Creatine Supplementation during Resistance Training in Older Adults—A Meta-analysis

MICHAELA C. DEVRIES and STUART M. PHILLIPS

Exercise Metabolism Research Group, Department of Kinesiology, McMaster University, Hamilton, Ontario, CANADA

ABSTRACT

DEVRIES, M. C., and S. M. PHILLIPS. Creatine Supplementation during Resistance Training in Older Adults—A Meta-analysis. *Med. Sci. Sports Exerc.*, Vol. 46, No. 6, pp. 1194–1203, 2014. **Introduction**: Age-related sarcopenia and dynapenia have negative effects on strength and the ability to perform activities of daily living. Resistance training (RT) increases muscle mass and strength in older adults and is an established countermeasure for sarcopenia and dynapenia, and creatine may enhance this effect. We aimed to determine whether the addition of Cr to RT increased gains in muscle mass, strength, and function in older adults over RT alone by conducting a systematic review and meta-analysis. **Methods**: PubMed and Healthstar databases were searched. Randomized, placebo-controlled trials that involved older adults supplemented with Cr and included RT regimens (>6 wk) were included. Data were analyzed using fixed or random (if data were heterogeneous) effects meta-analysis using RevMan 5. **Results**: The meta-analysis comprised 357 older adults (average ± SD Cr: 63.6 ± 5.9 yr, Pl: 64.2 ± 5.4 yr) with 12.6 ± 4.9 wk of RT. Cr + RT increased total body mass ($P = 0.004$) and fat-free mass ($P < 0.0001$) with no effect on fat mass as compared with RT alone. Cr + RT increased chest press ($P = 0.004$) and leg press ($P = 0.02$) one-repetition maximum to a greater extent than RT alone, with no difference in the effect on knee extension or biceps curl one-repetition maximum, isokinetic or isometric knee extension peak torque. Cr + RT had a greater effect than RT alone on the 30-s chair stand test ($P = 0.03$). **Conclusion**: Retention of muscle mass and strength is integral to healthy aging. The results from this meta-analysis are encouraging in supporting a role for Cr supplementation during RT in healthful aging by enhancing muscle mass gain, strength, and functional performance over RT alone; however, the limited number of studies indicates further work is needed. **Key Words:** SARCOPENIA, MUSCLE MASS, STRENGTH, FUNCTIONAL PERFORMANCE, AGING

Muscle strength peaks in the third decade of life remains reasonably constant through the fifth decade and then begins to decrease at a rate of 12%–15% each decade thereafter (22). Similarly, muscle mass loss accelerates with aging whereby adults lose 5%–10% of muscle mass between the ages of 20–50 yr compared with 30%–40% of muscle mass between the ages of 50–80 yr (22). The loss of muscle mass (myopenia) and strength (dynapenia) that occurs with aging, termed sarcopenia, is characterized by type II muscle fiber atrophy, myofiber necrosis, and myofiber type grouping, and increased intramuscular content of nonmuscle tissue such as intramyocellular lipid and connective tissue (22). In 2011, seniors (age 65+ yr) represented 15% and 13% of the total population in Canada and the United States, respectively (37,41), and these numbers are expected to increase. As our population ages, strategies to attenuate the negative consequences of sarcopenia are of importance to promote healthful aging.

Address for correspondence: Stuart Phillips, Ph.D., Ivor Wynne Centre, E210, McMaster University, 1200 Main St. W, Hamilton, Ontario L8S 4K1, Canada; E-mail: phillis@mcmaster.ca.
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Resistance training (RT) is known to increase muscle mass and strength in younger (21,25,28) and older populations (7,11,26,43). In older adults (ages 65–75 yr), 16 wk of progressive RT increased mixed muscle protein synthesis (MPS) by approximately 50%, muscle mass by 1.5 kg, and overall strength by 60% (43). In addition, similar gains in muscle hypertrophy, lean mass, and relative strength were seen in elderly men and women who underwent a 24-wk RT protocol (26). Notably, as type II muscle fiber atrophy predominates in age-related sarcopenia (22) and RT induces type II muscle fiber hypertrophy in older adults (27), RT is an important countermeasure to age-related muscle loss. The hypertrophic response to RT can be augmented by consuming a protein supplement near a resistance exercise bout as evidenced by a greater increase in fat-free mass (FFM) and strength (one-repetition maximum (1RM)) in both younger and older subjects (10). Both protein consumption and resistance exercise independently stimulate MPS, but when protein is consumed near resistance exercise, MPS is increased to a greater extent than either stimuli alone (5). Although protein consumption and RT increase MPS in both young and older individuals, it appears that a greater dose of protein (approximately 40 g) is required to maximally stimulate MPS in older (42) as compared with young (approximately 20 g) persons (29). As such, nutritional recommendations to enhance MPS, hypertrophy, and strength gains in response to RT should be tailored to an individual on the basis of age.

Creatine supplementation with or without concomitant RT has been found to increase lean body mass, strength, and performance during short (<90s), intense exercise bouts in two previous meta-analyses (4,15). Although these meta-analyses included subjects of all ages, the trials conducted up until the point of analysis used mainly young (<36 yr) subjects. In addition, these analyses included trials that investigated the effects of creatine alone along with trials that investigated creatine plus RT. Although it is important to determine whether creatine has beneficial effects independent of RT, the use of creatine supplementation as a strategy to attenuate sarcopenic changes is likely most pronounced and lasting if coupled with RT. The mechanism(s) by which creatine increases muscle mass and strength have not been fully elucidated. However, it is known that creatine does not work to increase muscle mass through the direct stimulation of MPS; however, it may attenuate rates of muscle protein breakdown (32). Mainly, creatine is thought to work by 1) increasing phosphocreatine (PCr) energy stores, 2) speeding PCr resynthesis, and 3) reducing muscle damage (35), enhancing one's ability to perform high-intensity exercise and allowing for greater force production and, ultimately, increased training volume, which in turn would act as a greater stimulus for MPS. As such, we believe that the use of creatine and RT concomitantly will have a much more profound effect on body composition, strength, and functional performance than creatine supplementation alone. In older adults, some (1,6,12,30), but not all (2,3,9,13,16,17), trials have found additive effects of creatine to RT on body composition and strength. As such, we conducted a meta-analysis to determine whether the addition of creatine to RT improves body composition and increases strength and functional performance in older adults.

