects reported mild constipation, diarrhea, heart burn, irritable bowel, and nausea. Two creatine group subjects reported mild to moderate muscle cramps. One placebo group subject reported mild nausea. Two placebo group subjects had higher than normal liver enzyme or bilirubin levels. One had mild low creatinine clearance.
Adverse effects reported in studies with male subjects		
Chrusch et al (2001)[33]	12-wk RT 11-wk Cr daily ingestion, with 5-d initial loading dose	Significant loose stools during the Cr loading phase compared to Pl group ($P < .01$); significant Cr increased muscle cramping ($P < .01$) and muscle strain ($P < .01$) between weeks 3 and 5 compared to Pl group.
Eijnde et al (2003)[14]	6-mo strength and endurance training 6-mo low-dose Cr daily ingestion	Five subjects (4 Cr and 1 Pl) developed ST-segment depression during the 3-mo (n = 3) or 6-mo (n = 2) exercise tests; 1 subject (Cr group) exhibited left shoulder joint overuse trauma

Abbreviations: Cr, creatine; Pl, placebo; RT, resistance training; Text modified to "ST-segment" in the body of the table since "ST" is not an abbreviation, they are a reference to heart EKG waves.

therapeutic implications of creatine supplementation for prolonged independence, delayed musculoskeletal condition onset such as sarcopenia, and reduced risk for falls in women.

Studies in male participants who utilized a daily low-dose creatine supplementation combined with RT for 12 weeks are in alignment with the studies conducted in women, supporting the long-term daily use of creatine supplementation for additive improvements in strength.[32,33] The ergogenic effects of creatine is not surprising as studies in athletes in both men and women have previously shown that continuous low-dose creatine supplementation allows for increases in training volume, resulting in enhanced muscular improvements.[2] However, replication of these effects in men aged 60 to 84 years[33] and 64 to 77 years[32] is a novel finding supporting the use of creatine supplementation for strength and power across the life span.

The exception, however, is the study conducted by Eijnde et al[14] in which a daily low dose of creatine combined with RT for 6 months failed to demonstrate increased isometric strength of knee extensor muscles. The major differences between this study and the studies by Chilibeck et al[32] and Chrusch et al[33] were the age range beginning at ages 55 to 75 years and the exercise program. The authors note that an initial adaptation was observed following 3 months of training but was lost by 6 months of training and there was no increase in training volume in the creatine group compared with placebo. These effects could be attributed to the choice of exercise program. While both Chilibeck et al[32] and Chrusch et al[33] utilized a whole-body RT program incorporating 12 exercises, specific guidelines for training volume progression and tapering of resistance prior to testing to avoid training fatigue, Eijnde et al[14] utilized combined endurance (cycle ergometry and treadmill walking/jogging) and RT that incorporated 7 exercises. Participants in the study by Eijnde et al[14] self-regulated their exercise workload and progression and tapering strategies were not included. Whether there is an intensity threshold that needs to be met prior to observation of creatine and RT additive effects remains to be determined but may account for the lack of creatine effect with the study by Ejinde et al.[14] Furthermore, this intensity threshold may vary considerably in men between the ages of 55 and 75 years.

All the studies in men in which the creatine dosing paradigm was restricted to training days only did not show creatine-specific effects over RT alone. While authors of these studies concluded that supplementation with creatine provides no additional benefit than RT alone in an older population,[13,20,23,31] it is important to note that some of these studies included a wide age range including 48 to 72 years[13,23] and thus initial strength differences and potential age-related exercise intensity thresholds differences cannot be overlooked. Bemben et al[13] acknowledged that the work performance per training session was predetermined for all participants and that the potential for "nonresponders" within their participants was possible.

