Review Article

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Creatine and strength training in older adults: an update

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Abstract: Aging is associated with numerous physiological, musculoskeletal, and neurological impairments including a loss of muscle, strength, function, bone mineral, and cognition. Strength training is an effective intervention to counter these age-associated declines. In addition, creatine supplementation is purported to enhance strength training gains in lean tissue mass, muscular strength, and function. There is emerging evidence that creatine combined with strength training can alter bone geometry and cognitive performance. The purpose of this review is to update previous meta-analyses examining creatine combined with strength training on lean tissue mass and bone density compared to strength training and placebo. A secondary purpose was to explore the effects of creatine and strength training on cognition. Updated meta-analyses revealed that creatine enhances lean tissue mass (mean difference [MD]: 1.18 kg, 95 % CI: 0.70–1.67; p<0.00001) and upper body muscular strength (standard mean difference [SMD]: 0.24, 95 % CI: 0.05–0.43; p=0.02) compared to strength training and placebo. Creatine combined with strength training had no greater effects compared to strength training and placebo on lower body muscular strength (SMD: 0.17, 95 % CI: −0.03–0.38; p=0.09), whole-body (MD: −0.00 g cm^{-2}; 95 % CI: −0.01–0.00, p=0.32), femoral neck (MD: −0.00 g cm^{-2}; 95 % CI: −0.01–0.00, p=1.00), or lumbar bone mineral density (MD: 0.00 g cm^{-2}, 95 % CI: −0.01–0.01; p=045). There is preliminary evidence that combining strength training and creatine is an effective strategy to improve bone geometry in postmenopausal females and cognitive function in older adults. Overall, the combination of creatine and strength training has favorable effects on lean tissue mass and upper body strength. In contrast, creatine combined with strength training does not enhance lower-body strength or bone mineral.

Keywords: aging; bone; muscle; strength; brain; health

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Introduction

A loss of muscle mass and strength, bone mineral, and cognition are leading causes of age-related disability and cost the health care system billions of dollars annually [1, 2]. For example, in Canada in 2021, reducing the prevalence of low handgrip strength by 10 % would have saved ~$546 million per year [1]. From a healthy aging perspective, interventions that are cost-effective, easily implemented, and effectively attenuate or reverse these age-related reductions are urgently needed. The most well-established and cost-effective strategy is exercise, with accumulating evidence demonstrating the positive impact of strength training for aging health [3]. Strength training is an effective and potent intervention to improve muscle, bone, and brain health [3–5]. Further, accumulating evidence suggest that creatine may augment muscle, bone, and brain strength training induced adaptations in older adults [6–10].

Creatine, α-methyl guandino-acetic acid, is a well-known ergogenic aid used by exercising individuals [11–14]. Creatine was first isolated and extracted from meat in 1832 by a French philosopher and scientist, Michel Eugene Chevreul. In 1926, the first oral creatine study was completed and revealed that creatine (~10–20 g/day for 28–44 days) can be ingested safely and retained in the body [15]. In the early 1990s, Drs. Roger Harris and Eric Hultman revealed that creatine supplementation elevated intra-muscular creatine stores by ~20 % in healthy males [16]. Harris and colleagues further demonstrated that most of the creatine is stored within skeletal muscle (~95 %) and that approximately 2/3rds is converted to phosphocreatine (PCr) with the rest stored as free creatine [16–18]. Phosphocreatine rapidly donates a phosphate (Pi) to adenosine diphosphate (ADP) to resynthesize adenosine triphosphate (ATP). This reaction is catalyzed by an enzyme known as creatine kinase [17]. This

PCr-ATP energy system can resynthesize ATP at a faster rate than either oxidative phosphorylation or anaerobic glycolysis [17].

Mechanistically, creatine can alter muscle adaptations via enhanced expression of growth factors (i.e. insulin like growth factor-I; IGF-I), myogenic transcription factors (MRFs), protein kinases, satellite cell proliferation and activation (increasing mature nuclei and the capacity for the muscle to grow), calcium flux at the sarcoplasmic reticulum, and reduces oxidative stress, inflammation, and muscle protein breakdown [19]. From a bone perspective, creatine has both indirect and direct effects [20]. Indirectly, creatine enhances strength and muscle mass which pulls on bones stimulating bone accretion over time [20–22]. Further creatine is known to enhance osteoblast (bone forming cells) activity in cell culture models [23]. Osteoblasts also inhibit osteoclasts through the production of osteoprotegerin [24]. In aging adults, creatine combined with strength training reduced the rate of bone mineral loss [25] and attenuated the cross-linked-N-telopeptides excretion [23]. For brain health, creatine provides non-oxidative energy, particularly during increased demands, and may reduce inflammation and oxidative stress leading to increased brain health [8, 26, 27]. For a detailed review on creatine and brain health mechanisms, we refer the reader to Candow et al., [8].