METHODS

Study inclusion/exclusion criteria. Studies were included if they were randomized, placebo (PL)-controlled trials investigating the effect of creatine supplementation on body composition, strength, and/or functional performance in middle-age/older adults (>45 yr) during a period of RT (>6 wk). In addition, we included trials irrespective of whether there was a creatine loading period at the start of the intervention. Studies were excluded if they included subjects with muscular degenerative disease, if they combined creatine supplementation with another dietary supplement known to influence anabolism and/or strength, if subjects did not perform RT for two sessions or more per week, or if the study was only published in abstract form. We did not restrict our search based on sex or training status (where documented), but we recorded these variables to allow for subgroup analyses where possible.

Methodological inclusion criteria for body composition [FFM, fat mass (FM)] analysis were limited to determination using dual-energy x-ray absorptiometry (DEXA), hydrodensitometry (underwater weighing), and whole-body air plethysmography (BodPod). Methodological inclusion criteria for strength included determination of maximal strength (1RM), estimated 1RM based on submaximal strength test (i.e., 3–5RM test), maximal isokinetic strength, and maximal isometric strength. Methodological inclusion criteria for functional performance included determination of performance using validated tests (i.e., 30-s chair stand test and short performance battery test).

Search strategy and study identification. A systematic search of MedLine and HealthStar databases was conducted up to June 2013. Search terms included *dietary supplement*, *creatine*, *creatine monohydrate*, *creatine supplementation*, *creatine loading*, *weight lifting*, *weight training*, *resistance training*, *resistance exercise*, *strength training*, *age*, *middle-age*, *older adults*, and *elderly*. The search was limited to articles conducted in humans. The preliminary search yielded 118 relevant citations once duplicates were removed. After all 118 abstracts were obtained and reviewed by the authors, 24 full text articles were retrieved for review. In addition, the reference lists of pertinent reviews and included trials were reviewed to ensure no trial had been missed. No additional trials were identified upon reference review. One additional trial was identified by an outside source during the review process and deemed to meet the inclusion criteria and is included in the meta-analysis (14); thus, 25 full text articles were reviewed. The flow through of studies through the review process is summarized in Figure 1.

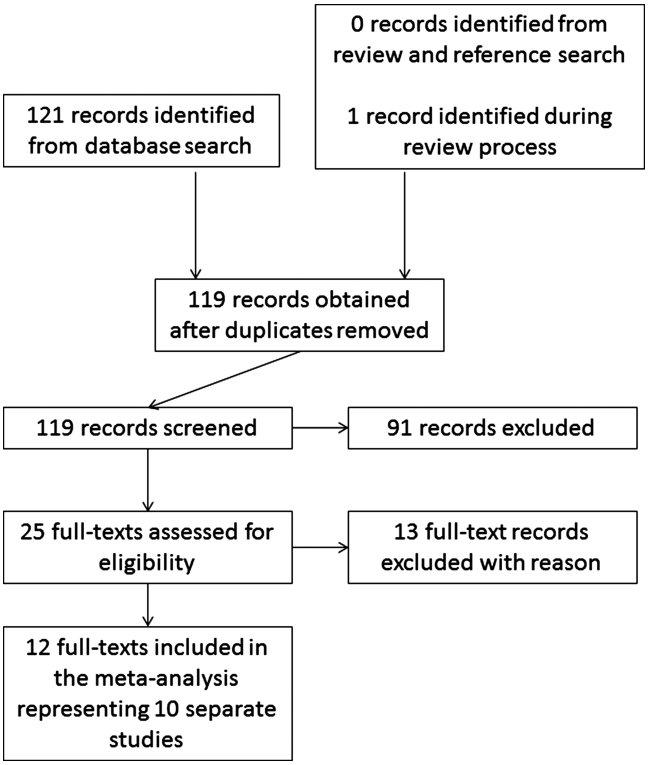


FIGURE 1—Flow through of articles through the search and review process.

Included studies, data extraction, and data syntheses. Twelve articles from 10 studies met the inclusion criteria for this meta-analysis. Three articles were identified from one study and presented data on dynamic strength changes (2), isokinetic strength changes (9), and body composition (17) and for the purpose of this review, when discussing methodological criteria, will be cited as the studies of Bemben et al. (2). All studies were evaluated for study quality using the Jadad scale (24). When different units of measure were used for a given outcome variable between studies (i.e., weight measured in pounds vs kilogram), data were transformed into the same units before input where possible. Study characteristics and data were extracted to RevMan 5 (Review Manager Version 5.1, The Cochrane Collaboration, 2011). Authors were contacted and asked to provide any missing data or needed information. When authors could not be reached or the data were no longer available, data were extracted directly from graphs or calculated based on baseline values and reported percentage change. Mean differences and SD change (SDΔ) were inputted. Mean differences for each group within a study were calculated as follows:

$$\text{mean difference} = \text{mean post} - \text{mean pre}$$

SDΔ was inputted from reported values where possible. When SDΔ was not reported and raw data were not available, SDΔ was calculated as follows:

$$\text{SD}\Delta = \left[(\text{SD}_{\text{pre}})^2 + (\text{SD}_{\text{post}})^2 - 2\ \text{corr}\ (\text{pre, post}) \times \text{SD}_{\text{pre}} \times \text{SD}_{\text{post}}\right]^{1/2}$$

where corr (pre, post) is the correlation between pre- and postvalues across participants and was calculated from studies that reported SDΔ and/or raw data for a given outcome and applied across trials as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (40).