The significant effects of daily low-dose creatine supplementation on strength become less apparent in studies in which participants include both men and women combined. While Brose et al[15] were able to replicate the findings described previously on increased lower body strength using daily low-dose creatine combined with 14 weeks of RT, Bermon et al[12] and Pinto et al[22] reported no additive effects of a daily low-dose creatine combined with RT. A limitation of the study by Bermon et al[12] was a low number of participants in each group (n = 8) and no distinction between baseline fitness levels for age and gender. Bermon et al[12] also utilized a different creatine-dosing paradigm that involved a larger loading dose of 20 g/d for 5 days, followed by a lower maintenance dose of 3 g/d for the remaining 7 weeks, which is lower than the maintenance dose more commonly reported (5 g-8 g/d) by others in this review.[10,29,32,33] Pinto et al[22] utilized a low sample size (n = 27) and the daily low-dose creatine ingestion was not preceded by a creatine loading phase. The authors acknowledge the lack of muscle creatine and phosphorylcreatine content analysis as a further limitation. Increases in muscle PCr content are reduced in the older adults compared

with younger individuals[26] and may vary among individuals depending on the muscle tested.[27] Thus, the effects of various creatine-loading phases, followed by maintenance phases on the degree of muscle creatine uptake, storage, and retention in older adults warrant further attention and may account for the differences observed in these studies.

Body Composition

Body composition results overall demonstrated significant creatine-induced improvements in lean mass, which was mostly consistent across studies.[3,10,15,22,33] Two of 6 studies demonstrated a positive effect of creatine on fat-free mass.[15,29] All studies were consistent in reporting no effects of creatine supplementation on percent body fat[14,20,25,29,33] and fat mass.[3,10,20,25,29,33] Results for body mass across the studies remain inconclusive, with both positive[12,15,31,33] and negative[16,20,25,29] reporting of creatine-specific effects.

Previous reports demonstrate that creatine supplementation, which leads to increased uptake and loading within the skeletal muscle leads to increases in body mass.[30] However, this relationship is not consistently observed across studies in older populations as indicated in this review. The large discrepancies in body mass reporting across studies have been attributed to an age-related decline in basal levels of total creatine and PCr concentrations,[24] concomitant with a decline in type II muscle fibers, which store creatine to a greater extent than type I fibers,[28] thus affecting the reciprocal relationship between creatine loading and body mass as the body ages. Furthermore, this relationship varies between males and females.[34] The evidence demonstrates that increases in body mass following creatine loading in older adults are small and while significant increases in total muscle PCr may occur, it is not necessarily associated with increases in body mass.[26] Of the 17 studies reviewed here, 2[14,20] conducted skeletal muscle biopsies to determine muscle creatine concentrations and fiber-type distribution. Future studies should include such analyses to corroborate any findings in domains of strength and body composition.

The body composition outcome measures in women varied greatly thus making comparisons across studies difficult. Gulano et al[10] and Aguiar et al[29] reported significant effects of creatine supplementation on fat-free mass and appendicular lean mass, respectively, while Chilibeck et al[21] failed to demonstrate significant creatine effects on whole body lean tissue mass. The daily low-dose creatine ingestion was comparable across the studies and all 3 studies utilized a long-term RT protocol (≥24 weeks). It has been previously shown that creatine supplementation results in increased creatine muscle accumulation that is highly specific to the muscle groups being exercised during RT as the engaged muscle receives increased blood flow and thus increased creatine transport.[35] Thus, any significant effects of creatine supplementation are likely specific to the exercised muscles in either the upper or lower body during RT. Consequently, whole-body measures of lean tissue as performed by Chilibeck et al[21] could have masked any creatine-specific lean tissue effects occurring in upper or lower body appendages. Furthermore, in the studies conducted in men and women, all 3 that investigated creatine effects on lean mass demonstrated significant creatine differences compared with the RT placebo group, which corroborates the findings discussed previously for lean mass.[3,15,22] Brose et al[15] reasoned that the subtle effects of creatine on body composition are best analyzed using DEXA, which demonstrates more sensitivity compared with the use of hydrodensitometry methods. Interestingly, Bemben et al,[13] using DEXA and Candow et al,[31] using air-displacement plethysmography methods, were the 2 studies conducted in men that did not show increased lean mass effects with creatine supplementation. While Bemben et al[13] suggested limitations in their RT protocol including predetermined workloads for participants as a hindrance to potential lean mass effects, Candow et al[31] reasoned that the dosing paradigm of creatine supplementation on training days only may have been insufficient for increasing lean mass. Creatine supplementation can improve lean mass regardless of gender, albeit subtle in some cases, and the optimal dosage for lean mass improvements appears to be a continuous low dose of creatine combined with RT for at least 12 weeks.