Therefore, the purpose was to provide an update on the importance of strength training combined with creatine from a healthy aging perspective (muscle, bone, and brain). When appropriate we conducted meta-analyses to determine the pooled effects. The previous meta-analysis conducted on creatine and bone mineral density was published in 2018 [20], since that time there has been three randomized controlled trials published [8, 28, 29]. Further, the largest (n=247) and longest (2 year) study every published on creatine and strength training on lean tissue mass and strength was published in 2023 [28], therefore it seems prudent to update our previous meta-analyses [6, 30] with these impactful studies. The summary of this article is presented in Figure 1.

Methods

We narratively reviewed the literature that investigated creatine in conjunction with strength training on muscle, bone, and brain health in older adults in a narrative review. When appropriate we employed meta-analysis. We previously published several meta-analyses examining creatine combined with strength training on lean tissue mass and muscular strength [6, 9, 19, 31, 32] and bone mineral [20] that followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA). We updated our previous meta-analyses with studies recently published. PubMed and SPORTDiscus databases were searched from origin till June 26, 2024. The complete search details and methodology are described in our previous systematic reviews and meta-analyses [6, 20, 30]. Briefly, the inclusion criteria for the meta-analyses was: (i) participants were healthy and free of chronic disease and were on average >50 years of age; (ii) the study used a randomized placebo-control design in combination with a structured strength training program for at least 5 weeks; and (iii) the study must have included a measure of lean tissue mass, upper body or lower body muscular strength, or a measure of bone mineral. The authors (S.C.F. and D.G.C.) evaluated each study to determine inclusion.

We extracted the averages and standard deviations from before and after supplementation for each study and determined the absolute changes (post value minus pre value). We estimated the change standard deviation (based on the equation below):

$$\text{SD change score} = \left[(\text{SD pre})^2 + (\text{SD post})^2 - 2 * (\text{correlation between pre and post scores}) * \text{SD pre} * \text{SD post} \right]^{1/2}$$

As previously described, an assumed correlation of 0.8 to predict SD change scores was used. To assess the heterogeneity, we examined the I^2 tests. Based on the Cochrane Handbook, a random effects model for the meta-analyses was used. Weighted mean differences were determined for lean tissue mass and bone mineral. In addition, the corresponding 95 % confidence intervals (CI) was reported. Standardized mean differences (SMD) were used for other outcome measures since measurements differed. Forest plots were made using Rev Man Web Version 8.0.0. Significance was set at $p<0.05$. To assess publication bias, funnel plots were visually inspected. A risk of bias assessment tool (Cochrane risk of bias 2-tool [RoB2]) was used to evaluate randomization, any deviations from the intended intervention, if there was any missing data, the outcome, and how the results were reported. Studies were identified as low risk, some concerns, or high risk of bias and are presented in the supplementary files (Figure S1).

Meta-analyses results

Summary characteristics of the recent studies are shown in Table 1 and Forest Plots are presented in Figures 2–7.

Figure 1: Graphical representation of this article. *Figure created with BioRender*.

Creatine in conjunction with strength training compared to strength training and placebo enhanced lean tissue mass (n=746; mean difference [MD]: 1.18 kg, 95 % CI: 0.70–1.67; p<0.00001) and upper body muscular strength (n=693; SMD: 0.24, 95 % CI: 0.05–0.43; p=0.02), as shown in Figures 2 and 3, respectively. Creatine combined with strength training had no greater effect compared to placebo and strength training on lower body muscular strength (n=663; SMD: 0.17, 95 % CI: −0.03–0.38; p=0.09), or whole-body (n=484; MD: −0.00 g cm^{-2}; 95 % CI: −0.01–0.00, p=0.32), femoral neck (n=416; MD: −0.00 g cm^{-2}; 95 % CI: −0.01–0.00, p=1.00), or lumbar bone mineral density (n=455; MD: 0.00 g cm^{-2}, 95 % CI: −0.01–0.01; p=0.45), as shown in Figures 4–7.

Discussion

The major findings of these updated meta-analyses were that creatine with strength training improves estimates of lean tissue mass and upper body muscular strength,

Table 1: Study characteristics and outcomes of recent (since 2018) research examining the effects of creatine with a resistance training program on muscle and bone.

First author, year	Study population	Intervention	Duration	Outcomes
Candow et al. 2019	n=39; healthy (17 men; 22 women); age ≥50 yrs (mean ~55 y)	RCT; CR-before + RT, CR-after + RT, PLA + RT. Creatine was provided 0.1 g/kg/day. RT=3 x/wk	8 mths	↔ BMD and BMC of the whole-body, limbs, femoral neck, lumbar spine, and total hip.
Candow et al. 2020	n=38; healthy men; age=49–67 yrs	RCT; CR + RT, PLA + RT. Creatine was provided 0.1 g/kg/day. RT=3 x/wk	12 mths	↔BMD and geometry; bone speed of sound. CR ↑(p=0.06) section modulus of the narrow part of the femoral neck.
Candow et al., 2021	n=70; healthy men and women; age=58 ± 6 yrs	RCT; CR+RT, PLA+RT. Creatine was provided 0.1 g/kg/day. RT=3 x/wk	12 mths	↑total bone area in the distal tibia and tibial shaft. ↑trabecular and cortical bone area in the tibia for men. ↑ lower leg muscle density.
Chilibeck et al. 2023	n=237; postmenopausal women; age: 59 yrs	RCT: PLA + RT + walking or CR + RT + walking. Creatine group received 0.14 g/kg/day. RT was performed 3 x/wk.	2 yrs	CR ↔ no BMD or upper and lower body 1RM strength. CR ↑ several markers of bone geometry (section modulus; buckling ratio). CR ↑ lean tissue mass in completers and 80 m walking performance.

