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Effects of creatine supplementation in older adults

SYSTEMATIC REVIEW

ÁREA CIENTÍFICA DE GERIATRIA

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ABSTRACT

Introduction: The age-related muscle and bone loss have a negative impact on the quality of life of older adults once they lead to a decrease of the ability to perform daily living tasks. Supplements for older adults are currently use in clinical practice. The purpose of this systematic review was to determine which are the effects of creatine supplementation in older adults.

Methods: MedLine, Embase and Cochrane databases were searched. Randomized placebo control trials, prospective observational studies with controls, retrospective matched-pair studies, and comparative studies involving supplementation with creatine in older adults (≥65 years) were considered. Additional articles were retrieved from reference lists found in these papers. Quality of the studies was evaluated by using Jadad Scale.

Results: 28 studies respecting the inclusion and exclusion criteria were selected for this systematic review with a total of 836 subjects taking part in the studies. There was a great diversity across the studies in terms of the participants included (healthy, COPD, Parkinson, rheumatoid arthritis, post total joint arthroplasty, ongoing chemotherapy for colorectal cancer), supplementation strategies (differences in types of creatine, doses and additional protein supplementation), exercise training (type, frequency), design (duration, setting) and Jadad score (from 1 to 5).

Discussion: Evidence suggests that body mass and fat free mass might beneficiate from creatine supplementation when it is conducted during a short period or for a moderate period combined with training. The effects of supplementation on muscular function seemed to be benefic, nevertheless it is not clear if creatine only improves the effects of training or if it has beneficial effects itself. The lack of evidence on COPD, Parkinson, rheumatoid arthritis patients and on safety issues prevents the author to make conclusions on those.

Conclusion: Further studies are needed to determine whether creatine is effective in the absence of training, which are the optimal doses of supplementation and to clarify the safety of the supplement in older adults.

Keywords: Creatine, Supplementation, Aged

INTRODUCTION

When there is a low dietary creatine (CR) uptake, mostly because of the small intake of meat and fish, CR is synthesized from arginine, glycine, and methionine in the kidneys, liver, and pancreas (1,2). Via a sodium-dependent creatine transporter, CR is stored in skeletal muscle, heart and brain where it plays an important role in the energy metabolism. CR is a component of phosphocreatine, a high-energy phosphate, which is needed to resynthesize adenosine diphosphate (ADP) to maintain adenosine triphosphate (ATP) during intense muscle contraction (i.e. PCr + ADP <-> ATP + Cr). (3–5)

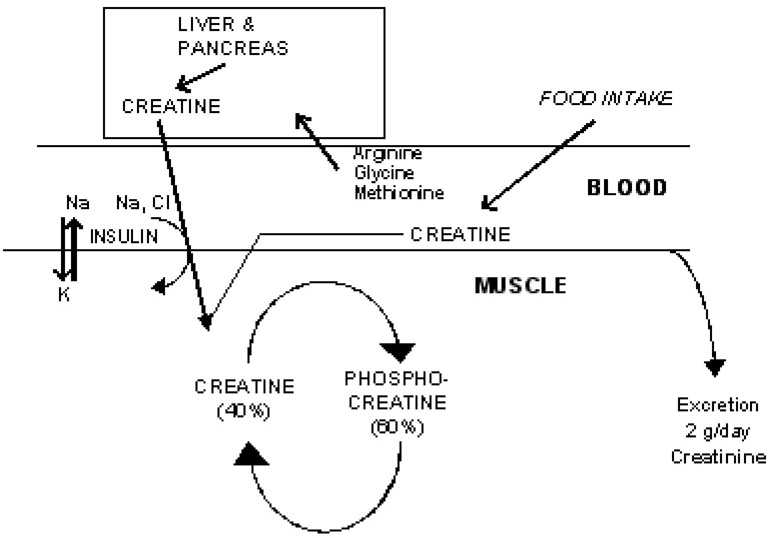

Figure 1 *Creatine metabolism.* Reproduced from Bogdanis, G. C., A. Papaspyrou, and M. Maridaki. "Muscle metabolism and fatigue during sprint exercise: effects of creatine supplementation." Serbian Journal of Sports Sciences 1.2 (2007): 37-57.

Muscle loss, known as sarcopenia, along with loss of strength (dynapenia) and reduction in bone mass are some of the biological changes that are widely known to be related with aging and they are associated with poorer health outcomes, including obesity, osteoporosis and type 2 diabetes. (6–8) Along with that, some authors suggest that diseases as Chronic Obstructive Pulmonary Disease (COPD) (9) and Parkinson (10) are more frequent in older than in younger ages.

Once aging is strongly related with the risk of falls and depression, which determine a lower quality of life, it is a widely recognize health issue. In addition, the number of hospital admissions of older adults are getting higher, consequently increasing health care costs. (11,12)

Many studies have concluded that supplementation with CR can enhance muscle strength, exercise tolerance and fat free mass among young people, making CR one of the most used ergogenic supplements among athletes. (13–15) Lately, research investigating the clinical use of CR among older adults has demonstrated that this supplementation might be beneficial. (3,16–

18) However, the safety of CR among older populations has been concerning scientists and doctors, particularly about its renal effects. (16)

This Systematic Review evaluates the benefits and adverse effects of CR supplementation in older people. The author included RCTs conducted on older adults using CR supplements with or without protein supplements along with or without resistance training. In most of the studies Placebo (PL) was used on the control group (17–43) except for one study that used no intervention in the control group. (44) One of the studies was part of a larger clinical trial so it didn't have a control group. (45) Effects on body composition, diet, muscle function, pulmonary function, cognitive function, mental status, Unified Parkinson's Disease Rating Scale (UPDRS) scores, liver and renal function were assessed.

METHODS

The author summarized all the data known about the effects of CR supplementation in older adults in order to determine whether CR might be or not a good supplement to attenuate the sarcopenic changes of aging, if it can work as an adjuvant therapy of diseases such as COPD, Parkinson or rheumatoid arthritis, and whether there are negative effects of its use. In order to get conclusions about this matter, author analyzed randomized-placebo-control trials, prospective observational studies with controls, retrospective matched-pair studies, and comparative studies conducted in older adults using CR as an intervention along or not with resistance training and protein supplements (PR). Pre and post supplementation data were compared inside and between groups. Outcomes measured were body composition, diet, muscle function, cognitive function, mental status, pulmonary function, UPDR scores, liver and renal function. Finally, in order to formulate conclusions about the effects of supplementation, period of CR use was divided in three different groups: short period (0-<2weeks), moderate period (2weeks-<24) weeks and long period (≥24 weeks).

Search and study selection

A comprehensive literature search was made using PubMed MEDLINE, EMBASE and Cochrane Library databases in October 2016. The search was limited to articles conducted only in humans, written in English, Portuguese, Spanish or French and published in the past twenty years (1996-2016). Mesh terms "Creatine","Dietary supplementation", "Aged", "Older adults" were used in the Pubmed search. The complete electronic search string is provided in supplementary table **S1**. Additional papers were identified through reference search in the selected articles and past reviews.

After duplicate deletion, two investigators independently screened titles and abstracts. Articles were excluded if both investigators agreed an eligibility criteria were met (**table 1**). A second review of the full-text articles was made; differences concerning article inclusion were resolved by consensus discussion.

Data collection

The data was extracted by the author to a Microsoft Excel spreadsheet using a form validated by the investigators. A second investigator confirmed the information collected. The data collected consisted in the following items: study author and date, sample size, participants' characteristics (mean age, sex, disease-specific group), type and duration of intervention and outcomes. The outcomes were pooled into similar subgroups and evaluated together for optimization of the analysis.

Two investigators independently assessed the quality of the studies using the Jadad Scale. (46) Differences were resolved by consensus. The results were not used to exclude any article.

Table 1. Study Inclusion and Exclusion Criteria		
	Inclusion Criteria	**Exclusion Criteria**
Population	Adults (mean age ≥ 60yr)	
Interventions	CR supplementation with or without protein supplementation, with or without training exercise	Additional interventions (eg: linoleic acid). Use of CR lesser than 5 days
Comparisons of interest	Control groups using placebo. Control groups with no intervention	
Outcomes measured	At least one of the following outcomes measured: body composition, exercise performance, physical rehabilitation, nutrition status and cognitive functioning in older adults	Other outcomes
Study design	RCT's. Due to the small number of RCT's, prospective observational studies with controls, retrospective matched-pair studies, and comparative studies were also included	Studies with no comparator group (for example, case series); non-matched retrospective studies and chart reviews
CR, Creatine, RCT, Randomized clinical trials		

RESULTS

The initial search yielded **450 articles**. After duplication removal **343** relevant citations were screened. **50** studies were left for resolving conflicts that were decided by the two investigators together, and according to the inclusion and exclusion criteria, 25 studies from the 50 were retrieved for full text review. **Three** studies found by hand search by the author were posteriorly add for full text review. At the end, **28** studies were selected for full text review.

The flow of studies through the review process is summarized in **Figure 1**. Details of the 28 included studies can be found in **table 2.**