Inputted data were then tested for heterogeneity and publication bias using RevMan 5. Heterogeneity was assessed using χ^2 and I^2 tests. The χ^2 test has low power to determine heterogeneity when there are few studies included in the meta-analysis and when sample sizes within studies are small; therefore, we set significance at $P < 0.1$ for heterogeneity. I^2 values >75% were considered to indicate significant heterogeneity. When heterogeneity was present, random effects meta-analysis was conducted, whereas when there was no heterogeneity, fixed effects meta-analysis was conducted. Publication bias was assessed by visual inspection of funnel plots; however, given the small number of studies (<10 per comparison) within the meta-analysis, a true assessment of publication bias is not recommended (38). Importantly, when funnel plot asymmetry and heterogeneity were both present, the results from both the fixed and random effects models were compared to ensure that the random effects estimate did not indicate that the intervention was more favorable (38).

Weighted mean differences were analyzed using fixed or random effects meta-analysis as described above. Standardized mean difference was used to determine the group effect for isometric strength because different studies reported changes in strength using different measurement units that could not be transformed to one standard unit. Forest plots were generated for each outcome to illustrate study-specific effect sizes (ES) and their 95% confidence intervals (CI) along with the overall pooled effect.

RESULTS

Study and subject characteristics. Ten studies from 12 published reports and including 357 subjects met the inclusion criteria for this meta-analysis (Fig. 1). The publication dates for the trials ranged from 1998 to 2013. Details of the included trials, including study quality, are provided in Table 1. Data from 357 subjects with an average age range between 55 and 71 yr (mean ± SD, Cr: 63.6 ± 5.9 yr, Pl: 64.2 ± 5.4 yr) were included in the analysis (Table 1). Of the included trials, two were conducted in women only (1,30), four in men only (2,8,12,16), and four in both men and women (3,6,13,14). One trial conducted in men and women (6) reported data from men and women separately with the exception of functional performance tests. Of the 10 trials, six were conducted in healthy subjects (1–3,6, 8,16), one in cardiac patients undergoing cardiac rehabilitation (13), one in patients with chronic obstructive pulmonary disease undergoing rehabilitation (14), one in women with knee osteoarthritis who were otherwise healthy (30), and one did not disclose the health status of the participants (12). In six trials, subjects had not participated in RT for at least 6 months (1–3,12,16,30), whereas the other four trials did not disclose the training status of the subjects (6,8, 13,14). Three of the included trials excluded subjects who were vegetarian (1,2,30), whereas the other trials did not indicate whether vegetarians were included or not (3,6,8, 12–14,16). Four of the included trials excluded subjects who had previously used creatine as a supplement (1,8,16,30), whereas the supplementation history of subjects in the remaining trials was not reported (2,3,6,12–14). Lastly, of the six studies that included women (1,3,6,13,14,30), in only one trial were subjects reported as being postmenopausal and not taking hormone replacement therapy (6). In the remaining five trials, the menstrual/hormonal status of the subjects was not disclosed (1,3,13,14,30).

RT protocol characteristics. The RT interventions ranged from 7 to 26 wk (mean ± SD, 12.6 ± 4.9 wk). Nine of the 10 trials reported that subjects trained three times a week (1–3,6,8,12–14,30), whereas the other trial reported two to three times a week (16). Eight of the 10 trials used whole-body training regimens (1,2,6,8,12–14,16), whereas one trial trained the legs only (three exercises [30]) and the other trial performed three exercises (two legs and one chest [3]). The number of exercises completed per session ranged from 3 to 12 with a mean ± SD of 5.0 ± 3.7 exercises per session. Three (13,14,16) of the 10 trials also incorporated cardiovascular training into the exercise protocol (Table 1).

TABLE 1. Details of included studies regarding subject characteristics, training regimen, and creatine/placebo supplementation protocol.