RCT, randomized controlled trial; PLA, placebo; RT, resistance training; CR, creatine; RM, repetition maximum; BMD, bone mineral density; BMC, bone mineral content; ↑, significant greater; ↔, no difference between conditions; wk, weeks; yrs, years; g, grams; kg, kilograms.

Study or Subgroup	Creatine Mean	Creatine SD	Creatine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Aguiar 2013	1.1	1.5	9	0	2.5	9	4.9%	1.10 [-0.80 , 3.00]
Bernat 2019	1.21	1.61	12	1.19	1.96	12	7.2%	0.02 [-1.42 , 1.46]
Brose 2003 (men)	1.4	4.6	5	0	3.5	2	0.6%	1.40 [-4.91 , 7.71]
Brose 2003 (women)	2	2.5	5	0.6	1.2	5	3.3%	1.40 [-1.03 , 3.83]
Candow 2008	2.1	1.4	13	0.6	2.1	12	7.4%	1.50 [0.09 , 2.91]
Candow 2015 (after)	3	1.9	12	0.5	2.1	12	6.3%	2.50 [0.90 , 4.10]
Candow 2015 (before)	1.8	2	15	0.5	2.1	12	6.5%	1.30 [-0.26 , 2.86]
Candow 2021	-0.93	5.3	18	-1.89	6.2	20	1.6%	0.96 [-2.70 , 4.62]
Chilibeck 2015	-1	2.9	15	-1.3	2.2	18	5.4%	0.30 [-1.49 , 2.09]
Chilibeck 2023	2.1	3.95	120	1.8	3.38	117	11.4%	0.30 [-0.64 , 1.24]
Chrusch 2001	3.3	4.2	16	1.3	3.2	14	2.9%	2.00 [-0.65 , 4.65]
Cooke 2014	2	4.8	10	0.5	6.9	10	0.8%	1.50 [-3.71 , 6.71]
Deacon 2008	1.1	2.5	38	0.7	2	42	10.8%	0.40 [-0.60 , 1.40]
Eijnde 2003	0.9	4.2	23	0.3	3.5	23	3.8%	0.60 [-1.63 , 2.83]
Eliot 2008	2.5	4.6	10	-0.4	7.8	10	0.7%	2.90 [-2.71 , 8.51]
Gualano 2011	3	1.3	13	0	1.3	12	10.6%	3.00 [1.98 , 4.02]
Johannsmeyer 2016	2.8	4.3	14	0.9	4.3	17	2.2%	1.90 [-1.14 , 4.94]
Neves 2011	1.1	3.9	13	0.8	3	11	2.7%	0.30 [-2.46 , 3.06]
Pinto 2016	1.8	1.3	13	0.6	1.3	14	11.0%	1.20 [0.22 , 2.18]
Total (95% CI)			**374**			**372**	**100.0%**	**1.18 [0.70 , 1.67]**

Heterogeneity: Tau² = 0.31; Chi² = 25.90, df = 18 (P = 0.10); I² = 31%
Test for overall effect: Z = 4.79 (P < 0.00001)
Test for subgroup differences: Not applicable

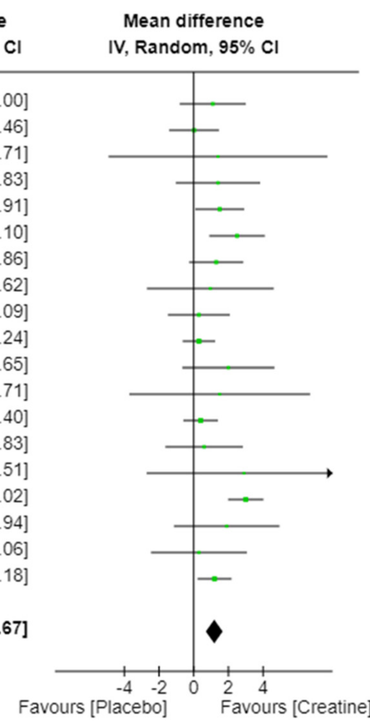

Figure 2: Forest plot of studies investigating creatine and strength training on lean tissue mass.

however, creatine did not enhance gains in lower body muscular strength or bone mineral. These results partially support our previous meta-analyses (i.e., statistically significant improvement in lean tissue mass and upper body strength, while creatine was unable to alter BMD), however, in contrast to previous meta-analyses, creatine with strength training did not enhance lower body strength compared to strength training and placebo. Below we also discuss the purported benefits and evidence of creatine and strength training on bone geometry and cognitive function.