Studies of creatine effects on bone in older adults are limited. While there were 2 reports in this review showing creatine-specific effects on BMD of the femoral neck[21] and BMC of the arms,[21,32] respectively, several others reported no significant regional BMD effects of creatine supplementation.[10,22,32] The discrepancies in these collective data are difficult to interpret due to the scarcity of total studies and heterogeneous sample for age and gender; however, an understanding of creatine-specific effects on bone may shed some light. Creatine has been shown to regulate bone both directly via effects on osteoblast activity[36] and indirectly via increasing training volume capacity over time and subsequently increasing the muscle load on bone, triggering bone formation.[32] Thus, creatine-induced effects on bone are likely dependent on the dosing paradigm for direct creatine regulation of bone-signaling molecules in addition to the exercise protocol intensity to facilitate indirect creatine effects. In addition, the duration of RT, in this case, long term would be necessary to allow for creatine effects on molecular bone signaling to translate to significant bone accrual. A closer look at these studies reveals that the creatine-induced decreased rate of femoral neck BMD loss in the study by Chilibeck et al[21] was found after 12 months of creatine combined with RT. Conversely, Pinto et al[22] and Chilibeck et al[32] also analyzed regional BMD but the duration was 12 weeks and both reported no effects of creatine on BMD. All 3 studies used a similar daily low-dose creatine dosing paradigm and 3 d/wk RT program. Interestingly, Gualano et al[10] demonstrated significant creatine effects on appendicular lean mass in older women but failed to show differences in regional (lumbar spine, femoral neck, total femur) measures of BMD between creatine- and placebo-trained groups after 6 months of RT combined with daily low-dose creatine. These results

are difficult to explain but the authors speculate a role of lower bone mass in postmenopausal women as well as the 6-month follow-up being too early to detect significant changes in bone.[10] Ideally, identifying a creatine dose and duration that maximizes both direct and indirect creatine effects would be ideal in producing significant improvements in BMD and BMC over RT alone.

Cognition

Previous studies have demonstrated creatine-specific positive effects on depression,[37] memory and spatial recall,[5] and neuroprotection during unfavorable environmental conditions.[4] The neuroprotective actions are thought to partly occur through maintenance of mitochondrial bioenergetics and reduction of oxidative stress.[38] As exercise alone has shown to have neuroprotective properties in the brain, it was of interest to Alves et al[9] to investigate the potential additive effects of creatine combined with strength training on indices of mental health including emotional state and cognition. While the study reported positive effects of strength training on emotional state, there were no creatine-specific effects reported. Direct creatine supplementation–mediated effects in the CNS are likely very low due to the low efficiency of creatine crossing the blood-brain barrier.[39] The effects may be dependent on basal levels of brain creatine, and turnover rates, which may also vary across the life span. Furthermore, previous studies have shown positive creatine effects in the brain under stressed conditions, which suggest that any cognitive benefits may occur in individuals with underlying deficits in brain energy metabolism or demand.[4,9]

Adverse Effects of Creatine Supplementation

The gastrointestinal adverse events were categorized as few and minimal and did not affect activities of daily living or hinder the ability to continue with RT.[21,33] To our knowledge, the reported ST-segment depression observed during the electrocardiogram-controlled maximal exercise tests in the study by Ejinde et al[14] is the first report of cardiovascular-related adverse events following long-term (6 months) daily ingestion of creatine and warrants further attention. Although all participants were cleared to participate in the study from preliminary electrocardiographic tests, 11 participants were excluding during this phase because they also demonstrated significant ST depression or other cardiovascular events at baseline.[14] It remains possible that the 4 participants who showed ST depression during the first phase of the study had underlying cardiovascular conditions that were not picked up during the initial screening.