						Training Regimen					Creatine Supplementation		
Author, Year	Subjects	No., PL	No., Cr	Age, PL	Age, Cr	Length (wk)	Frequency	Intensity (Reps)	Sets	Type	Loading	Daily dose	Placebo
Aguiar, 2013	Women, healthy, UT	9	9	65 ± 6	65 ± 4	12	3× wk^{-1}	10–15	2	WB	None	5 g·d^{-1} CrM, 1× d^{-1} in CHO drink	Maltodextrin
Bemben, 2010/ Carter, 2005/ Eliot, 2008	Men, healthy, UT	10	10	56 ± 4	56 ± 6	14	3× wk^{-1}	8 at 80% 1RM	3	WB	Gatorade + 7 g CrM, 3× wk^{-1}, 2 wk	Gatorade + 5 g CrM (posttraining only)	Gatorade
Bermon, 1998	Both sexes, healthy, UT	8	8	69 ± 1	71 ± 5	7	3× wk^{-1}	8 at 80% 1RM	3	LP, KE, CP	5 g CrM + 2 g glucose, 4× d^{-1}	3 g CrM + 2 g glucose, 1× d^{-1}	Glucose
Brose, 2003	Men, healthy, TNS Women, healthy, TNS	7 7	8 6	68 ± 3 70 ± 6	69 ± 5 71 ± 6	14	3× wk^{-1}	10–12 at 50% (start)–80% (end) 1RM	1–3	WB	None	5 g CrM + 2 g dextrose per day in juice	7 g dextrose
Candow, 2008	Men, healthy, TNS	12	13	64 ±3	65 ± 3	10	3× wk^{-1}	10 at 70% 1RM or 10RM	3	WB	None	0.1 g·kg^{-1} CrM + 0.75 g·kg^{-1} sucrose in three doses per day, training days only	1.2 g of sucrose in three doses per day, training days only
Cornelissen, 2010	Both sexes, cardiac pts, TNS	37	33	60 ± 7	55 ± 10	12	3× wk^{-1}	8–12 at 8–12RM	2–3	WB + cardio	5 g CrM, 3× d^{-1}, 1 month	5 g CrM per day in malto/sweetener	Maltodextrin
Chrusch, 2001	Men, Und, UT	14	16	70 ± 6	71 ± 7	12	3× wk^{-1}	10 at 50% 1RM	3	WB	0.3 g·kg^{-1} BW per day, 5 d, in three doses per day in sucrose-flour mix	0.07 g·kg^{-1} BW per day in three doses per day in sucrose–flour mix	Sucrose–flour mix
Deacon, 2008	Both sexes, COPD, TNS	42	38	68 ± 8	68 ± 7	7	3× wk^{-1}	10 at 60%–70% 1RM	3	WB + cardio	22 g CrM per day, in four doses per day	3.76 g CrM per day	Lactose
Eijnde, 2003	Men, healthy, UT	23	23	62 ± 6	64 ± 5	26	2–3 wk^{-1}	30 at 30RM	2	WB + cardio	None	5 g CrM per day in three doses per day	Not specified
Neves, 2011	Women, KO, UT	11	13	56 ± 3	58 ± 3	12	3× wk^{-1}	8–12 at 8–12RM	4	LB	5 g Cr, 4× d^{-1}, 7 d	5 g Cr per day, 1× d^{-1} in juice	Dextrose

Cardio, subjects also performed cardiovascular exercise as part of the protocol; COPD, chronic obstructive pulmonary disease; CP, chest press; CrM, creatine monohydrate; KE, knee extension; KO, knee osteoarthritis; LB, lower body only training regimen; LP, leg press; pts, patients; TNS, training status not specified; Und, health status of subjects not specified; UT, untrained; WB, whole body training regimen.

Creatine supplementation regimen characteristics. Six of the 10 trials included a creatine loading phase as part of the protocol (2,3,12–14,30). The loading dose used ranged from 7 to 25 $g \cdot d^{-1}$ with an average ± SD of 18.9 ± 6.6 $g \cdot d^{-1}$. In one trial, the loading dose was ingested in one dose (7 g) and only on 3 $d \cdot wk^{-1}$ (2). In the remaining five trials (3, 12–14,30), the loading dose was split into three or four doses spread equally throughout the day. The dose of creatine used during the maintenance phase of the trials ranged from 3 to approximately 8.6 $g \cdot d^{-1}$ with a mean ± SD of 5.0 ± 1.4 $g \cdot d^{-1}$. In 3 of the 10 trials, the daily dose was split into three doses to be ingested throughout the day (8,12,16). In the remaining seven trials, the daily dose was ingested at one time point (1–3,6,13,14,30). In two trials, creatine was only ingested on the 3 $d \cdot wk^{-1}$ that subjects performed RT (2,8). In 4 of the 10 trials, creatine was ingested with a carbohydrate beverage (1,2,6,30), whereas in four trials, creatine was ingested with a small (2 g of glucose, or maltodextrin/sweetener, or a sucrose/flour mixture) or large (0.75 $g \cdot kg^{-1}$ of body weight) amount of sugar (3,8,12,13). In the remaining two trials, it was not indicated if creatine was ingested with any other compound (14,16). The placebo used varied between studies and included maltodextrin, Gatorade, glucose, dextrose, lactose, sucrose, or a sucrose/flour mixture.

Publication bias and heterogeneity. All data sets were analyzed for publication bias using funnel plots; however, given the small number of trials that were included in some analyses, interpretation of these plots is limited. Asymmetry was observed in the knee extension 1RM, biceps 1RM, and isometric strength plots. For the knee extension 1RM plots, all data points were around the zero effect line, whereas for biceps 1RM and isometric strength, the data points crossed both sides of the effect line but did not form a typical inverted funnel. However, given the small number of trials that were included in the analysis, it is not recommended that publication bias be interpreted (38).

Significant heterogeneity ($P < 0.1$), due to small number of included trials, was found for the following outcome variables: total body mass (TBM) ($\chi^2 = 24.81$, $P = 0.002$, and $I^2 = 68\%$), FFM ($\chi^2 = 32.25$, $P < 0.0001$, $I^2 = 75\%$), chest press 1RM ($\chi^2 = 12.95$, $P = 0.04$, $I^2 = 54\%$), knee extension 1RM ($\chi^2 = 11.75$, $P = 0.04$, $I^2 = 57\%$), isometric strength ($\chi^2 = 30.31$, $P < 0.0001$, $I^2 = 84\%$), biceps curl 1RM ($\chi^2 = 11.53$, $P = 0.009$, $I^2 = 74\%$), and 30-s chair stand test (χ^2, P and $I^2 = 5.28$, $P = 0.07$, $I^2 = 62\%$). As such, random effects models were used for these comparisons. In no instances, where both heterogeneity and funnel plot asymmetry existed, were the results of the random versus fixed effects meta-analysis greater. Differences in subjects' sex explained a portion of the heterogeneity; however, given the small number of trials included in the analysis, subgroup analysis was not performed.