Study or Subgroup	Creatine Mean	Creatine SD	Creatine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. mean difference IV, Random, 95% CI
Aguiar 2013	14	17	9	9	5	9	3.6%	0.38 [-0.55 , 1.31]
Alves 2013	3.4	4	12	2.7	2.2	10	4.3%	0.20 [-0.64 , 1.05]
Bemben 2010	42	13	10	33	6	10	3.7%	0.85 [-0.07 , 1.78]
Bermon 1998	1	1	8	0.6	0.4	8	3.2%	0.50 [-0.50 , 1.50]
Bernat 2019	19	12.9	12	17.58	7	12	4.6%	0.13 [-0.67 , 0.93]
Brose 2003 (men)	30	20	7	22	12	7	2.9%	0.45 [-0.61 , 1.52]
Brose 2003 (women)	15	14	6	13	7	6	2.6%	0.17 [-0.97 , 1.30]
Candow 2008	11	11	13	9	14	12	4.8%	0.15 [-0.63 , 0.94]
Candow 2015 (after)	16	13	12	2	15	12	4.2%	0.96 [0.11 , 1.82]
Candow 2015 (before)	15	13	15	2	15	12	4.6%	0.91 [0.10 , 1.71]
Candow 2021	11	20.9	18	22	21	20	6.4%	-0.51 [-1.16 , 0.13]
Chilibeck 2015	18	15	15	11	14	18	5.7%	0.47 [-0.22 , 1.17]
Chilibeck 2023	10.5	8.58	120	10.8	8.41	117	16.1%	-0.04 [-0.29 , 0.22]
Chrusch 2001	19	13	16	16	11	14	5.5%	0.24 [-0.48 , 0.96]
Cooke 2014	8	9	10	7	13	10	4.0%	0.09 [-0.79 , 0.96]
Gualano 2011	8	16	13	13	8	12	4.7%	-0.38 [-1.17 , 0.42]
Gualano 2014	2.6	4.3	15	1.8	4.9	15	5.5%	0.17 [-0.55 , 0.89]
Hass 2007	0.2	0.07	10	0.1	0.06	10	3.1%	1.47 [0.46 , 2.48]
Johannsmeyer 2016	15	20	14	13	22	17	5.6%	0.09 [-0.62 , 0.80]
Pinto 2016	12	5	13	11	6	14	5.1%	0.17 [-0.58 , 0.93]
Total (95% CI)			**348**			**345**	**100.0%**	**0.24 [0.05 , 0.43]**

Heterogeneity: Tau² = 0.04; Chi² = 25.28, df = 19 (P = 0.15); I² = 25%
Test for overall effect: Z = 2.42 (P = 0.02)
Test for subgroup differences: Not applicable

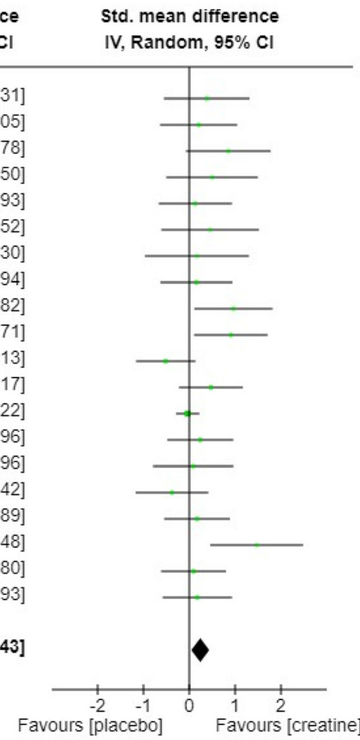

Figure 3: Forest plot of studies investigating creatine and strength training on upper body strength.