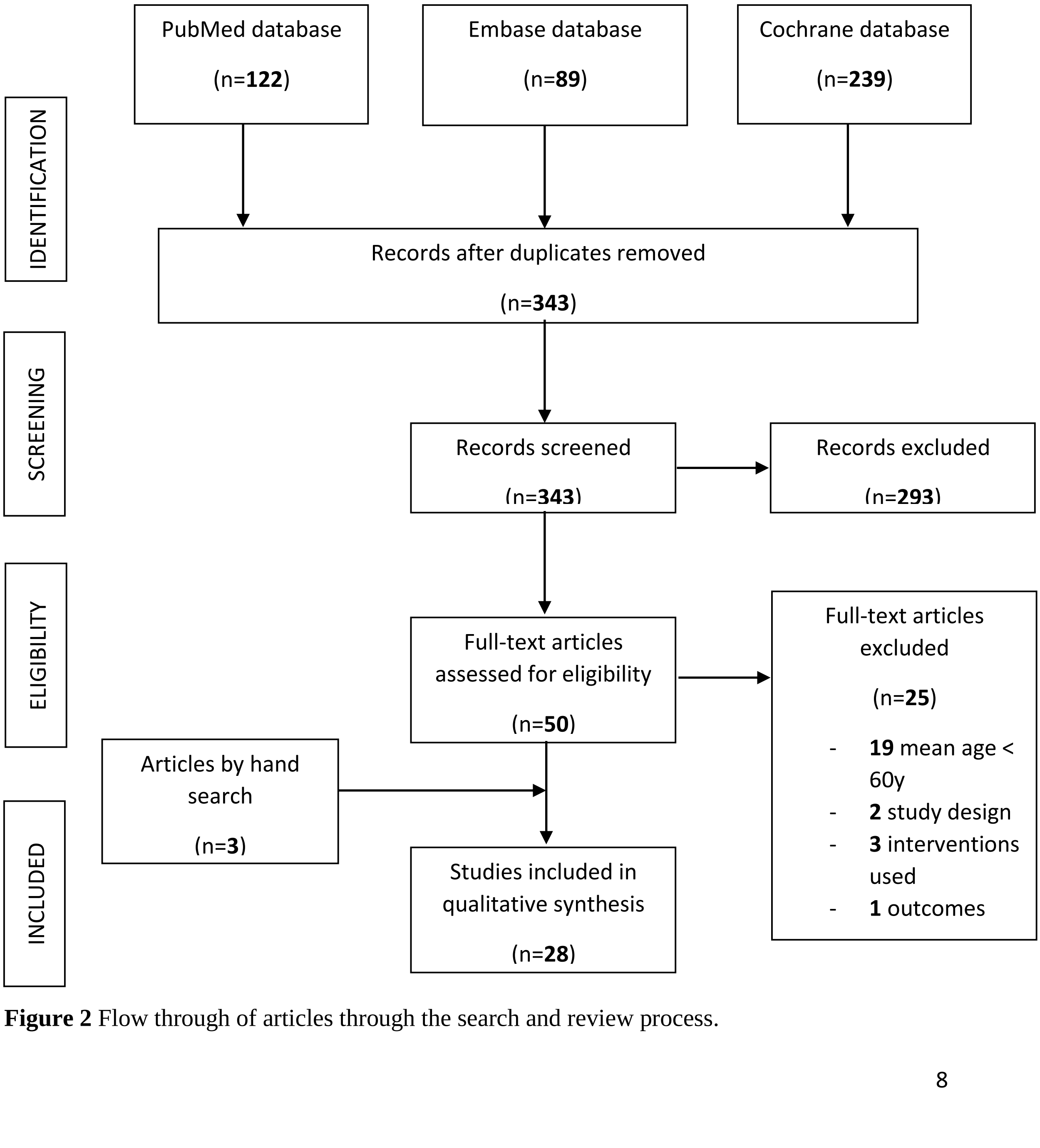

Figure 2 Flow through of articles through the search and review process.

The studies involved a total of 836 subjects, ranged in sample size from 12(35) to 80 (28) participants and varied in duration between 5 days (35,38,43) and 2 years. (21) Of these studies 13 only included two comparison groups (CR or PL) without any other intervention. (21,24,32,33,35–43) In 15 studies participants went in a training program (18–20,22,23,25–31,34,44,45) and 3 of these studies also used protein as a supplement along with CR. (23,44,45) The majority of these studies (12 out of 15) used resistance training as training program (18–20,22,23,25,26,29,34,44,45) and 3 used a specific Pulmonary Rehabilitation program. (28,30,31) Creatine monohydrate was the mostly used supplementation (18–20,22–24,27–29,31–35,37–40,42–44), Di-Creatine-Citrate was used by one study (41) and 6 studies did not specify the type of CR used. (21,25,26,30,36,45) The doses of CR supplementation varied from single dose of 5 grams per day (19,22,29,35,36) to 20 grams per day. (17) Most of the studies used a loading dose followed by a lower dose for the remain of the trial: 8 used a loading dose for 5 days (18,20,25,26,28,34,42,44), 4 for 7 days (27,30,37,41), 2 for 10 days (39,40), 1 for 14 days (31) and 1 one for 6 months. (21) These data is presented in **table 2.**

Study population groups included healthy older subjects (22,36,41), older men (23,25–27,29,35,38,39,43,44), older women (19,24,33,34), subjects with frailty (45), vulnerable older women (34), COPD (28,30,31), Parkinson (18,21), ongoing chemotherapy of colorectal cancer (37), recovering of total joint arthroplasty (40) and rheumatoid arthritis. (42)

Using the Jadad Scale, investigators scored 4 studies with the total score of 5 (20,28,34,42) , 13 with the score of 4 (19,22–24,26,27,30–32,37,38,40), 8 were qualified with the total score of 3 (18,21,29,33,35,39,41,45), another 2 was given the total score of 2 (43,44) and 1 study had 1 point for the total score. (36) The Jadad Scale table is presented on supplementary table **S2.**

Table 2. Details of the included studies regarding subject characteristics, creatine and protein supplementation protocol and training

Author/year	Study design	Mean age (SD)	Sample size	% males	Population	Durantion (weeks)	Intervention	Creatine (dose)	Protein (dose)	Placebo (dose)	Exercise type, Duration (sessions/week)
Aguiar A.F. 2012	RCT	64.9(5)	CR=9 PL=9	0%	Older women	24	Creatine + Training	CrM+dextrose= 5g+2g/d	–	Dextrose=7g/d	Resistance, 3 sessions/w for the last 12w
Alves, C. et al 2013	RCT	66.9 (4.9)	CR=13 PL=12 CR+TR=12 PL+TR=10	0%	Older women	24	Creatine + Training	CrM=20g/d for 5d followed by 5g/d	–	Dextrose= 20g/d for 5d followed by 5g/d	Resistance, 2s/w
Bender, A et al 2008	Randomized Pilot Trial	60 (9.4)	CR=40 PL=20	CR=71% PL=78%	Parkinson Disease	96	Creatine	Cr=20g/d for 6d followed by 2g/d for 6m and 4g/d	–	?	–
Brose A. Et al 2003	RCT	68.7(4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g+2g/d	–	Dextrose=7g/d	Resistance, 3 s/w
Candow, D. et al 2008	RCT	65.6(2.7)	CrP=10 CR=12 PL=12	100%	Older Men	10	Creatine + Protein + Training	CrM= 0.1 g/kg/D	Protein= 0.3 g/kg/d	Chocolate and Cherry-flavored sucrose powder =1.2 g/kg	Resistance 3s/w
Cañete, S et al 2006	Single-blind design	68(4)	CR=10 PL=6	0%	Older Women	1	Creatine	CrM=0,3g/kg x3/d for 7d	–	Powdered Cellulose=0.3G/Kg x3/d for 7d	–
Chilibeck, P. D. et al 2005	RCT	70(6.6)	CR=16 PL=13	100%	Older Men	12	Creatine + Training	Cr=0.3g/d 1st 5d followed by 0.07g/d	–	Sucrose Fluor Mixture=0.3g/d 1st 5d followed by 0.07g/d	Resistance, 3 s/w
Chrusch, M. et al 2001	RCT	70.4(1.6)	CR=16 PL=14	100%	Older Men	12	Crreatine + Training	Cr+sucrose=0.3 g/kg/d for the first 5d followed by 0.07 g/kg/d	–	Sucrose Fluor Mixture=0.3g/d for the first 5d followed by 0.07g/d	Resistance , 3s/w
Collins, J. et al 2015	Small-scale exploratory trial	70.33(?)	CR+PR=9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w

Cooke, M. B. et al 2014	RCT	61.4 (5.0)	CR= 10 PL=10	100%	Older men	12	Creatine + Training	CrM+CHO= 20 g + 5 g /d for 7 days followed by 0.1 g/kg/d of crM + 5 g/d of glucose on training days	–	CHO= 20 g of glucose only for 7 days followed by 5 g of glucose on training days	Resistance, 3s/w
Deacon, S.J. et al 2008	RCT	68.2(8.2)	CR=38 PL=42	CR=50 % PL=74 %	COPD	7	Creatine + Training	CrM=22g/d for 5d followed by 3.76g/d during pulmonary rehabilitation	–	Lactose=24g/d for 5d followed by 4g/d during pulmonary rehabilitation	Pulmonary rehabilitation, 21 s/7w
Eijnde, B.O. et al 2003	RCT	65.3(1.3)	CR=15 PL=21	100%	Older Men	12m	Creatine + Training	CrM=5g/d	–	?	Endurance + Resistance, 2-3 s/w
Faager, G. et al 2006	RCT	66.0(6.0)	CR=13 PL=10	CR=46 % PL=40 %	COPD	8	Creatine + Training	CR?=0.3g/kg/d during 7d followed by 0.07g/kg/d during the remaining 7 weeks	–	Glucose= ?	Pulmonary Rehabilitation, 2 s/w
Fuld, J.P. et al 2005	RCT	61.7(8.0)	CR=14 PL=11	?	COPD	12	Creatine + Training	CrM + glucose= 5g+35g 3xday for 14 days followed by 5g+35 1xday for 10weeks	–	Glucose polymer= 40.7g 3xday for 14 days followed by 40.7g 1xday for 10 weeks	Pulmonary Rehabilitation, 2s/w
Gotshalk L.V.J., et al 2002	RCT	65.4(1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–
Gotshalk L.V.J., et al 2008	RCT	63.3(1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–
Gualano, B. et al 2014	RCT	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine + Training	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w
Hass, C. J. et al 2007	RCT	68.1(3.8)	CR=10 PL=10	85%	Parkinson Disease	12	Creatine + Training	CrM= 20g for the first 5d followed by 5g/d f	–	Lactose Monohydrate= 20g for the first 5d followed by 5g/d	Resistance Training=2 sessions/w
Jakobi, J.M. et al 2001	RCT	72.0(2.0)	CR=7 PL=5	100%	Older Men	<1	Creatine	CrM + Maltodextrin= 5g/d	–	Maltodextrin= 5g/d	–

McMorris et al 2007	RCT	76.4 (8.48)	CR=15 PL=17	CR=53 % PL= 47%	Older subjects	2	Creatine	PL= 5g/d followed by CrM=5g/d	–	Maxijoule?= 5g/d	–
Norman, K. et al 2006	RCT	65.1 (12.55)	CR=16 PL=15	CR=62, 5% PL=66, 7%	Colorectal Cancer	8	Creatine	CrM= 20g/d in the first week followed by 10g/d	–	Cellulose=20g/d in the first week followed by 10g/d	–
Rawson, E.S. et al 1999	RCT	66.7 (1.9)	CR=10 PL=10	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–
Rawson E.S. et al 2000	RCT	65.0(2.1)	CR=9 PL=8	100%	Older Men	<1	Creatine	CrM+sucrose= 20g+4g/d	–	PL=equivalent volume of look-alike Sucrose	–
Roy, B.D. et al 2005	RCT	63.3(10.2)	CR=18 PL=19	CR=50 % PL=42 %	Total joint arthroplasty	6	Creatine	CrM+dextrose= 10g+8g d on the 10d before surgery and 5g+4g/d for 30d after surgery	–	Dextrose= 14g on 10d before surgery and 7g/d for 30d after surgery	–
Stout, J.R. et al 2007	Double blind cross-over design	74.5(6.4)	7 male + 8 female	47%	Older subjects	2	Creatine	Di-Creatine-Citrate=20g/d during week 1 and 10g/d week 2	–	Flavored effervescent powder blend	–
Villanueva, M.G. 2014	RCT	68.1(6.1)	PR+TR=7 TR=7 C=8	100%	Older Men	12	Creatine + Protein + Training	CrM= 0.3g/kg/d for 5d followed by 0.07g/kg/d	Liquid protein= 35g/d	–	Resistance, 3 s/w
Wilkinson, T.J. et al 2016	RCT	63.0(10.0)	CR=15 PL=20	CR=23 % PL= 30%	Rheumatoid Arthritis	12	Creatine	CrM= 20g/d for the initial 5d followed by 3g/d	–	Flavored drink powder	–
Wiroth J.B. et al 2001	RCT	69.4(?)	CRsedentary=7 PLsedentary=7 Cttrained=7 Pltrained=7	100%	Older men	<1	Creatine	CrM+sucrose=15g+ 30g/d	–	Casein+sucrose= 30g+15g/d	–

RCT, Randomized Control Trial; CR, creatine; PL, placebo; PR, protein; CrM, Creatine Monohydrate; CHO, CrM-carbohydrate; TR, Training; COPD, Chronic Obstructive Pulmonary Disease

BODY COMPOSITION

Body Mass

Even though most of the studies described an increase in body mass after the period of supplementation with CR (19,22,27–33,35,37–39,41–43) only 5 of them stated that the increase was significant ($p<0.05$). (22,27,32,35,38) From these, 3 studies were performed for a short period. (32,35,38)

Cooke et al (27) demonstrated that PL group also had a significant ($p<0.05$) increase but the increase in CR group was significantly ($p<0.05$) higher than PL group. Through the duration of this study participants went through a resistance training program.