Intervention effects. An overview of the characteristics of all included trials is given in Table 1. Table 2 provides an overview of the study effects for each outcome of interest. Not all trials reported on all outcomes of interest.

TABLE 2. Individual study results (creatine vs placebo) of outcomes included in the meta-analysis.

Author, year	CrM Age (*n*)	Pl Age (*n*)	Outcomes										
			TBM	FFM	FM	%BF	LP 1RM	CP 1RM	KE 1RM	BC 1RM	Isometric	Isokinetic	30-s Chair Stand
Aguiar, 2013	65 ± 4 (9)	65 ± 6 (9)	↑	↑	↑	↑		↑	↑	↑			
Bemben, 2010/Carter, 2005/Eliot, 2008	56 ± 6 (10)	56 ± 4 (10)	↑	↑	↑	↑	↑	↑	↑		↑	↑	
Bermon, 1998	71 ± 5 (8)	69 ± 1 (8)	↑			↑	↑	↑	↑		↑		
Brose, 2003													
Men	69 ± 5 (7)	68 ± 3 (8)	↑	↑	↑	↑	↑	↑	↑	↑	↑		↑
Women	71 ± 6 (7)	70 ± 6 (6)	↑	↑	↑	↑	↑	↑	↑	↑	↑		↑
Candow, 2008	65 ± 3 (13)	64 ± 3 (12)	↑	↑	↑	↑	↑	↑					
Cornelissen, 2010	55 ± 10 (37)	60 ± 7 (33)									↑	↑	
Chrusch, 2001	71 ± 7 (14)	70 ± 6 (16)	↑	↑	↑	↑	↑	↑	↑				
Deacon, 2008	68 ± 7 (38)	68 ± 8 (42)	↑	↑	↑						↑	↑	
Ejinde, 2003	64 ± 5 (23)	62 ± 6 (23)	↑	↑		↑					↑	↑	
Neves, 2011	58 ± 3 (11)	56 ± 3 (13)	↑	↑	↑	↑	↑						↑

BC, biceps curl; CP, chest press; CrM, creatine monohydrate; KE, knee extension; LP, leg press; ↑, greater increase in creatine group; →, no difference in response between creatine and placebo groups.

For body composition, TBM was reported in 9 of 10 trials with 10 comparisons possible, FFM in 8 of 10 trials with 9 comparisons possible, FM in 7 of 10 trials with 8 comparisons possible, and percentage body fat (%BF) in 8 of 10 trials with 9 comparisons possible. For strength, leg press and chest press 1RM were reported in six trials with seven comparisons possible, knee extension 1RM was reported in five trials with six comparisons possible, biceps curl 1RM in three trials with four comparisons possible, isokinetic strength in four trials with four comparisons possible, and isometric strength in five trials with six comparisons possible. Lastly, functional performance assessed as the number of chair stands performed in 30 s was reported in three trials with three comparisons possible.

Body composition. Four outcomes relative to body composition were included in the meta-analysis—TBM, FFM, FM, and %BF. Compared with placebo, creatine supplementation during RT significantly increased TBM (weighted mean difference, 1.00 kg; 95% CI, 0.32–1.67 kg; P = 0.004, ES, 0.69; Fig. 2A) and FFM (weighted mean difference, 1.33 kg; 95% CI, 0.79–1.86 kg; $P < 0.0001$, ES, 1.0; Fig. 2B) with a strong trend (due to the effect of creatine on FFM, not FM) to decrease %BF (weighted mean difference, −0.36 kg; 95% CI, −0.73 to 0.02 kg; P = 0.06, ES, −0.11). There was no greater effect of creatine supplementation during RT on FM (weighted mean difference, −0.1 kg; 95% CI, −0.71 to 0.52 kg; P = 0.76, ES, −0.17).

Dynamic strength. Four dynamic strength outcomes were included in the meta-analysis—leg press, chest press, knee extension, and biceps curl 1RM. Compared with placebo, creatine supplementation during RT significantly increased leg press (weighted mean difference, 3.25 kg; 95% CI, 0.47–6.03 kg; P = 0.02, ES, 0.11; Fig. 3A) and chest press 1RM (weighted mean difference, 1.74 kg; 95% CI, 0.56–2.91 kg; P = 0.004, ES, 0.55; Fig. 3B). There was no additional effect of creatine supplementation on knee extension (weighted mean difference, −0.44 kg; 95% CI, −2.62 to 1.75 kg; P = 0.69, ES, −0.06) or biceps curl 1RM (weighted mean difference, 0.47 kg; 95% CI, −1.48 to 2.43 kg; P = 0.64, ES, 0.26).

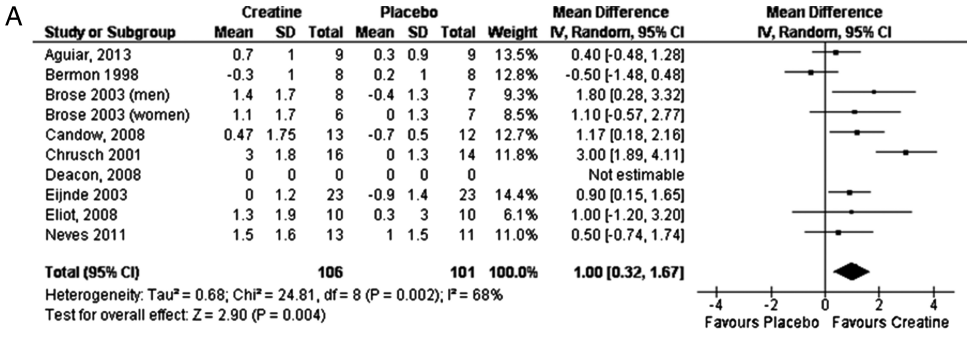
Isometric and isokinetic strength. There was no additional effect of creatine supplementation during RT on either isokinetic (weighted mean difference, −1.03 N·m; 95% CI, −4.97 to 2.91 N·m; P = 0.61, ES, 0.12) or isometric (standardized mean difference, 0.43; 95% CI, −0.31 to 1.16; P = 0.25, ES, 0.91) peak torque.