Study or Subgroup	Creatine Mean	Creatine SD	Creatine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. mean difference IV, Random, 95% CI
Alves 2013	17	14	12	8	9	10	4.3%	0.72 [-0.15 , 1.59]
Bemben 2010	40	16	10	33	32	10	4.2%	0.27 [-0.62 , 1.15]
Bernat 2019	144.5	96.1	12	83.91	54.6	12	4.6%	0.75 [-0.08 , 1.58]
Brose 2003 (men)	50	33	7	65	23	7	3.1%	-0.49 [-1.56 , 0.58]
Brose 2003 (women)	42	36	6	47	18	6	2.8%	-0.16 [-1.30 , 0.97]
Candow 2008	20	18	13	21	17	12	5.1%	-0.06 [-0.84 , 0.73]
Candow 2015 (after)	41	38	12	6	35	12	4.5%	0.93 [0.08 , 1.77]
Candow 2015 (before)	37	27	15	6	35	12	4.9%	0.98 [0.17 , 1.79]
Candow 2021	69	35.6	18	76	38.1	20	6.9%	-0.19 [-0.82 , 0.45]
Chilibeck 2015	54	49	15	50	45	18	6.2%	0.08 [-0.60 , 0.77]
Chilibeck 2023	26.8	16.88	120	26.1	15.52	117	16.8%	0.04 [-0.21 , 0.30]
Chrusch 2001	50	24	16	29	19	14	5.3%	0.94 [0.18 , 1.70]
Cooke 2014	67	46	10	64	52	10	4.3%	0.06 [-0.82 , 0.94]
Gualano 2011	14	16	13	13	8	12	5.1%	0.08 [-0.71 , 0.86]
Gualano 2014	14	13	15	10	9	15	5.8%	0.35 [-0.37 , 1.07]
Johannsmeyer 2016	28	23	14	36	24	17	5.9%	-0.33 [-1.04 , 0.38]
Neves 2011	10	11	13	11	11	11	4.9%	-0.09 [-0.89 , 0.72]
Pinto 2016	54	47	13	71	33	14	5.3%	-0.41 [-1.17 , 0.36]
Total (95% CI)			**334**			**329**	**100.0%**	**0.17 [-0.03 , 0.38]**

Heterogeneity: Tau² = 0.05; Chi² = 23.21, df = 17 (P = 0.14); I² = 27%
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable

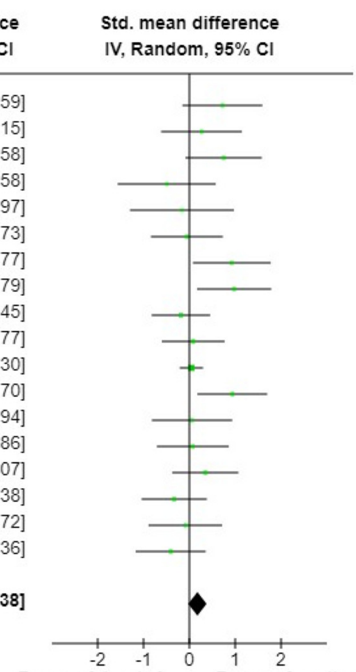

Figure 4: Forest plot of studies investigating creatine and strength training on lower body strength.

Study or Subgroup	Creatine Mean	Creatine SD	Creatine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Candow 2019 (after)	0.002	0.017674	12	0.004	0.010604	12	23.1%	-0.00 [-0.01 , 0.01]
Candow 2019 (before)	-0.001	0.020748	15	0.004	0.010604	12	21.5%	-0.01 [-0.02 , 0.01]
Candow 2021	0	0.088	18	0.01	0.00825	20	1.9%	-0.01 [-0.05 , 0.03]
Chilibeck 2005	0.005	0.06	16	0.006	0.07	13	1.4%	-0.00 [-0.05 , 0.05]
Chilibeck 2015	-0.008	0.02	15	0.002	0.02	18	16.7%	-0.01 [-0.02 , 0.00]
Chilibeck 2023	-0.011	0.05977	120	-0.012	0.07465	117	10.6%	0.00 [-0.02 , 0.02]
Gualano 2014	0	0.02	15	0	0.02	15	15.3%	0.00 [-0.01 , 0.01]
Pinto 2016	0.01	0.03	13	0.004	0.02	14	8.4%	0.01 [-0.01 , 0.03]
Tarnopolsky 2007 (men)	0.03	0.08	11	0.04	0.07	8	0.7%	-0.01 [-0.08 , 0.06]
Tarnopolsky 2007 (women)	0.02	0.08	10	0.02	0.08	10	0.6%	0.00 [-0.07 , 0.07]
Total (95% CI)			**245**			**239**	**100.0%**	**-0.00 [-0.01 , 0.00]**

Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 9 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable

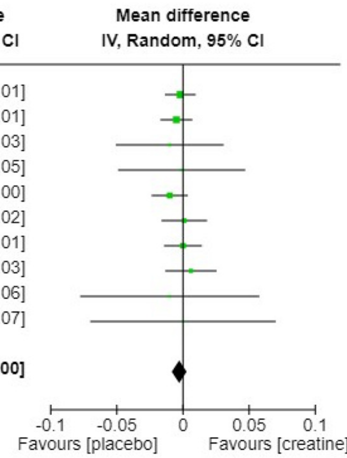

Figure 5: Forest plot of studies investigating creatine and strength training on whole-body BMD.