In the study conducted by *Roy et al* (40) evaluating the supplementation with CR after total joint arthroplasty the body mass decreased both CR and Pl groups without significant *p* value.

Fat Free Mass (FFM)

Even though FFM increased with no significant *p* value in 4 studies (33,34,38,40) the increase on FFM was significant in 6 studies with *p* value <0.05 (23,26–28,32) and in 2 studies with *p* value <0.01. (19,31) From these studies 1 was performed in a long period (19), 6 during a moderate period (23,26–28,31,45) and 1 in a short period of time. (32) Nevertheless, in 3 studies FFM increased with no significant *p* value. (33,38,40)

Cooke et al (27) and *Chrusch et* al (26) documented a significant ($p<0.05$) increase on PL group. Sidelong with *Fuld et al* (31), *Cooke et al* (27) detected that the increase on CR group was significantly ($p<0.05$) higher than PL group .

Collins et al (45) reported a significant increase in FFM on both CR+PR and PR groups and *Candow et al* (23) observed a significant ($p<0.05$) increase in both PL and CR+PR groups.

Rawson et al (39) described a decrease on FFM after the supplementation with CR. No training was used in this study.

Body Fat

Despite the fact most of the studies described a decrease in body fat after the period of supplementation with CR (19,22,26,27,29,32,33,38–40,44) only 2 of them concluded the decrease was significant ($p<0.05$). (25,29) While one of this studies was performed in a long period (29) the other occurred during a moderate period of time. (26)

Eijnde BO et al (29) described a significant ($p<0.05$) decrease in both CR and PL groups after 12 months of endurance plus resistance training along with CR supplementation.

Only one study by *Wilkinson et* al (43) described an increase in body fat after CR supplementation, but with no statistical significance.

Bone Mineral Content (BMC)

BMC was noticed to be increased without significant *p* value after a moderate period of resistance training and CR supplementation. (25) An non-significant increase was noticed in CR+PR and PR groups after a moderate period of training along with supplementation in the study conducted by *Collis J et al.* (45)

Gualano B et al (34) documented a non-significant decrease in BMC after a long period of CR supplementation and training.

Bone Mineral Density (BMD)

Chilibeck et al (25) concluded that the increase of BMD was significant ($p<0.05$) in both CR and PL groups. There was one study which did not observe changes in BMD (34) and another detected a non-significant increase in both CR+PR and PR groups. (45) In all these studies patients practiced resistance training along with the CR supplementation for a moderate period (25,45) and for a long period. (34)

Muscle Fibers

Even though both studies studying muscle fibers documented an increase in muscle fibers content after CR supplementation the *p* values were not significant. (22,27) Patients practiced exercise training along with the supplementation for a moderate period of time.

Muscle Creatine

Despite the fact that in studies where biopsy was performed it was detected an increase in muscle CR after CR supplementation and exercise training (22,29) the increase was only significant ($p<0.05$) in the one performed in a moderate period of time. (22)

Muscle Phosphocreatine

In both *Brose A et* al and *Eijnde BO et* al (22,29) studies a significant ($p<0.05$) increase in muscle phosphocreatine was documented after supplementation with CR along with training during a moderate (22) and long (30) period of time.

Details regarding body composition are presented on supplementary **tables S3.**

NUTRIENTS INTAKE

Proteins

Half of the articles studying nutrients intake stated that protein intake increased with non-significant *p* value after CR supplementation (20,23,34) while 2 studies documented a non-significant decrease. (27,39) In *Collins J et* al study (45) patients also used PR along with CR supplementation and this group (CR+PR) decreased protein intake without significant *p* value. (23) *Gualano B et al* (45) compared CR+PR and PR supplementation and both groups increased protein intake with no significant *p* value.

Carbohydrates

Carbohydrate intake decreased without significance in CR group in three studies in which patients went in a resistance training program. (23,27,34) In *Candow D et* al study (23) patients also used PR supplementation and PR group also noticed a non-significant decrease in carbohydrate intake. Increase in carbohydrates intake was documented by two studies (20,39), one using resistance training along with CR supplementation (20) and one where there was no training. (39) Neither of the studies documented the increase was significant.

C*ollins J et* al revealed a decrease on CR+PR group while PR increase carbohydrate intake. (45)

Fat

While the majority of the studies stated a non-significant decreased of fat intake (20,27,39) two studies investigating fat intake after CR supplementation documented its increase without significant *p* values. (23,34)

Candow D et al (23) noticed a non-significant fat intake increase in CR group while the CR+PR group decreased fat intake without significance.

In *Collins J et* al study (45) CR+PR group decreased fat intake while PR group increased it without significant *p* values.

Energy

Most of the studies described a non-significant decrease in energy intake after the period of supplementation with CR (23,27,39) and in one of them the comparing group PR also showed a non-significant decrease. (23)

On *Collins J et* al study (45) both CR+PR and PR groups revealed a non-significant decrease on energy intake.

Gualano B et al (34) stated the amount of kilocalories/day increased without significance after 24 weeks of creatine supplementation together with resistance training.

Nutrients intake data is presented on supplementary **tables S4.**

DYNAMIC AND ISOMETRIC STRENGTH

1RM Bench Press

Even if all the studies describing 1RM Bench Press described an increase after CR supplementation (19,32–34) only in two studies the increase was significant (*p*<0.05). (19,32) While *Gotshalk LVJ et al* (32) used a short period of supplementation *Aguiar AF et al* (19) performed the study during a long period of time.

In *Villanueva MG et* al study (44) PR was used along with CR supplementation and CR+PR group described a non-significant increase.

1RM Leg Press

1RM Leg Press increased without significance in all the studies after CR supplementation. (20,22,32–34) *Collins J et* al (44) also detected an increase in 1RM Bench Press in CR+PR group.

1RM Knee Extension

Despite the fact that all the studies describing 1RM Knee extension described an increase after CR supplementation (19,22,32) only two studies (19,32) revealed the increase was significant (p<0.05). While *Gotshalk LVJ et al* (32) used a short period of supplementation *Aguiar AF et al* (19) performed the study during a long period of time.

Bench Press Strength

All the studies which evaluated Bench Press Strength revealed a significant (*p*<0.05) increase in both CR and PL groups. (23,25,26)

Candow et al (23) concluded that also CR+PR group had a significant (*p*<0.05) increase on bench press strength. Furthermore, they noticed that CR+PR group had a significant (*p*<0.05) greater increase than CR and PL groups.

All the studies used resistance training along with CR supplementation for a moderate period.

Leg Press Strength

Leg Press Strength evaluation revealed a significant (p<0.05) increase in both CR and PL groups after CR supplementation in all studies which run this test. (23,25,26) All the studies used resistance training along with CR supplementation for a moderate period.

Candow et al (23) also described a significant (p<0.05) increase in CR+PR group and concluded that the increase was significant (p<0.05) greater in CR+PR than CR group.

Handgrip Strength

Although all the studies which evaluated Hangrip Strength revealed an increase after CR supplementation (22,30,37,40,41) it was only significant (*p*<0.05) in two of the studies. (30,41) *Faager G et* al (30) revealed the significant (*p*<0.05) increase was also noticed in PL group.
Collins J et al (45) noticed a significant (*p*<0.05) increase in hand grip strength in both CR+PR and PR groups.

Two studies from *Gotshalk LVJ et al* with identical characteristics (CR supplementation vs PL supplementation for 7d) but performed separately in different populations (Older Women (33) vs Older Men (32)) evaluated **Lower Body Peak Power (LBPP), Lower Body Mean Power (LBMP), Upper Body Peak Power (UBPP) and Upper Body Mean Power (UBMP)**

Both studies revealed an increase in LBPP and LBMP being the increases significant (*p*<0.05) in the study conducted on older men. (32)
LBMP and UBMP also increased in both studies but it was not significant in any group.

Dynamic and isometric strength data is presented on supplementary **tables S5.**

FUNCTIONAL CAPACITY

Sit Stand test

Despite the fact that all the studies which rolled the sit stand test observed a decrease on the time needed for sit and stand (24,32,33) only two studies documented the decrease was significant. (24,32) All the studies were performed in a short period of time and neither exercise training or protein supplementation were used.

Timed Stands test

Only in *Collins J et* al study (45) there was a significant (p<0.05) increase in the number of repetitions on time stands test in both CR+PR and PR groups. The rest of the studies performing time stands test detected a non-significant increase in the number of repetitions in both CR and PL groups. (34,41,42)

Timed Up to Go test

Collins J et al (45) observed a significant (*p*<0.05) decrease in PR group while the CR group showed a significant (p<0.05) increase in time that the participants required to complete the test. *Gualano B et al* (34) observed a non-significant decrease in both CR and PL groups in vulnerable older women.

Details regarding functional capacity are presented on supplementary **tables S6.**

QUALITY OF LIFE, COGNITIVE AND MENTAL OUTCOMES

Three were the studies evaluating the quality of life of the participants. (20,21,37)

Geriatric Depression Scale was used by *Alves C et* al (20) and the author reported that after 24 weeks of intervention, PL and CR groups which went on resistance training had significant (*p*<0.05) reductions in depression scores when compared with either the PL and CR groups that did not go on resistance program.

Bender A et al (21) used **SF-36 scores** and detected a non-significant decrease.

Emotional and **social functioning** were evaluated by *Norman K et* al (37) who documented a non-significant increase of these variables in CR group. The same author measured **global health status** and reported a non-significant decrease in CR group.

Minimal Mental State Examination (MMSE) and **Brief Battery of Cognitive Screening (BBCS)** were measured by *Alves C et* al (20) who documented a non-significant increased after CR supplementation.

All **memory tests** (random number generation, number recall test forward number, number recall test forward spatial, number recall test backward spatial, long term memory) performed by *McMorris et al* (36) showed an increased after CR supplementation but only the results of number recall test backward spatial and long term memory tests were significant (p<0.01) in CR groups.

Cognitive functioning measured by *Normal K et* al (37) presented no changes in CR group.