Functional performance. A 30-s chair stand test was used in three trials to assess functional performance. Creatine supplementation, as compared with placebo, during RT significantly increased the number of chair stands completed in 30 s (weighted mean difference, 1.93 stands; 95% CI, 0.19 to 3.67 stands; P = 0.03, ES, 1.19; Fig. 3C).

DISCUSSION

This is the first meta-analysis to be conducted investigating the effects of creatine supplementation on changes in body composition, strength, and functional performance

A



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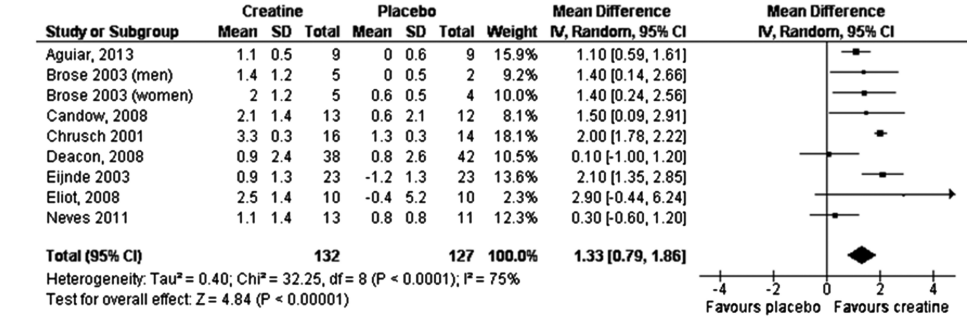

FIGURE 2—Forest plot of the results of a random effects meta-analysis shown as mean differences with 95% CI on (A) TBM and (B) FFM in older adults taking creatine versus placebo during a period of RT. A, Weighted mean difference, 1.00 kg; 95% CI, 0.32 to 1.67 kg; P = 0.0004. B, Weighted mean difference, 1.33 kg; 95% CI, 0.79 to 1.86 kg; $P < 0.00001$. The *shaded circle* represents the point estimate for each individual trial and the *horizontal line* extending from each circle represents the upper and lower limits of the 95% CI. The size of the shaded circle indicates the relative weight of the trial in the meta-analysis. The diamond represents the overall mean difference of the trials.

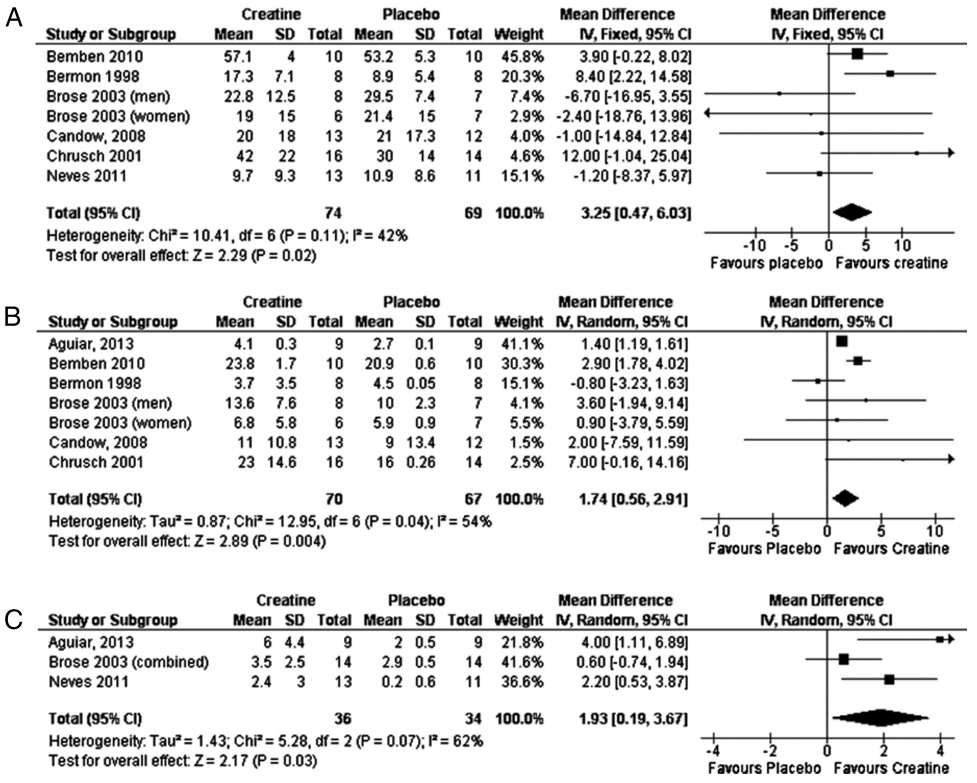

FIGURE 3—Forest plot of the results of a random effects meta-analysis shown as mean differences with 95% CI on (A) leg press 1RM, (B) chest press 1RM, and (C) 30-s chair stand test repetitions in older adults taking creatine versus placebo during a period of RT. A, Weighted mean difference, 3.25 kg; 95% CI, 0.47 to 6.03 kg; $P = 0.02$. B, Weighted mean difference, 1.75 kg; 95% CI, 0.56 to 2.91; $P = 0.004$. C, Weighted mean difference, 1.93 reps; 95% CI, 0.19 to 3.67 kg; $P = 0.03$. The *shaded circle* represents the point estimate for each individual trial, and the *horizontal line* extending from each circle represents the upper and lower limits of the 95% CI. The size of the *shaded circle* indicates the relative weight of the trial in the meta-analysis. The *diamond* represents the overall mean difference of the trials.