Study or Subgroup	Creatine Mean	Creatine SD	Creatine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Candow 2019 (after)	-0.014	0.030046	12	-0.006	0.010604	12	18.0%	-0.01 [-0.03 , 0.01]
Candow 2019 (before)	-0.011	0.033592	15	-0.006	0.010604	12	18.0%	-0.00 [-0.02 , 0.01]
Candow 2021	0.007	0.084	18	-0.023	0.076	20	2.9%	0.03 [-0.02 , 0.08]
Chilibeck 2015	-0.01	0.03	15	-0.03	0.029	18	15.1%	0.02 [-0.00 , 0.04]
Chilibeck 2023	-0.013	0.067082	120	-0.015	0.063108	117	20.4%	0.00 [-0.01 , 0.02]
Gualano 2014	-0.01	0.048	15	-0.01	0.036	15	7.6%	0.00 [-0.03 , 0.03]
Pinto 2016	-0.005	0.03	13	0.006	0.015	14	17.9%	-0.01 [-0.03 , 0.01]
Total (95% CI)			**208**			**208**	**100.0%**	**-0.00 [-0.01 , 0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 7.59, df = 6 (P = 0.27); I² = 21%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

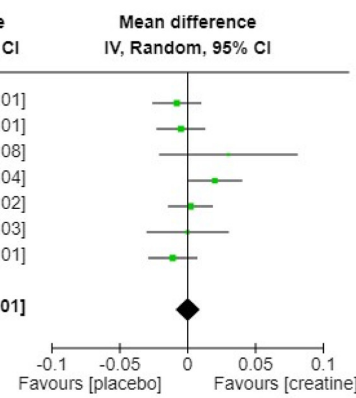

Figure 6: Forest plot of studies investigating creatine and strength training on femoral neck BMD.

Study or Subgroup	Creatine Mean	Creatine SD	Creatine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
Candow 2019 (after)	0.001	0.03799	12	-0.007	0.030046	12	14.7%	0.01 [-0.02 , 0.04]
Candow 2019 (before)	-0.008	0.025688	15	-0.007	0.030046	12	24.0%	-0.00 [-0.02 , 0.02]
Candow 2021	-0.007	0.092	18	0.001	0.093	20	3.2%	-0.01 [-0.07 , 0.05]
Chilibeck 2015	0.005	0.044	15	-0.007	0.044	18	12.1%	0.01 [-0.02 , 0.04]
Chilibeck 2023	-0.007	0.083506	120	-0.008	0.091093	117	22.2%	0.00 [-0.02 , 0.02]
Gualano 2014	0.01	0.055	15	-0.01	0.055	15	7.1%	0.02 [-0.02 , 0.06]
Pinto 2016	-0.009	0.04	13	-0.01	0.04	14	12.1%	0.00 [-0.03 , 0.03]
Tarnopolsky 2007 (men)	0	0.092	11	0	0.042	8	2.9%	0.00 [-0.06 , 0.06]
Tarnopolsky 2007 (women)	0	0.066	10	-0.01	0.108	10	1.8%	0.01 [-0.07 , 0.09]
Total (95% CI)			**229**			**226**	**100.0%**	**0.00 [-0.01 , 0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 1.50, df = 8 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable

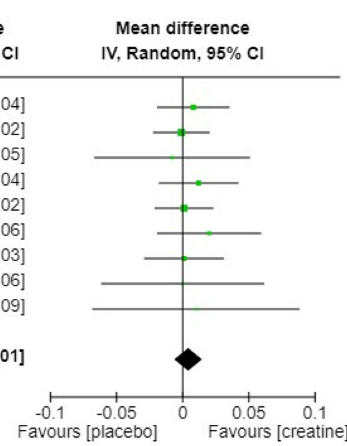

Figure 7: Forest plot of studies investigating creatine and strength training on lumbar BMD.

Creatine and muscle

Mechanistically, creatine is a pleiotropic molecule that can impact cells in a variety of different ways. First, creatine supplementation increases PCr levels (~20 %), thereby increasing the capacity of the PCr-ATP energy system [14, 19]. The addition of creatine with carbohydrates will increase both creatine uptake and glycogen re-synthesis, which again will increase energy availability [19]. Creatine also stimulates IGF-I, leading to a cascade of events that will indirectly increase (mTOR) and may indirectly increase muscle protein synthesis [33]. Creatine also increases myogenic regulatory factors (MRFs), primarily through water retention and cell swelling, which appears to be associated with creatine uptake during the loading phase [34]. Importantly, MRFs stimulate satellite cells that subsequently proliferate and differentiate into mature nuclei. Increasing the number of nuclei within a cell increases the capacity for the muscle to grow (known as the myonuclear domain theory) [19]. In addition, creatine does not appear to increase the ratio of intracellular water (ICW) to skeletal muscle mass over the long-term [35]. From an anti-catabolic perspective, creatine has anti-oxidant capacity since it aids with transport of ATP which is formed in the mitochondria to myofilaments (i.e., sites of utilization) and has anti-inflammatory effects [36]. Collectively, creatine has the capacity to increase anabolic processes and to attenuate catabolic processes [30, 37].