Quality of life, cognitive and mental data is presented on supplementary **tables S7.**

SPECIFIC DISEASES

COPD

Three studies were conducted in COPD patients who went through a pulmonary rehabilitation program along with CR supplementation for a moderate period of time. (28,30,31)

Deacon SJ et al (28) compared the effects of CR supplementation after the loading phase with the effects shown after pulmonary rehabilitation. After loading phase Body mass, FFM, ISWT (Incremental Shuttle Walking Test), ICQ (Isokinetic Concentric Quadriceps) and IT (Isokinetic Triceps) showed a significant increase with p value <0.01 while IB (Isokinetic Biceps) showed a significant increase with p value <0.05. Once patients went through the pulmonary rehabilitation the values of ESWT (Endurance Shuttle Walking Test), ISWT and IB showed a significant increase with p value <0.01 while FFM, ICQ and IQ showed an increase with p value <0.05.

Faager J et al (30) compared PL and CR groups, both going on pulmonary rehabilitation. Significant increases with p value <0.01 in CR were detected in ESWT and breathing rate and with p value <0.05 were detected in BM, Body Mass Index (BMI) and grip strength. PL group significantly increased BM and grip strength with $p<0.05$ and heart rate with $p<0.01$. Breathing rate decreased on PL group with p value <0.05.

Fuld JP et al (31) compared the CR and PL groups before and after pulmonary rehabilitation. After CR supplementation without pulmonary rehabilitation BM, FFM, Upper Limb Muscle Function (ULMF), peak torque, Lower Limb Muscle Function (LLMF) and time walked showed a significant ($p<0.01$) increase. Differences between groups were significantly higher in CR group in BM, FFM, ULMF and peak torque with p value <0.01 and in LLMF with p value <0.05.
While on pulmonary rehabilitation CR group presented a significant increase with p value <0.01 in FFM, ULFM, peak torque, LLMF and time walked. Increase with p value <0.05 was observed in peak force and distance walked. Significant decreases were observed in St George's Respiratory Questionnaire (SGRQ) activity with p value <0.01 and in Incremental Exercise Test (IET) and SGRQ total score with p value <0.05.
After pulmonary rehabilitation PL group showed significant increases in LLM and time walked with p value <0.01 and ULMF, peak torque, distance walked and SGRQ activity with p value <0.05. Differences between groups showed a significant greater increase in CR group with p value <0.05 in FFM, peak force, ULMF, peak torque and LLMF and with p value <0.01 in the time walked. PL group had a significant greater increase with p value <0.05 in distance walked and SGRQ total score and in SGRQ activity with p value <0.01.

Outcomes evaluated simultaneously across the three studies are presented next.

Endurance Shuttle Walking Test (ESWT)

Both *Deacon SJ et al* (28) and *Faager J et* al (30) detected a significant (*p*<0.01) increase in ESWT values. The increase was also significant (*p*<0.01) in PL group in *Deacon SJ et al* (28) study.

Fat Free Mass

FFM was estimated using diseased specific regression equations by *Deacon SJ et* al (28) and *Fuld JP et* al (31) and both studies documented a significant increase in CR group with *p value*<0.01 (28) and *p value* <0.05. (32) *Deacon SJ et al* (29) also documented a significant increase in PL group with *p value*<0.05.

Fat Mass

Fat Mass decreased without significant *p* value after the period of pulmonary rehabilitation combined with CR supplementation on both *Deacon SJ et al* (29) and *Fuld JP et al* (32) studies.

Details regarding COPD data are presented on supplementary **tables S8.**

Parkinson

Two studies were conducted on Parkinson patients. (18,21) *Hass CJ et* al (18) used resistance training along with CR supplementation and *Bender A et* al (21) had no other intervention besides CR supplementation.

Unified Parkinson's Disease Rating Scale (UPDRS) scores

A significant (p<0.05) decrease in UPDRS motor and total scores in CR group along with a significant (p<0.05) increase in PL group was detected by *Hass CJ et* al. (19) Same authors detected that UPDRS mental and UPDRS Activity of Daily Living (ADL) significantly (*p*<0.05) increased on both CR and PL groups.

Bender A et al (22) detected a non-significant increase of UPDRS values on both groups.

Levodopa and Agonist doses and SPECT variables

Bender A et al (22) documented the dose of agonist significantly (*p*<0.05) increased in both CR and PL groups while the dose of levodopa increased in both groups with no significant *p* value. The same study concluded there was no overall treatment effect on SPECT variables.

Parkinson variables data is presented on supplementary **tables S9.**

Rheumatoid Arthritis

CR supplementation was study in rheumatoid arthritis patients by *Wilkinson TJ et al* (42) who showed greater significant (p<0.05) increases in CR group than PL group on appendicular lean mass (ALM), total body water (TBW), intracellular water (ICW) and extracellular water (ECW).

SAFETY ISSUES

Renal Function

Plasma creatinine

Most of the studies analyzing plasma creatinine detected its increase after CR supplementation (22,32,33) but only in *Brose A et* al (22) and *Gotshalk LVJ et al* (33) studies the increase was significant (p<0.05). Plasma CR increased from 111.4(24.4) µmols/L to 126.2(33.4) µmols/L (22) and from 89.4(15.7) µmols/L to 97.9(17.8) µmols/L. (32)

Plasma Urea and Blood Urea Nitrogen (BUN)

Plasma Urea was analyzed by two studies. *Collins J et* al (46) detected a non-significant increase after CR+PR and PR supplementation and *Cañete S et* al (25) did not observe changes on plasma urea values.

BUN was analyzed by *Gotshalk LVJ et al* in two different studies. (33,34) In the one performed in older women BUN had a non-significant decrease after CR supplementation (33) while in the one performed in older men authors did not detect changes on its values. (32)

Liver Function

Albumin

While *Cañete S et* al (24) documented no changes on albumin concentration after CR supplementation *Gotshalk LVJ et al* (32) noticed a non-significant decrease. Studies had the same characteristics (CR supplementation vs Placebo for 7d) but while the first was conducted on Older Women, the second was performed on Older Men. (32)

Aspartate Transaminase (AST)

Two studies documented a non-significant decrease on AST values after CR supplementation. (32,33)

Collins J et al (46) documented AST decrease on both CR+PR and PR groups.

Cañete S et al did not detect changes on AST values after CR supplementation. (24)

Alanine Transaminase (ALT)

After CR supplementation, ALT values presented different non-significant changes across the studies: one documented its increase (33), one its decrease (32) and other presented no changes on ALT values. (24) After CR+PR and PR supplementation ALT increased in both groups on *Collins J et al* study. (45)

Gama Glutamil Transferase (GGT)

Two studies evaluating GGT documented its non-significant decrease after CR supplementation (24,32) while one study stated its non-significant increase. (33) After CR+PR GGT increased without significant *p* values while after PR it decreased also without significance. (45)

Reported Adverse Effects

Few of the studies of this review reported adverse effects of its participants. (22,23,26,32,39)
Gastrointestinal distress was reported in four studies which stated it to be higher in CR groups than PL groups. (22,26,32,39)
In four studies muscle cramping, soreness and stiffness was documented in both CR and PL groups. (23,26,32,39)
Skin rash was reported in one participant on CR supplementation. (39)

Safety issues data is presented on supplementary **tables S10.**

DISCUSSION

MAIN FINDINGS

A careful reading of the articles assessed for eligibility leads the author to a total of 28 studies of older adults (≥ 65 years) in which CR supplementation combined or not with PR supplementation and/or training is used to improve body mass, functional capacity, cognitive performance and COPD, Parkinson and rheumatoid arthritis variables.

Seventeen studies conducted in older adults, using CR monohydrate in a dose varying from 0.1/kg/day to 5g/day evaluated the effects of CR supplementation in body mass. Five studies have shown with significant evidence that short period supplementation with CR and moderate period of supplementation combined with training have positive effects on body mass gain. Studies have shown the increase of FFM with significant evidence when supplementation with CR monohydrate is conducted during a short period and during a moderate to long period of time combined with training. Once PL groups also had significant increases on FFM when training was performed, evidence suggests that the effect of training is greater than the CR supplementation on improving FFM. According to the evidence, body fat seems to decrease after CR supplementation with and without training. Significant p values (<0.05) were found in two studies.

In which refers to body composition, body mass and FFM showed to be increased when the supplementation is rolled either during a short period of time or during a moderate/long period along with resistance training. The use of resistance training seems to have a strong impact on FFM leading the effects of CR hard to be understandable. More investigation about the use of CR to improving FFM without training must be done.

Evidence suggests there are no overall effects of CR supplementation on dietary intake.

The present evidence about dynamic strength suggests that CR monohydrate might be benefic increasing 1RM bench press and 1RM knee extension when it is given during a short period of time or for a long period of time combined with resistance training. However, the evidence about this matter is poor once only 2 and 3 studies evaluating 1RM bench press and 1RM knee extension respectively detected an increase in this outcomes. Leg press strength and bench press strength were evaluated by 3 studies conducted during a moderate period of time combined with resistance training varying the dose of CR from 0.07g/kg/day to 0.1mg/kg/day. The evidence suggests that resistance training might have a greater effect than CR increasing isometric strength once PL groups also demonstrated a significant increase in leg and bench press strength. Three out of 6 studies rolled during a moderate period demonstrated significant increases in handgrip strength in CR groups. Resistance training was used in two of the studies that were not clear about the dose and type of CR used. One of them also demonstrated a significant increase in PL group. According to that, there is not enough evidence to conclude about the benefits of CR supplementation increasing handgrip strength. Two studies performed for a short period using either 0.3mg/kg/day or 0.9mg/kg/day of CR monohydrate detected a significant decrease on sit stands test on CR groups. According with that, this review failed to demonstrate that CR supplementation for a short period might improve the neuromuscular control under stressful conditions.

Evidence suggests CR supplementation to be a successful supplement improving muscular performance in older adults (≥60 years). The evidence is stronger if considered either short period of supplementation or moderate/long period of supplementation combined with resistance training.

Only three studies evaluated the quality of life, social and mental outcomes and the evidence on this matter is not clear to formulate any conclusions. Geriatric depression scale showed significant increases in one study, which make author believe more studies must be done to take any definitive conclusion.

Despite the fact outcomes evaluated by the 3 studies on COPD patients have shown significant increases on CR group variables, most of the times the same results were present on PL groups without significant differences between groups. This leads to the conclusion that pulmonary rehabilitation might be the key to a greater recovery on COPD patients and CR does not appear to increase this effect. Nevertheless, more studies must be done on this matter once the evidence is low giving the number of studies. Studies conducted on Parkinson patients suggest there is no overall effect of CR supplementation. However, evidence on this subject is low once only 2 studies were conducted on these patients. One study on rheumatoid arthritis patients revealed significant improvements on body composition after CR supplementation but as it is the only study on this subject the evidence is very low. Author encourage researchers to study the potential effects of CR supplementation on rheumatoid arthritis patients.

The effects on renal function, evaluated by 4 studies, suggests that CR might increase plasma creatinine once the increase was significant in 2 of the studies which were conducted in a short period of time with a dose of 0.3mg/kg/day and during a moderate period with a dose of 5g/day. Plasma CR increased from 111.4(24.4) µmols/L to 126.2(33.4) µmols/L (22) and from 89.4(15.7) µmols/L to 97.9(17.8) µmols/L. (32) Nevertheless, the number of studies going on this matter is small consequently, the evidence is not clear. Liver function seemed to be unchanged after CR supplementation but then again only 4 studies went through this matter leading author to the conclusion that more research must be done on CR safety. Despite the fact that few studies reported adverse effects of CR supplementation it is clear for the author that the most common adverse effect documented is gastrointestinal distress. The period of intervention does not seem to modify the results once the collateral effect was documented on both short and moderate periods of intervention.