during a period of RT in older adults. Given the demographic trends in aging and the age-related decline in muscle mass, strength, and functional performance, it is important to identify compounds that might offset these declines to preserve function and promote independence with aging. The most widely recognized intervention to offset declines in muscle mass and function is RT, and this meta-analysis supports a role for creatine supplementation paired with RT in attenuating adverse sarcopenia-related changes. Notably, we show that creatine supplementation during RT (≥6 wk) favorably influenced body composition, strength, and functional performance to a greater extent than RT alone in older adults.

In the current meta-analyses, we chose to include only creatine supplementation trials that were conducted with older adults as subjects and included an RT regimen. Given that the population is aging and muscle mass, strength, and function decline with increasing age (22), regimens that prevent/attenuate these changes are of importance. It is well established that RT can attenuate age-related sarcopenic changes (7,11,22,26,43); however, RT may not be enough to completely prevent sarcopenia. Dietary strategies that may act synergistically with RT, such as creatine or protein supplementation (10), could also have clinical significance within this population. Some (18,19,39), but not all (23,34,36), trials investigating the effects of acute creatine supplementation in older adults have found positive effects on strength and functional performance. The mechanisms by which creatine increases strength are multifaceted and include increasing PCr energy stores and/or speeding PCr resynthesis and reducing muscle damage (reviewed in Ref. [35]), which would enhance the ability to perform short, intense exercise bouts such as RT and also speed recovery. As such, we believe that the use of creatine and RT concomitantly will have a much more profound effect on body composition, strength, and functional performance than creatine supplementation alone.

Previous meta-analyses have been conducted investigating the effects of creatine supplementation during RT in subjects of all ages as well as the effects of creatine supplementation with or without RT on body composition and strength (4,15,31). One meta-analysis investigated the effects of creatine supplementation during RT (vs placebo) in subjects of all ages (31); however, of the 18 trials included in this analysis, only one study used older adults as subjects. Furthermore, in the two meta-analyses investigating the effects of creatine supplementation with or without concomitant RT on body composition, strength, and/or performance, only 2 and 6 of the 20 and 96 included trials were conducted in older adults (4,15). Thus, the results of these previous meta-analyses are more indicative of the effects of creatine supplementation in younger individuals. Since the time of publication of these meta-analyses, further research has been

conducted on the effects of creatine supplementation during RT in older adults allowing us to now conduct a meta-analysis of the effect of creatine paired with RT to determine age-specific effects of creatine on outcomes that relate specifically to the maintenance of optimal health in our aging population.

Within the current meta-analysis, there were situations where significant heterogeneity existed. In these situations, a random effects model was used to determine the overall effect of creatine supplementation on the given outcome. It is not surprising that there was heterogeneity in this meta-analysis given the small number of differences between trials with respect to subjects' sex (men, women, or both sexes combined) and RT protocol (training length, training volume, and number of exercises performed); however, the small number of trials included in the analysis precluded subgroup analysis. Informally, when analyses were run on data from studies including only men, women, or both sexes, heterogeneity decreased substantially. Should further research be completed investigating the effects of creatine supplementation during RT in older adults, subgroup analyses based on subject sex and training characteristics, particularly training length, should be conducted and reported to decrease the heterogeneity between trials.

Why some (1,6,12,30), but not all (2,3,8,9,13,14,16,17), trials have found beneficial effects of creatine supplementation during RT on body composition, strength, and functional performance is complex. Table 3 illustrates some of the factors that may influence whether creatine supplementation is effective at improving body composition, strength, and functional performance as well as whether these factors were considered in the trials included in this meta-analysis. Specifically, whether the RT protocol was progressive and resulted in a greater training volume being completed by the subjects in the creatine group, whether creatine stores increased as a result of supplementation, and whether creatine was consumed with a carbohydrate are likely factors that may contribute to different findings between trials. As discussed previously, creatine works to increase muscle PCr stores, speed PCr resynthesis, and decrease muscle recovery time—all factors that would allow subjects to complete a greater training volume. Although 9 of the 10 trials included in this meta-analysis stated that the RT protocols were progressive (1–3,6,8,12–14,30), only three of the trials reported training volume data (1,12,16). Of the three trials, two identified that the creatine group performed a greater training volume as compared with the placebo group (1,12), whereas the other trial reported equal training volumes between groups. Accordingly, the two trials where training volume was greater in the creatine group also reported improvements in body composition, strength, and functional performance, whereas the other trial found no additional effects of creatine on body composition or strength as compared with RT alone. Whether subjects lifted loads to failure during the RT protocols was not specifically reported in any of the included studies. Our laboratory has previously shown (28) that low- and high-load RT result in similar

TABLE 3. Factors that may influence creatine effectiveness and how they apply to included trials as well as study quality (Jadad) scores.