From a muscle or lean tissue mass perspective, a large body of evidence has demonstrated that creatine supplementation combined with strength training enhances adaptations [6, 9, 19, 31, 32, 38, 39]. The evidence is strong that to achieve gains in muscle mass, creatine must be combined with strength training [32], thus the primary driver of anabolism and hypertrophy is strength training. Furthermore based on limited evidence, it appears that males experience larger absolute gains in lean tissue mass compared to females [32]. The sex based differences may be associated with females having higher resting creatine levels in skeletal muscle compared to males [40] and/or that responders to creatine have lower baseline values [41]. Overall, based on our updated meta-analysis, creatine supplementation increases whole-body lean tissue mass by ~1 kg. Some of these gains may be associated with water retention [40]. In a recent systematic review of regional gains in muscle thickness (assessed using B-mode ultrasound) demonstrated that creatine is statistically an effective supplement (equally enhancing elbow and knee flexors and extensors), however, context is important since the effect sizes were small to modest (1–1.6 mm increase in muscle thickness) [9]. Despite, these small increases in muscle size, it is also well-known that creatine enhances gains in muscular strength and function [6]. For example, Candow et al. [42] had older adults (50–71 years of age) ingest either creatine (0.1 g/kg/day) or placebo with strength training for 32 weeks. The creatine groups increased leg press strength (absolute change leg press strength: creatine=~38 kg vs. placebo=6 kg; absolute change in chest press strength: creatine=~15.5 kg vs. placebo=1.9 kg). In the most recent study, Chilibeck et al. [43] examined daily creatine (0.14 g/kg/day) for 2 years in postmenopausal females (n=237). Participants strength trained 3 times per week and walked 6 days per week. Creatine had no effect on muscular strength (1 repetition maximum bench press and hack squat), however, creatine reduced walking time over 80 m (i.e., improved functionality). Despite no effect on muscular strength, creatine did enhance lean tissue mass in a sub-analysis of valid completers compared to placebo ($p=0.046$). Our updated meta-analyses partially support these previous findings [6, 30]. Creatine with strength training was effective at enhancing upper body muscular strength, however, there was no effect on lower body muscular strength. These findings may be relevant for activities of daily living that require increased upper body strength. It is unclear why there may be differences in upper and lower body strength gains, but it may be associated with baseline intramuscular creatine stores [30], fiber type differences [41], and muscle cross sectional area [41]. Syrotuik and Bell [41] identified that responders have lower levels of baseline creatine within their muscles, had more type II (fast twitch) muscle fibers (responders=~63.1 % vs. non-responders=39.5 % type II muscle fibers), and had larger limb circumferences. Potentially a higher dose of creatine may be necessary to achieve improvements in leg press muscular strength [6]. We previously found that studies using a dose of creatine (>5 g/day) had greater increases in lower body strength while studies using a dose of ≤5 g/day did not alter lower body strength [6]. As such, a well-designed dose response study may be required. Other factors, such as being a vegetarian or vegan and the associated lower baseline levels of creatine within their muscle may further alter responsiveness to creatine supplementation [44]. With regards to creatine timing, the current evidence suggests to take creatine in close proximity to exercise [45, 46], however whether you ingest creatine before or after exercise does not appear to influence strength training muscle adaptations [47]. Exercise appears to increase the sensitivity of creatine transporters and enhance creatine uptake [48]. Lastly, the best form of creatine appears to be creatine monohydrate since it has the most evidence, it has a strong safety profile, and is the most economical [49]. Collectively, creatine enhances strength training adaptations, including gains in muscle mass, upper body strength, and function [12] in adults over the age of 50 years. Our updated meta-analyses revealed that creatine does not appear to enhance lower body strength and the effect size is relatively small. Future research is warranted to explore possible mechanisms to explain the differing effects between upper and lower body responses. In addition, research exploring the impact of creatine and strength training on participants with sarcopenia will be critical. Collectively, it is clear that strength training is the most important stimulus and determinant of aging muscle health and creatine may have a further, although small, benefit.

Creatine and bone

In addition to muscle, creatine may also influence measures of aging bone [20, 50]. In theory, creatine can impact bone directly since bone forming cells (osteoblasts) use the creatine kinase reaction and creatine increases osteoblast activity in cell culture models [23, 51]. Based on a small systematic review in 2018 [20] that included 5 RCTs there was no effect of combining creatine and strength training on bone mineral (density or content). Since that review, there have been three new RCTs published [8, 28, 29], which we updated in our meta-analyses. Despite greater statistical power, creatine with strength training still had no effect on bone mineral (Figures 5–7). There was speculation that the effectiveness of creatine on bone mineral may be dose related [51]. However, with regards to bone mineral this does not appear to be supported by the current literature. For example, the most recent, largest and longest study to date was published in 2023 and used a high dose of creatine (0.14 g/kg/day) [43]. The authors conducted a 2-year randomized control trial in postmenopausal women (n=237) and reported that creatine was unable to impact bone mineral density (primary outcome variable), but found numerous benefits of creatine with strength training on bone geometry [28]. Specifically, bone geometry and cortical thickness at the femoral shaft were improved compared to placebo. Sectional modulus is an indicator of bone bending strength and buckling ratio is associated with reduced cortical bending with compressive forces [52, 53]. Furthermore, subperiosteal width was increased following creatine supplementation, which is associated with a decreased risk of fractures [28, 52, 53]. Collectively, creatine with strength training may enhance bone strength via altered bone geometry but has no effect on bone mineral. Future research examining the potential of creatine to reduce the impact on falls is warranted.