LIMITATIONS & STRENGTHS

This study presents a currently issue of interest once worldwide population is getting older and interventions to improve quality of life are increasing its importance. This systematic review is pioneer in evaluating the full spectrum of CR supplementation effects in older adults. Once studies from 5 days to 2 years of intervention were included in this review author is able to conclude about the effects of CR varying on the time of intervention. In order to get a good quality of the review author chose to use PRISMA checklist and to include results of the outcomes measured the same way in at least two studies and present the ones were the differences were significant with p values <0.05 and <0.01.

Only the study conducted by *Wilkinson TJ et* al (43) performed a post-intervention follow up after 12 weeks of the intervention. The rest of the studies included in this systematic review did not perform a follow up of the patients, which makes author unaware of how long the effects of the supplementation were kept. The impact of the co-supplementation with protein is still not clear once few are the studies doing the co-supplementation. (23,44,45) In order to enhance the evidence on the subject more studies must be done on the creatine supplementation combined with protein supplementation in older adults.

Few studies evaluate safety issues of CR supplementation in terms of renal and liver function (22,24,32,33,45) and the reporting of adverse effects is also poor. (22,23,26,32,39) This lack of evidence does not allow the author to make conclusions about CR safety in older adults.

The reduced number of studies evaluating CR effects in specific diseases such as Parkinson and rheumatoid arthritis prevents the author to conclude about the effects of this supplement on improving the conditions of these patients. The author encourages investigators to perform research on CR effects on improving these diseases. Some studies do not provide clearly information about the type (21,25,26,30,45) and dose (45) of CR used. Furthermore, once doses of supplementation are not presented in the same way across the studies the effect of the dose of CR cannot be clearly understand.

Along with the reviews conducted by *Denison H et al* (47) and *Devries M et al* (48) this review suggests beneficial effects of CR combined with training on improving muscular performance in older adults. Additionally, the results of this review support the idea that moderate to long use of CR is no more effective than short supplementation in muscle function improvement if it is not combined with training. The findings of this review prove with moderate evidence that CR supplementation is a potential strategy for the prevention and management of sarcopenia in older adults once there is proof that it improves muscular function. Furthermore, according with the evidence found, CR seems to be a good supplement to improve FFM. Still, author cannot guarantee the good results found on this review are a product of CR supplementation itself or if the supplementation with CR only improves the effects of training.

More research must be done in order to define which cognitive benefits of CR are and which impact they have in the quality of life of older adults. CR showed some positive effects on illnesses as COPD and rheumatoid arthritis still with poor evidence. For that reason, the author believes investigation of the benefits of CR on diseases associated with the process of aging might bring some exciting findings.

The use of CR as a supplement in older adults is not well clarified once the dose to be used and its period of time are not well stablished. Additionally, the insufficient evidence of the safety issues is still preventing the clinical use of CR as supplement to manage the consequences of aging process.

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APPENDIX

Database	Full electronic search
Medline	("creatine"[MeSH Terms] OR "creatine"[All Fields]) AND ("dietary supplements"[MeSH Terms] OR “dietary supplements”[All Fields] OR “food supplements” [All Fields]) AND (“aged” [MeSH Terms] OR “aged” [All Fields] OR “older adults” [All Fields] OR “elderly” [All Fields])
Cochrane	ID Search #1 MeSH descriptor: [Creatine] explode all trees #2 MeSH descriptor: [Dietary Supplements] explode all trees #3 MeSH descriptor: [Aged] explode all trees #4 MeSH descriptor: [Middle Aged] explode all trees #5 (#1 and #2)
Embase	#1 ‘creatine’/exp OR ‘creatine’ AND ([english]/lim OR [french]/lim OR [portuguese]/lim OR [Spanish]/lim) AND ([middle aged]/lim OR [aged]/lim) AND [humans]/lim # 2 ‘diet supplementation’ #3 #1 AND #2

***S1* –** Full electronic search strategy of Medline, Cochrane and Embase databases.

Study	*Randomization (0-2)*	*Blinding (0-2)*	*Withdrawals and drop outs (0-1)*	*Total Score*
Aguiar, 2012	1	2	1	4
Alves, 2013	2	2	1	5
Bender, 2008	1	1	1	3
Brose, 2003	1	2	1	4
Candow, 2008	1	2	1	4
Cañete, 2006	1	2	1	4
Chilibeck, 2005	1	2	1	4
Chrusch, 2001	1	2	1	4
Collins, 2015	1	1	1	3
Cooke, 2014	1	2	1	4
Deacon, 2008	2	2	1	5
Eijnde, 2003	1	1	1	3
Faager, 2006	1	2	1	4
Fuld, 2005	1	2	1	4
Gotshalk, 2002	1	2	1	4
Gotshalk, 2008	1	2	0	3
Gualano, 2014	2	2	1	5
Hass, 2007	1	2	0	3
Jakobi, 2001	1	2	0	3
McMorris, 2007	0	1	0	1
Norman, 2006	1	2	1	4
Rawson, 1999	1	2	0	3
Rawson, 2000	1	2	1	4
Roy, 2005	2	2	0	4
Stout, 2007	1	2	0	3
Villanueva, 2014	1	0	1	2
Wilkinson, 2016	2	2	1	5
Wiroth, 2001	1	1	0	2

S2 – *Jadad Scale* : review authors' judgements about each risk of bias.

S3- Details regarding **body composition.**

1) Body mass

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Aguiar, 2012	64.9 (5)	CR=9 PL=9	0%	Older women	24	Creatine + Training	CrM+dextrose= 5g+2g/d	–	Dextrose=7g/d	Resistance, 3 s/w for the last 12w	↑	Both CR and PL groups increased body mass with no significant differences within and between groups.
Brose, 2003	68.7 (4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g+2g /d	–	Dextrose=7g/d	Resistance, 3 s/w	↑ **Pre:** 84.1(14)kg **Post:** 85.5(13.5) kg	CR group significantly ($p<0.05$) increased body mass while PL group decreased. No significant differences between groups.
Cooke, 2014	61.4 (5.0)	CR= 10 PL=10	100%	Older men	12	Creatine + Training	CrM+CHO= 20 g + 5 g /d for 7 days followed by 0.1 g/kg/d of CrM + 5 g/d of glucose on training days	–	CHO= 20 g of glucose only for 7 days followed by 5 g of glucose on training days	Resistance, 3s/w	↑ **Pre:** 88.2(12.4) kg **Post:** 89.9(11.8) kg	Both CR and PL groups significantly (p 0<0.05) increased body mass. Increase on CR group was significantly ($p<0.05$) greater than PL group.
Deacon, 2008	68.2 (8.2)	CR=38 PL=42	CR=50% PL=74%	COPD	7	Creatine + Training	CrM=22g/d for 5d followed by 3.76g/d during pulmonary rehabilitation	–	Lactose=24g/d for 5d followed by 4g/d during pulmonary rehabilitation	Pulmonary rehabilitation, 21 s/w	↑	Both CR and PL groups increased body mass with no significant differences within or between groups
Eijnde, 2003	65.3 (1.3)	CR=15 PL=21	100%	Older Men	48	Creatine + Training	CrM=5g/d	–	?	Endurance + Resistance, 2-3 s/w	↑	CR group increased body mass while PL group decreased. No significant differences within or between groups.
Faager, 2006	66.0 (6.0)	CR=13 PL=10	CR=46% PL=40%	COPD	8	Creatine + Training	CR?=0.3g/kg/d during 7d followed by 0.07g/kg/d during the remaining 7 weeks	–	Glucose= ?	Pulmonary Rehabilitation, 2 s/w	↑	Both CR and PL groups increased body mass with no significant differences within or between groups
Fuld, 2005	61.7 (8.0)	CR=14 PL=11	?	COPD	12	Creatine + Training	CrM + glucose= 5g+35g 3x/d for 14 days followed by 5g+35 1x/d for 10weeks	–	Glucose polymer= 40.7g 3x/d for 14 days followed by 40.7g 1x/d for 10 weeks	Pulmonary Rehabilitation, 2s/w	↑	Both CR and PL groups increased body mass with no significant differences within or between groups.
Gotshalk, 2002	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	↑ **Pre:** 84.8(13.02)kg **Post:** 86.45(17.11)kg	CR group significantly ($p<0.05$) increased body mass while PL group decreased. No significant differences between

groups.

Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=?	–	↑	Both CR and PL groups increased body mass with no significant differences within or between groups
***Jakobi,* 2001**	72.0 (2.0)	CR=7 PL=5	100%	Older Men	<1	Creatine	CrM + Maltodextrin= 5g/d	–	Maltodextrin= 5g/d	–	↑ **Pre:** 83(4)kg **Post:** 84(4)kg	CR group significantly (p<0.05) increased body mass while PL group had no changes. No significant differences between groups.
***Norman*, 2006**	65.1 (12.6)	CR=16 PL=15	CR=62,5 % PL=66,7 %	Colorectal Cancer	8	Creatine	CrM= 20g/d for the first week followed by 5/d for 7w	–	Cellulose= 20g/d for the first week followed by 5g/d for 7w	–	↑	Both CR and PL groups increased body mass with no significant differences within or between groups
***Rawson*, 1999**	66.7 (1.9)	CR=10 PL=10	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–	↑	Both CR and PL groups increased body mass with no significant differences within or between groups.
***Rawson*, 2000**	65.0 (2.1)	CR=9 PL=8	100%	Older Men	<1	Creatine	CrM+sucrose= 20g+4g/d	–	Equivalent volume of look-alike sucrose=?	–	↑ **Pre:** 86.2(3.4)kg **Post:** 86.7(3.4)kg	CR group significantly (p<0.05) increased body mass while PL group had no changes. No significant differences between groups.
***Roy,* 2005**	63.3 (10.2)	CR=18 PL=19	CR=50% PL=42%	Total joint arthroplasty	6	Creatine	CrM+dextrose= 10g+8g d on the 10d before surgery and 5g+4g/d for 30d after surgery	–	Dextrose= 14g on 10d before surgery and 7g/d for 30d after surgery	–	↓	Both CR and PL groups decreased body mass with no significant differences within or between groups.
***Stout,* 2007**	74.5 (6.4)	CR=? PL=?	47%	Older subjects	2	Creatine	Di-Creatine-Citrate=20g/d during for the first week followed by 10g/d	–	Flavored effervescent powder blend=?	–	↑	CR group increased body mass while PL group decreased. No significant differences between groups.
***Wilkinson,* 2016**	63.0 (10.0)	CR=15 PL=20	CR=23% PL= 30%	Rheumatoid Arthritis	12	Creatine	CrM= 20g/d for the initial 5d followed by 3g/d	–	Flavored drink powder	–	↑	Both CR and PL groups increased body mass with no significant differences within or between groups
Wiroth 2001	69.4(?)	CR=14 PL=14	100%	Older men	<1	Creatine	CrM+sucrose=15g+30g/d	–	Casein sucrose= 30g+15g/d	–	↑	All groups increased body mass with no significant differences within or between groups.