Author, Year	Subjects	Creatine Dose/Mixed with	RT Program Progressive	Training Volume	Muscle Creatine Stores	Results	Jadad Score
Aguiar, 2013	Women	5 g·d^{-1} in CHO drink	Yes	Cr > PL—heavier weights lifted	NR	Increased strength, FFM, and muscle mass	4
Bemben, 2010/Carter, 2005/Eliot, 2008	Men	5 g·d^{-1} in Gatorade only on training days	Yes	NR	NR	Cr > PL (NS) strength, body composition	4
Bermon, 1998	Men and women	3 g·d^{-1} + 2 g glucose	Yes	NR	NR	No effects on body composition or strength	3
Brose, 2003	Men and women	5 g·d^{-1} + 2 g dextrose in juice	Yes	NR	Increased TCr in both (men > women) PCr increased in men only	Increased TBM, FFM, and strength; men only: increased biceps 1RM	3
Candow, 2008	Men	0.1 g·kg^{-1}·d^{-1} + 0.75 g·kg^{-1}·d^{-1} sucrose in H_2O	Yes	No difference in training volume	NR	No effects on strength or body composition	4
Cornelissen, 2010	Men and women	9-g dose (5 g Cr, 4 g malto/sweet)	Yes	NR	NR	No effects on isokinetic or isometric strength	5
Chrusch, 2001	Men	0.07 g·kg^{-1} BW per day (average 6 g·d^{-1}) in sucrose flour	Yes	Cr > PL (31% kg lifted × reps)	NR	Increased TBM, LBM, strength, endurance, isokinetic power	3
Deacon, 2008	Men and women	3.76 g CrM	Yes	NR	Increased TCr, Cr, and PCr	No effects on body composition, isokinetic or isometric strength	5
Eijnde, 2003	Men	5 g·d^{-1}	NR	Cr = PL	Cr (31%) and TCr (5%) increased; no change: PCr or ATP	No effects on body composition or strength	3
Neves, 2011	Women, knee OA	5 g·d^{-1} preferably in juice	Yes	NR	NR	Increased physical function, increased lower limb lean mass, no effect on strength	5

In the studies that reported changes in muscle creatine stores, the data reported in this table is for increases in muscle creatine stores in subjects supplemented with creatine only. In subjects supplemented with placebo, muscle creatine stores did not change. Jadad scores range from 0 to 5 with 0 being poor quality and 5 being optimal quality.
CrM, creatine monohydrate; NR, not reported.

amounts of muscle hypertrophy so long as the weights are lifted to failure. The number of repetitions per set in the studies included in this meta-analysis ranged from 8 to 30 repetitions (Table 1). In 9 of the 10 articles included in this meta-analysis (2,3,6,8,12–14,16,30), the load lifted (relative to 1RM) and the number of repetitions completed at that load are reported (Table 1). Interpretation of these data would suggest that in seven (2,3,8,13,14,16,30) of the nine studies that reported the load lifted and the repetitions completed, the load lifted would have resulted in muscle fatigue at the end of the set. In addition, although the load lifted at the start of the study conducted by Brose et al. (6) may not have been sufficient to result in muscle fatigue by the end of the set (10–12 repetitions at 50% 1RM), the load lifted by the end of the study (10–12 repetitions at 80% 1RM) would have been sufficient. In the remaining study (1) where the weight lifted (relative to 1RM) was not indicated, the authors did state that if a subject was able to complete 15 repetitions for a given exercise, then the weight was increased by 1 kg for every one to two repetitions above 15 that were completed. As such, it appears that protocol intensity was sufficient to induce muscle hypertrophy in the studies included in this meta-analysis and is not likely to explain differing results between studies.

As compared with creatine consumption alone, when creatine is consumed with a carbohydrate (doses range from 1 $g \cdot kg^{-1}$ upward of 90–100 g of carbohydrate), muscle creatine stores increase and urinary creatine loses decrease (20,33). As such, differences between outcomes in the current meta-analysis might be reflective of what was coingested with the creatine dose. In 5 of the 10 included trials, creatine was consumed with carbohydrate (sucrose) or carbohydrate beverage (juice, Gatorade, and unspecified carbohydrate drink) (1,2,6,8,30). In three of these trials, positive effects of creatine on body composition, strength, and/or functional performance were found (1,6,30). Interestingly, in one trial (2) that did not show a significant effect of creatine supplementation paired with a carbohydrate drink on the outcomes of interest, the authors did note that there were nonsignificant trends for creatine to have a greater effect on strength and body composition as compared with placebo. In addition, in this (2) and the other trial that did not find a creatine effect when creatine was paired with carbohydrate (8), subjects only consumed creatine on the days where they were training (3 $d \cdot wk^{-1}$), thus perhaps the dosing regimen was not sufficient to elicit significant changes. Importantly, of the five trials (3,12–14,16) where carbohydrate was not coingested with creatine, four (3,13,16) did not find positive effects of creatine supplementation on the outcomes of interest. As such, it does appear that carbohydrate coingestion is important to optimize creatine effects on body composition, strength, and functional performance in older adults.

In conclusion, the current meta-analysis confirms a role for concurrent creatine consumption during RT in older adults to attenuate sarcopenic changes. Specifically we show greater increases in BW, FFM, leg press and chest press 1RM, and 30-s chair stand test with a strong trend toward a decrease in %BF. This meta-analysis is limited in that heterogeneity existed within certain comparisons due to differences between trials with respect to subject sex and training protocols. Subgroup analyses were precluded due to the small number of included trials. Further research should be conducted to determine whether older men and women respond similarly to creatine supplementation during RT because the greatest amount of heterogeneity in this meta-analysis was a result of including trials with different sexes. Importantly, to see additive effects of creatine and RT, the training must be progressive in nature and creatine should be coingested with a carbohydrate drink.

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