Creatine and brain

Emerging research has shown that creatine ingestion can enhance brain creatine levels [26, 27] and that this can alter cognitive function [54]. The brain is different than the muscle since the brain has the capacity to synthesize its own creatine and creatine has a very limited capacity to cross the blood brain barrier [8]. In hippocampal neuron cultures, the administration of creatine increased the mitochondrial activity [55] and in rats, 30 min following creatine injection cAMP-response element binding protein (CREB) was upregulated [56]. In an animal model, four weeks of creatine supplementation improved memory, learning, and hippocampal mitochondrial function [57]. In humans, there is some evidence that creatine may benefit older adults, however there is limited evidence that creatine influences younger adults cognitive function in a rested situation [27, 54, 58]. The most comprehensive review on the topic was recently published [8] and noted that doses above 5 g/day of creatine for a longer duration may be required. The authors also noted that the effects of creatine may be more robust when the brain is stressed, either with hypoxia, sleep deprivation, or following a mild-traumatic brain injury or concussion [8].

To date, there is limited research that assessed creatine and strength training on overall cognition (e.g., MOCA) in older adults [59, 60]. Smolarek et al. [59] investigated 5 g/day of creatine with strength training (16 weeks) compared to a non-exercise, non-placebo control group. The results appear promising, however, since there was no exercise and placebo control group, it is not possible to know if creatine had any further benefit compared to strength training alone. In addition, there is one study in stroke survivors [60] that combined progressive strength training and creatine (0.1 g/kg/day) for 10 weeks. The pilot study was small (n=8; n=5 creatine, n=3 placebo) and included both younger and older adults, however the average age was 51 years in the creatine group and 73 years in the placebo group. The results revealed a main effect of time on cognitive function (MOCA), with no differences between groups, highlighting the importance of strength training. There were also reductions in depression scores. The only improvement in the creatine group was on walking performance, which as stated previously creatine appears to improve functionality. In theory creatine may have a greater effect on the brain following a stroke or in people with dementia but more robust research (e.g., larger sample sizes) is warranted. Collectively, creatine is an emerging nootropic and may alter cognitive function in aging adults [54], however, future research is required to examine if creatine and strength training provides any further benefits compared to strength training alone on cognition.

Limitations and future directions

Currently, there are several gaps within the literature exploring creatine and strength training in older adults. First, most studies do not assess creatine stores (i.e., intramuscular or brain creatine levels) before and after supplementation. Furthermore, most studies only include estimates of fat-free mass or lean tissue mass. Lean tissue mass includes muscle and other non-contractile components such as water. Future research is required to use more advanced tools to assess the direct effect of creatine on muscle. From a tissue specific perspective (muscle, bone, and brain) it is important to determine the optimal dose [61]. From a brain perspective, different regions may be impacted differently with creatine supplementation [62]. In addition, conducting longitudinal studies is challenging, particularly with participant recruitment and retention, thus limiting the statistical power. To overcome this challenge, meta-analyses, such as in the current study are useful, however, this review is not a comprehensive systematic review, thus bias may exist, and caution is warranted.

Conclusions

In summary, creatine has a large body of evidence to suggest that it has a significant but small to modest effect on augmenting strength training muscle adaptations in aging adults (i.e., lean tissue mass and upper body strength). Further, emerging evidence exist that creatine can alter bone geometry, despite no effect on bone mineral. Lastly, creatine combined with strength training has the ability to impact brain health and cognitive function, however, there is limited evidence. Future research is warranted to determine the clinical and therapeutic effects of creatine on individuals with sarcopenia and osteoporosis [10], diabetes, or other impairments (e.g., dementia) or following a stroke [60]. Importantly, creatine in the recommended doses is safe [63] and despite numerous misconceptions [64], creatine in addition to strength training is an effective strategy in older adults.

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Informed consent: Not applicable.
Author contributions: SCF and DGC conceptualized. SCF wrote the first draft. DGC provided edits and finalized the manuscript.
Competing interests: S.C.F. has received creatine donations for scientific studies; sold creatine education resources; and is a sports nutrition advisor for the International Society of Sports Nutrition (ISSN); is a scientific advisor for Bear Balanced (a company which manufactures creatine products). D.G.C. has conducted industry-sponsored research involving creatine supplementation and received creatine donations for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. In addition, D.G.C. serves on the Scientific Advisory Board for Alzchem and Create (companies that manufacture creatine products) and as an expert witness/consultant in legal cases involving creatine supplementation.
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