2) Fat Free Mass (FFM)

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Aguiar, 2012	64.9(5)	CR=9 PL=9	0%	Older women	24	Creatine + Training	CrM+dextrose= 5g+2g/d	–	Dextrose=7g/d	Resistance, 3 sessions/w for the last 12w	↑ **Pre:** 35.1(2.3)kg **Post:** 36.2(2.5)kg	Both CR and PL groups increased body mass. The increase was significant ($p<0.01$) on CR group. No significant differences between groups
***Collins*, 2016**	70.33 (?)	CR+PR= 9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↑ **Pre:** 44.1(7.6)kg **Post:** 44.5(9.4)kg	Both CR+PR and PR groups significantly ($p<0.05$) increased FFM without significant differences between groups.
***Deacon*, 2008**	68.2 (8.2)	CR=38 PL=42	CR=50% PL=74%	COPD	7	Creatine + Training	CrM=22g/d for 5d followed by 3.76g/d during pulmonary rehabilitation	–	Lactose=24g/d for 5d followed by 4g/d during pulmonary rehabilitation	Pulmonary rehabilitation, 21 s/7w	↑ **0.9(1.6) kg**	Both groups significantly increased FFM. CR group with $p<0.01$ and PL with $p<0.01$. No significant differences between groups.
***Fuld*, 2005**	61.7 (8.0)	CR=14 PL=11	?	COPD	12	Creatine + Training	CrM + glucose= 5g+35g 3x/d for 14 days followed by 5g+35 1x/d for 10weeks	–	Glucose polymer= 40.7g 3x/d for 14 days followed by 40.7g 1x/d for 10 weeks	Pulmonary Rehabilitation, 2s/w	↑ **2.0 (1.9) kg**	CR group significantly ($p<0.01$) increased FFM while PL group decreased it. The differences between groups are significant ($p<0.05$).
***Gotshalk*, 2002**	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Cellulose powder=0.3 g/kg	–	↑**Pre:** 61.10(6.58)kg **Post:** 63.32(7.80)kg	CR group significantly($P<0.05$) increased FMM while PL group had no changes. No significant differences between groups.
***Gotshalk*, 2008**	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↑	Both CR and PL groups increased FFM with no significant differences within or between groups.
***Rawson* 1999**	66.7 (1.9)	CR=10 PL=10	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–	↓	CR group decreased FFM while PL group increased. No significant differences within or between groups

											80)kg	between groups.
Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↑	Both CR and PL groups increased FFM with no significant differences within or between groups.
Gualano, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↑	CR group increased FFM while PL decreased. No significant differences within or between groups.
***Rawson* 1999**	66.7 (1.9)	CR=10 PL=10	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–	↓	CR group decreased FFM while PL group increased. No significant differences within or between groups
***Rawson* 2000**	65.0 (2.1)	CR=9 PL=8	100%	Older Men	<1	Creatine	CrM+sucrose= 20g+4g/d	–	Equivalent volume of look-alike sucrose=?	–	↑	CR group increased FFM while PL group decreased. No significant differences within or between groups.
***Roy,* 2005**	63.3 (10.2)	CR=18 PL=19	CR=50% PL=42%	Total joint arthroplasty	6	Creatine	CrM+dextrose= 10g+8g d on the 10d before surgery and 5g+4g/d for 30d after surgery	–	Dextrose= 14g on 10d before surgery and 7g/d for 30d after surgery	–	↑	Both CR and PL groups increased FFM with no significant differences within or between groups

3) Body Fat

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
***Aguiar,* 2012**	64.9 (5)	CR=9 PL=9	0%	Older women	24	Creatine + Training	CrM+dextrose= 5g+2g/d	–	Dextrose=7g/d	Resistance, 3 sessions/w for the last 12w	↓	CR group decreased body fat while PL group increased. No significant differences inside or between groups
***Brose,* 2003**	68.7 (4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g+2g /d	–	Dextrose=7g/d	Resistance, 3 s/w	↓	Both CR and PL groups decreased Body Fat with no significant differences within or between groups.
***Chrusch* 2001**	70.4 (1.6)	CR=16 PL=14	100%	Older Men	12	Crreatine + Training	Cr+sucrose=0.3 g/kg/d for the first 5d followed by 0.07 g/kg/d	–	Sucrose Fluor Mixture=0.3g/d for the first 5d followed by 0.07g/d	Resistance , 3s/w	↓ **Pre:** 88.0(3.6)% **Post:** 91.0(3.8)%	Both CR and PL groups significantly ($p<0.05$) decreased body fat without significant differences between

												groups.
***Cooke*, 2014**	61.4 (5.0)	CR= 10 PL=10	100%	Older men	12	Creatine + Training	CrM+CHO= 20 g+5 g /d for 7 days followed by 0.1 g/kg/d of crM + 5 g/d of glucose on training days	–	CHO= 20 g of glucose only for 7 days followed by 5 g of glucose on training days	Resistance, 3s/w	↓	CR group decreased body fat while PL group had no changes. No significant differences within or between groups.
***Eijnde*, 2003**	65.3 (1.3)	CR=15 PL=21	100%	Older Men	48	Creatine + Training	CrM=5g/d	–	?	Endurance + Resistance, 2-3 s/w	**↓ Pre:** 27.2(1.2)% **Post:** 26.2(1.2)%	Both CR and PL groups significantly ($p<0.05$) decreased body fat without significant differences between groups.
***Gotshalk*, 2002**	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Cellulose powder=0.3 g/kg	–	↓	Both CR and PL groups decreased body fat without significant differences within or between groups.
***Gotshalk*, 2008**	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Cellulose powder=?	–	↓	Both CR and PL groups decreased body fat without significant differences within or between groups.
***Rawson* 1999**	66.7 (1.9)	?	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–	↓	CR group decreased body fat while PL group increased. No significant differences within or between groups
***Rawson* 2000**	65.0 (2.1)	CR=9 PL=8	100%	Older Men	<1	Creatine	CrM+sucrose= 20g+4g/d	–	Equivalent volume of look-alike sucrose=?	–	↓	CR group decreased body fat while PL group increased. No significant differences within or between groups
***Roy*, 2005**	63.3 (10.2)	CR=18 PL=19	CR=50% PL=42%	Total joint arthroplasty	6	Creatine	CrM+dextrose= 10g+8g d on the 10d before surgery and 5g+4g/d for 30d after surgery	–	Dextrose= 14g on 10d before surgery and 7g/d for 30d after surgery	–	↓	Both CR and PL groups decreased body fat without significant differences within or between groups.
***Villanueva*, 2014**	68.1 (6.1)	PR+TR=7 TR=7 C=8	100%	Older Men	12	Creatine + Protein + Training	CrM= 0.3g/kg/d for 5d followed by 0.07g/kg/d	Liquid protein=35g/d	–	Resistance, 3 s/w	↓	Both CR+PR and PR groups decreased body fat without significant differences inside and between groups.

***Wilkinson* 2016**	63.0 (10.0)	CR=15 PL=20	CR=23% PL= 30%	Rheumatoid Arthritis	12	Creatine	CrM= 20g/d for the initial 5d followed by 3g/d	–	Flavored drink powder=?	–	↓	Both CR and PL groups increased body fat without significant differences within or between groups.

4) Bone Mineral Content

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
***Chilibeck*, 2015**	70 (6.6)	CR=16 PL=13	100%	Older Men	12	Creatine + Training	Cr=0.3g/d 1st 5d followed by 0.07g/d	–	Sucrose Fluor Mixture=0.3g/d 1st 5d followed by 0.07g/d	Resistance, 3 s/w	↑	CR group increased BMC while PL decreased. No significant differences within or between groups.
***Collins*, 2016**	70.33 (?)	CR+PR= 9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↑	Both CR and PL groups increased BMC without significant differences within or between groups.
***Gualano*, 2014**	66.1 (4.8)	CR=15 PL=15 CR+TR= 15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↓	Both CR and PL groups decreased BMC without significant differences within or between groups.

5) Bone Mineral Density

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
***Chilibeck*, 2015**	70 (6.6)	CR=16 PL=13	100%	Older Men	12	Creatine + Training	Cr=0.3g/d 1st 5d followed by 0.07g/d	–	Sucrose Fluor Mixture=0.3g/d 1st 5d followed by 0.07g/d	Resistance, 3 s/w	↑ **Pre:** 0.980(0.088)g/cm2 **Post**:0.985(0.088)g/cm2	Both CR and PL groups significantly ($p<0.05$) increased BMD without significant differences between groups.
***Collins*, 2016**	70.33 (?)	CR+PR= 9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↑	Both CR+PR and PR groups increased BMD without significant differences within or between groups
***Gualano*, 2014**	66.1 (4.8)	CR=15 PL=15 CR+TR= 15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	0	Both CR and PL groups presented no changes in BMD.

		PL+TR=15										

6) Muscle fibers

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
***Brose* 2003**	68.7 (4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g+2g /d	–	Dextrose=7g/d	Resistance, 3 s/w	↑	Both CR and PL groups increased muscle fibers with no significant differences within or between groups.
***Cooke*, 2014**	61.4 (5.0)	CR= 10 PL=10	100%	Older men	12	Creatine + Training	CrM+CHO= 20 g + 5 g /d for 7 days followed by 0.1 g/kg/d of CrM + 5 g/d of glucose on training days	–	CHO= 20 g of glucose only for 7 days followed by 5 g of glucose on training days	Resistance, 3s/w	↑	Both CR and PL groups increased muscle fibers. CR group had a significant increase in muscle fibers <u>type II.</u> No significant differences between groups.

7) Muscle creatine

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
***Brose* 2003**	68.7 (4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g+2g /d	–	Dextrose=7g/d	Resistance, 3 s/w	↑ **Pre:** 116.8(14.5)mmolkg-1dm **Post:** 159.3(23.9)mmolkg-1dm	CR group significantly($P<0.05$) increased muscle creatine while PL decreased. No significant differences between groups.
***Eijnde*, 2003**	65.3 (1.3)	CR=15 PL=21	100%	Older Men	48	Creatine + Training	CrM=5g/d	–	?	Endurance + Resistance, 2-3 s/w		CR group increased muscle creatine while PL group decreased. No significant differences within or between groups.

8) Muscle phosphocreatine

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
***Brose* 2003**	68.7 (4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g+2g /d	–	Dextrose=7g/d	Resistance, 3 s/w	↑ **Pre:** 67.4(19.7)mmol kg-1dm **Post:** 88.0(20.5)mmol kg-1dm	Cr group significantly (*p*<0.05) increased muscle phosphocreatine while PL decreased. No significant differences between groups.
***Eijnde,* 2003**	65.3 (1.3)	CR=15 PL=21	100%	Older Men	48	Creatine + Training	CrM=5g/d	–	???	Endurance + Resistance, 2-3 s/w	↑ **Pre:** 102.3(4.2)mmol /kgdrywt **Post:** 114.2(5.0)mmol /kgdrywt	CR group significantly(P<0.05) increased muscle phosphocreatine while PL decreased. No significant differences between groups.