Effects in Women and Creatine Mechanism of Action

While it is established that healthy aging is attributed to a continuous decline in the third decade of steroid hormones including androgens, estrogens, and insulin-like growth factor-1 in both men and women, the decline in the circulating hormone, estradiol, is most robust in older women, particularly at menopause.[40] This natural decline in serum levels of sex steroid bioavailability correlates with reductions in muscle mass and BMD and increases in body fat, which is further linked to increased risks of sarcopenia, fractures, cognitive decline, and overall well-being.[40] Bone and CNS health is highly dependent on circulating levels of estradiol; thus, the age-related effects on musculoskeletal and CNS health, strength, and functionality[40] are accelerated in older women following estradiol depletion.

To combat this loss, RT exercise has been shown to trigger increases in anabolic hormones, testosterone, and growth hormone[40] as well as muscle insulin-like growth factor-1 levels in older adults.[41] Mechanistic studies identify insulin-like growth factor-1 among several other myogenic regulatory proteins as being upregulated in response to creatine intake acutely.[42] Studies of creatine effects on anabolic steroid regulation in older adults are limited and warrant further investigation. The effects of creatine supplementation combined with RT seen in the studies with women are likely partly attributed to creatine combating the substantial loss of serum hormone bioavailability that occurs at this age resulting in improvements in muscle mass and strength.

The effects of creatine appear to be multifactorial as it has also been shown to stimulate satellite cell proliferation and muscle protein synthesis.[27,30,43] These effects have mostly been reported in young healthy individuals, with some reports of creatine-induced satellite cell proliferation in older adults.[44] In addition to anabolic protein effects, creatine also causes intracellular water retention,[45] which may be another mechanism in addition to increased muscle protein synthesis for the observed increases in total body and muscle mass.[15,29,31,33] Water retention–induced muscle hypertrophy may also be functionally correlated to improvements in strength following creatine supplementation.[45]

Limitations

The age of participants in the included studies ranged between 48 and 77 years and included both men and women. Outcome measures in the strength and endurance category varied greatly contributing to the heterogeneity of the results in addition to slight variations in RT protocols across the studies. The duration of studies also varied across the categories including 1 to 24 weeks for strength, functionality, and endurance; 1 week to 1 year for body composition; and 24 weeks for cognition. The degree of baseline physical fitness also varied among participants. Although most studies reported their participants as being untrained, significant initial strength improvements may have been more pronounced in the previously more sedentary participants due to neural adaptations compared with those who had a prior history of RT. Differences in participant and study characteristics make generalizability difficult, although we were able to tease apart gender differences on several categories including strength, functional tasks, and body composition.

CONCLUSIONS

This systematic review suggests that the beneficial effects of creatine supplementation on upper and/or lower body

strength, functional capacity, lean mass, and potential regional BMD of the femur require a continuous low daily dose of creatine combined with moderate RT for at least 12 weeks with at least 1 year before any effects on bone health may be observed. One-third of the studies that reported creatine-specific effects also utilized an initial 1-week loading phase with higher creatine concentrations before initiating the low-dose maintenance phase. Adverse effects with creatine supplementation combined with RT include minimal gastrointestinal irritability and muscle cramping as well as 1 study reporting ST depression occurring in 4 participants during exercise testing.

These creatine and RT additive effects have the potential to translate to improvements in abilities to perform activities of daily living as well as prolonging the development of musculoskeletal disorders including osteoporosis. Additional large-scale and long-term randomized controlled trials are needed to establish a role for creatine in conjunction with exercise to positively impact BMD. Randomized controlled trials specifically investigating the additive effects of creatine and exercise on cognitive measures including memory as well as anxiety and depression are currently lacking. Creatine supplementation combined with RT offers a safe an effective therapeutic strategy to support healthy musculoskeletal aging.

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