CR, creatine; PL, placebo; PR, protein; CrM, Creatine Monohydrate; CHO, CrM-carbohydrate; COPD, Chronic Obstructive Pulmonary Disease

S4- Details regarding **nutrients intake.**

1) Proteins

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Alves, 2013	66.9 (4.9)	CR=13 PL=12 CR+TR=12 PL+TR=10	0%	Older women	24	Creatine + Training	CrM=20g/d for 5d followed by 5g/d	–	Dextrose= 20g/d for 5d followed by 5g/d	Resistance, 2s/w	↑	Both CR and PL groups increased protein intake without significant differences within or between groups.
Cando w, 2008	65.6 (2.7)	CrP=10 CR=12 PL=12	100%	Older Men	10	Creatine + Protein + Training	CrM= 0.1 g/kg/D	Protein?= 0.3 g/kg/d	Chocolate and Cherry-flavored sucrose powder =1.2 g/kg/d	Resistance 3s/w	↑	Both CR and PL groups increased protein intake while CR+PR group decreased. No significant differences within or between groups.
Collins, 2016	70.33 (?)	CR+PR=9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↑	Both CR+PR and PR groups increased protein intake without significant differences within or between groups.
Cooke, 2014	61.4 (5.0)	CR= 10 PL=10	100%	Older men	12	Creatine + Training	CrM+CHO= 20 g + 5 g /d for 7 days followed by 0.1 g/kg/d of crM + 5 g/d of glucose on training days	–	CHO= 20 g of glucose only for 7 days followed by 5 g of glucose on training days	Resistance, 3s/w	↓	CR group decreased protein intake while PL group increased. No significant differences within or between groups
Gualan o, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↑	CR group increased protein intake while PL group decreased. No significant differences within or between groups
Rawson 1999	66.7 (1.9)	CR=10 PL=10	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g/d	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–	↓	Both CR and PL groups decreased protein intake without significant differences within or between groups.

2) Carbohydrates

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Alves, 2013	66.9 (4.9)	CR=13 PL=12 CR+TR=12 PL+TR=10	0%	Older women	24	Creatine + Training	CrM=20g/d for 5d followed by 5g/d	–	Dextrose= 20g/d for 5d followed by 5g/d	Resistance, 2s/w	↑	Both CR and PL groups increased carbohydrates Intake without significant differences within or between groups.
Cando w 2008	65.6 (2.7)	CrP=10 CR=12 PL=12	100%	Older Men	10	Creatine + Protein + Training	CrM= 0.1 g/kg/D	Protein?= 0.3 g/kg/d	Chocolate and Cherry-flavored sucrose powder =1.2 g/kg	Resistance 3s/w	↓	All groups (CR, CR+PR, PL) decreased carbohydrates Intake. No significant differences within or between groups
Collins, 2016	70.33 (?)	CR+PR=9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↓	CR+PR group decreased carbohydrates intake while PR increased. No significant differences within or between groups
Cooke, 2014	61.4 (5.0)	CR= 10 PL=10	100%	Older men	12	Creatine + Training	CrM+CHO= 20 g + 5 g /d for 7 days followed by 0.1 g/kg/d of crM + 5 g/d of glucose on training days	–	CHO= 20 g of glucose only for 7 days followed by 5 g of glucose on training days	Resistance, 3s/w	↓	CR group decreased carbohydrate Intake while PL group increased. No significant differences within or between groups
Gualan o, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↓	CR group decreased carbohydrate Intake while PL group increased. No significant differences within or between groups
Rawson 1999	66.7 (1.9)	CR=10 PL=10	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–	↑	CR group increased carbohydrate Intake while PL group decreased. No significant differences within or between groups.

3) Fat

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Alves, 2013	66.9 (4.9)	CR=13 PL=12 CR+TR=12 PL+TR=10	0%	Older women	24	Creatine + Training	CrM=20g/d for 5d followed by 5g/d	–	Dextrose= 20g/d for 5d followed by 5g/d	Resistance, 2s/w	↓	CR group decreased Fat Intake while PL group increased. No significant differences within or between groups
Candow 2008	65.6 (2.7)	CrP=10 CR=12 PL=12	100%	Older Men	10	Creatine + Protein + Training	CrM= 0.1 g/kg/D	Protein?= 0.3 g/kg/d	Chocolate and Cherry-flavored sucrose powder =1.2 g/kg	Resistance 3s/w	↑	Both CR and PL groups increased fat intake while CR+PR group decreased. No significant differences within or between groups.
Collins, 2016	70.33 (?)	CR+PR=9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↓	CR+PR group decrease fat intake while PR group increased. No significant differences within or between groups
Cooke, 2014	61.4 (5.0)	CR= 10 PL=10	100%	Older men	12	Creatine + Training	CrM+CHO= 20 g + 5 g /d for 7 days followed by 0.1 g/kg/d of crM + 5 g/d of glucose on training days	–	CHO= 20 g of glucose only for 7 days followed by 5 g of glucose on training days	Resistance, 3s/w	↓	CR group decreased fat intake while PL group increased. No significant differences within or between groups.
Gualano, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↑	CR group increased fat intake while PL group decreased. No significant differences within or between groups.
Rawson 1999	66.7 (1.9)	CR=10 PL=10	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–	↓	CR group decreased fat intake while PL group increased. No significant differences within or between groups.

4) Energy Intake

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Alves, 2013	66.9 (4.9)	CR=13 PL=12 CR+TR=12 PL+TR=10	0%	Older women	24	Creatine + Training	CrM=20g/d for 5d followed by 5g/d	–	Dextrose= 20g/d for 5d followed by 5g/d	Resistance, 2s/w	–	–
Candow 2008	65.6 (2.7)	CrP=10 CR=12 PL=12	100%	Older Men	10	Creatine + Protein + Training	CrM= 0.1 g/kg/D	Protein?= 0.3 g/kg/d	Chocolate and Cherry-flavored sucrose powder =1.2 g/kg	Resistance 3s/w	↓	Both CR and CR+PR groups decreased energy intake while PL group increased. No significant differences within or between groups.
Collins, 2016	70.33 (?)	CR+PR= 9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↓	Both CR+PR and PR groups decreased energy intake without significant differences within or between groups.
Cooke, 2014	61.4 (5.0)	CR= 10 PL=10	100%	Older men	12	Creatine + Training	CrM+CHO= 20 g + 5 g /d for 7 days followed by 0.1 g/kg/d of crM + 5 g/d of glucose on training days	–	CHO= 20 g of glucose only for 7 days followed by 5 g of glucose on training days	Resistance, 3s/w	↓	CR group decreased energy intake while PL group increased. No significant differences within or between groups.
Gualano, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↑	CR group increased energy Intake while PL group decrease without significant differences within or between groups.
Rawson 1999	66.7 (1.9)	CR=10 PL=10	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g dextrose	–	↓	CR group decreased energy intake while PL group increased. No significant differences within or between groups.

CR, creatine; PL, placebo; PR, protein; CrM, Creatine Monohydrate; CHO, CrM-carbohydrate; COPD, Chronic Obstructive Pulmonary Disease

S5- Details regarding **dynamic and isometric**

1RM Bench Press

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Aguiar 2012	64.9 (5)	CR=9 PL=9	0%	Older women	24	Creatine + Training	CrM+dextrose= 5g+2g/d	–	Dextrose=7g/d	Resistance, 3 sessions/w for the last 12w	**↑14.3(6.7) %**	Both groups increased 1RM Bench Press. The increased was significant ($p<0.05$) in Cr group. No significant differences between groups.
Gotshalk, 2002	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	**↑?**	Both groups increased 1RM Bench Press. The increased was significant ($p<0.05$) in CR group. No significant differences between groups.
Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↑	Both groups increased 1RM Bench Press. No significant differences within or between groups.
Gualano, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↑	CR group increased 1RM Bench Press while PL group decreased. No significant differences within or between groups
Villanueva, 2014	68.1 (6.1)	PR+TR=7 TR=7 C=8	100%	Older Men	12	Creatine + Protein + Training	CrM= 0.3g/kg/d for 5d followed by 0.07g/kg/d	Liquid protein=35g/d	–	Resistance, 3 s/w	↑	Both CR+PR and PL groups increased 1RM Bench Press. No significant differences within or between groups.

1RM Leg Press

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Alves, 2013	66.9 (4.9)	CR=13 PL=12 CR+TR=12 PL+TR=10	0%	Older women	24	Creatine + Training	CrM=20g/d for 5d followed by 5g/d	–	Dextrose= 20g/d for 5d followed by 5g/d	Resistance, 2s/w	↑	Cr group increased 1RM Bench Press while PL group decreased. No significant differences within or between groups
Brose 2003	68.7(4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g+2g/d	–	Dextrose=7g/d	Resistance, 3 s/w	↑	Both groups increased 1RM Leg Press. No significant differences within or between groups.

Gotshalk, 2008	63.3(1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↑	Both groups increased 1RM Leg Press. No significant differences within or between groups.
Gualano, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↑	Both groups increased 1RM Leg Press. No significant differences within or between groups.
Villanueva, 2014	68.1(6.1)	PR+TR=7 TR=7 C=8	100%	Older Men	12	Creatine + Protein + Training	CrM= 0.3g/kg/d for 5d followed by 0.07g/kg/d	Liquid protein=35g/d	–	Resistance, 3 s/w	↑	Both CR+PR and PL groups increased 1RM Leg Press. No significant differences between groups.

1RM Knee Extension

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Aguiar, 2012	64.9(5)	CR=9 PL=9	0%	Older women	24	Creatine + Training	CrM+dextrose= 5g+2g/d	–	Dextrose=7g/d	Resistance, 3 sessions/w for the last 12w	**↑ 8.6(2.7) %**	Both groups increased 1RM Knee extension. The increased was significant ($p<0.05$) in CR group. No significant differences between groups.
Brose A. Et al 2003	68.7(4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g +2g/d	–	Dextrose=7g/d	Resistance, 3 s/w	↑	Both groups increased 1RM Knee extension. No significant differences within or between groups.
Gotshalk, 2002	65.4(1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	**↑ ?**	Both groups increased 1RM Knee extension. The increased was significant ($p<0.05$) in CR group. No significant differences between groups.

Bench Press Strength

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Candow, 2008	65.6 (2.7)	CrP=10 CR=12 PL=12	100%	Older Men	10	Creatine + Protein + Training	CrM= 0.1 g/kg/D	Protein= 0.3 g/kg/d	Chocolate and Cherry-flavored sucrose powder =1.2 g/kg	Resistance 3s/w	↑ **12(3)%**	All groups (CR, CR+PR, PL) significantly ($p<0.05$) increased bench press strength. CR+PR group significant ($p<0.05$) greater increase than CR and PL groups.
Chilibeck, 2015	70 (6.6)	CR=16 PL=13	100%	Older Men	12	Creatine + Training	Cr=0.3g/d 1st 5d followed by 0.07g/d	–	Sucrose Fluor Mixture=0.3g/d 1st 5d followed by 0.07g/d	Resistance, 3 s/w	↑ **Pre:** 76(24)kg **Post:** 98(26)kg	Both CR and PL groups significantly ($p<0.05$) increased bench press strength. No significant differences between groups.
Chrusch, 2001	70.4 (1.6)	CR=16 PL=14	100%	Older Men	12	Crreatine + Training	Cr+sucrose=0.3 g/kg/d for the first 5d followed by 0.07 g/kg/d	–	Sucrose Fluor Mixture=0.3g/d for the first 5d followed by 0.07g/d	Resistance , 3s/w	↑?	Both CR and PL groups significantly ($p<0.05$) increased bench press strength. No significant differences between groups.

Leg Press Strength

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Candow, 2008	65.6 (2.7)	CrP=10 CR=12 PL=12	100%	Older Men	10	Creatine + Protein + Training	CrM= 0.1 g/kg/D	Protein= 0.3 g/kg/d	Chocolate and Cherry-flavored sucrose powder =1.2 g/kg	Resistance 3s/w	↑ **12(3)%**	All groups (CR, CR+PR, PL) significantly ($p<0.05$) increased leg press strength. CR+PR had a significant ($p<0.05$) greater increase than CR group.
Chilibeck, 2015	70 (6.6)	CR=16 PL=13	100%	Older Men	12	Creatine + Training	Cr=0.3g/d 1st 5d followed by 0.07g/d	–	Sucrose Fluor Mixture=0.3g/d 1st 5d followed by 0.07g/d	Resistance, 3 s/w	↑ **Pre:** 140(44) kg **Post:** 190(56) kg	Both CR and PL groups significantly ($p<0.05$) increased leg press strength. No significant differences between groups.
Chrusch 2001	70.4 (1.6)	CR=16 PL=14	100%	Older Men	12	Crreatine + Training	Cr+sucrose=0.3 g/kg/d for the first 5d followed by 0.07 g/kg/d	–	Sucrose Fluor Mixture=0.3g/d for the first 5d followed by 0.07g/d	Resistance , 3s/w	↑?	Both CR and PL groups significantly ($p<0.05$) increased leg press strength. No significant differences between groups.

Handgrip Strength

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Brose 2003	68.7 (4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g +2g/d	–	Dextrose=7g/d	Resistance, 3 s/w	↑	Both CR and PL groups increased handgrip strength. No significant differences within or between groups.
***Collins,* 2016**	70.33 (?)	CR+PR= 9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↑ **Pre:** 18.5(8.1)kg **Post:** 22.4(9.3)kg	Both CR+PR and PR groups significantly ($p<0.05$) increased handgrip strength. No significant differences between groups.
Faager, 2006	66 (6.0)	CR=13 PL=10	CR=46% PL=40%	COPD	8	Creatine + Training	CR?=0.3g/kg/d during 7d followed by 0.07g/kg/d during the remaining 7 weeks	–	Glucose= ?	?	**↑?**	Both CR and PL groups significantly ($p<0.05$) increased handgrip strength. No significant differences between groups.
***Norma* *n,* 2006**	65.1 (12.6)	CR=16 PL=15	CR=62,5 % PL=66,7 %	Colorectal Cancer	8	Creatine	CrM= 20g/d for the first week followed by 5/d for 7w	–	Cellulose= 20g/d for the first week followed by 5g/d for 7w	–	↑	Both CR and PL groups increased handgrip strength. No significant differences within or between groups.
Roy, 2005	63.3 (10.2)	CR=18 PL=19	CR=50% PL=42%	Total joint arthroplasty	6	Creatine	CrM+dextrose= 10g+8g d on the 10d before surgery and 5g+4g/d for 30d after surgery	–	Dextrose= 14g on 10d before surgery and 7g/d for 30d after surgery	–	↑	CR group increased Hand Grip strength while PL group decreased. No significant differences within or between groups
Stout, 2007	74.5 (6.4)	CR=?	47%	Older subjects	2	Creatine	Di-Creatine-Citrate=20g/d during for the first week followed by 10g/d	–	Flavored effervescent powder blend=?	–	↑ **Pre:** 28.4(0.2)kg **Post:** 30.3(0.2)kg	Cr group significantly ($p<0.05$) increased handgrip strength while PL group decreased. No significant differences between groups

Lower Body Peak Power (LBPP)

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Gotshalk, 2002	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	↑ **Pre:** 7.13(1.19) Wkg-1 **Post:** 7.84(1.28) Wkg-1)	CR group significantly ($p<0.05$) increased LBPP while PL group decreased. No significant differences between groups.
Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↑	Both CR and PL groups increased LBPP. No significant differences within or between groups.

Lower Body Mean Power (LBMP)

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Gotshalk, 2002	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	↑ **Pre:** 5.48(0.9) Wkg-1 **Post:** 6.18(1.44)Wkg-1	CR group significantly ($p<0.05$) increased LBMP while PL group decreased. No significant differences between groups.
Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↑	CR group increased LBMP while PL group decreased. No significant differences between groups

Upper Body Peak Power (UBPP))

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Gotshalk, 2002	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	↑	CR group increased UBPP while PL group decreased. No significant differences within or between groups
Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↑	Both CR and PL groups increased UBPP. No significant differences within or between groups.

Upper Body Mean Power (UBMP)

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Gotshalk, 2002	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	↑	Both CR and PL groups increased UBMP. No significant differences within or between groups.
Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↑	Cr group increased UBMP while PL group had no changes. No significant differences within or between groups

CR, creatine; PL, placebo; PR, protein; CrM, Creatine Monohydrate; CHO, CrM-carbohydrate; COPD, Chronic Obstructive Pulmonary Disease

S6- Details regarding **functional capacity.**

Sit Stand Test

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Cañete 2006	68 (4)	CR=10 PL=6	0%	Older Women	1	Creatine	CrM=0,3g/kg x3/d for 7d	–	Powdered Cellulose=0.3G/Kg x3/d for 7d	–	↓?	Both CR and PL groups decreased time to sit and stand. The decreased was significant ($p<0.05$) in Cr group. No significant differences between groups.
Gotshalk, 2002	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	↓?	Both CR and PL groups decreased time to sit and stand. The decreased was significant ($p<0.05$) in Cr group. No significant differences between groups.
Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder=??	–	↓	Both CR and PL groups decreased time to sit and stand. No significant differences within or between groups.

Time-stands-test

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Collins, 2016	70.33 (?)	CR+PR= 9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	↑**Pre:** 10(4)reps **Post:**14(7)reps	Both CR+PR and PR groups significantly ($p<0.05$) increased the number of repetitions of sit and stand. No significant differences between groups.
Gualano, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	–	Dextrose=20g/day for 5 days followed by single daily doses of 5g	Resistance, 2 s/w	↑	Both CR and PL groups increased the number of repetitions of sit and stand. No significant differences within or between groups.
Stout, 2007	74.5 (6.4)	CR=? PL=?	47%	Older subjects	2	Creatine	Di-Creatine-Citrate=20g/d during for the first week followed by 10g/d	–	Flavored effervescent powder blend=?	–	↑	Both CR and PL increased the number of repetitions of sit and stand. No significant differences within or between groups.
Wilkinson 2016	63.0 (10.0)	CR=15 PL=20	CR=23% PL= 30%	Rheumatoid Arthritis	12	Creatine	CrM= 20g/d for the initial 5d followed by 3g/d	–	Flavored drink powder	–	↑	Both CR and PL increased the number of repetitions of sit and stand. No significant differences within or between groups.

Time Up and Go Test

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Collins, 2016	70.33 (?)	CR+PR=9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	Collins, J. et al 2016	70.33(?)	Resistance, 2s/w	↓ **Pre:** 7.8(2.2) s **Post:** 8.7(1.5) s	CR+PR significantly increased time to up and go while PR group significantly ($p<0.05$) decreased time to up and go. No significant differences between groups.
Gualano, 2014	66.1 (4.8)	CR=15 PL=15 CR+TR=15 PL+TR=15	0%	Vulnerable Older Women	24	Creatine	CrM=20g/d for 5 days followed by single daily dose of 5g	Gualano, B. et al 2014	66.1 (4.8)	Resistance, 2 s/w	↓	Both CR and PL groups decreased time to up and go. No significant differences within or between groups.

CR, creatine; PL, placebo; CrM, Creatine Monohydrate;

S7- Details regarding **quality of life, mental and cognitive outcomes**

Life Quality

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose)	Proteins (dose)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Outcomes	Conclusions
Alves, 2013	66.9 (4.9)	CR=13 PL=12 CR+TR=12 PL+TR=10	0%	Older women	24	Creatine + Training	CrM=20g/d for 5d followed by 5g/d	–	Dextrose= 20g/d for 5d followed by 5g/d	Resistance, 2s/w	**Geriatric Depression Scale**	After 24 weeks of intervention, the PL+TR and CR+TR groups had significant reductions in depression scores when compared with either the PL group or the CR
Bender 2008	60 (9.4)	CR=40 PL=20	CR=71% PL=78%	Parkinson Disease	96	Creatine	Cr=20g/d for 6d followed by 2g/d for 6m and 4g/d	–	?	–	**SF-36 scores**	CR group decreased SF-36 scores while PL group had no changes. No significant differences within or between groups.
Norman2006	65.1 (12.55)	CR=16 PL=15	CR=62,5% PL=66,7%	Colorectal Cancer	8	Creatine	CrM= 20g/d in the first week followed by 10g/d	–	Cellulose=20g/d in the first week followed by 10g/d	–	**Global health status**	CR group decreased Global Health status while PL group increased. No significant differences within or between groups.
											Emotional functioning	CR group increased emotional functioning while PL group had no changes. No significant differences within or between groups.
											Social functioning	Both PL and CR groups increased social functioning. No significant differences within or between groups.

Cognitive Measures

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose)	Proteins (dose)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Outcomes	Conclusions
Alves, 2013	66.9 (4.9)	CR=13 PL=12 CR+TR=12 PL+TR=10	0%	Older women	24	Creatine + Training	CrM=20g/d for 5d followed by 5g/d	–	Dextrose= 20g/d for 5d followed by 5g/d	Resistance, 2s/w	**MMSE**	CR group increased MMSE while PL group decreased. No significant differences within or between groups.
											BBCS	Both CR and PL groups increased BBCS without significant differences within or between groups.
McMorris, 2007	76.4 (8.48)	CR=15 PL=17	CR=53% PL= 47%	Older subjects	2w	Creatine	PL= 5g/d followed by CrM=5g/d	–	Maxi joule?= 5g/d	–	**Random number generation test**	Both CR and PL groups increased RNG without significant differences within or between groups.
											Number recall test forward number	Both CR and PL groups increased NRTFN without significant differences within or between groups.
											Number recall test backward number	Both CR and PL groups increased NRTBN without significant differences within or between groups.
											Number recall test forward spatial	Both CR and PL groups increased NRTFS without significant differences within or between groups.
											Number recall test backward spatial	CR group significant ($p<0.01$) increased NRTBS while PL group significant decreased ($p<0.05$)
											Long term memory test	CR group significant ($p<0.01$) increased LTMT while PL group decreased
Norman2006	65.1 (12.55)	CR=16 PL=15	CR=62,5 % PL=66,7 %	Colorectal Cancer	8	Creatine	CrM= 20g/d in the first week followed by 10g/d	–	Cellulose=20g/d in the first week followed by 10g/d	–	**Cognitive functioning**	CR group had no changes on cognitive functioning while PL group increased it. No significant differences within or between groups.

CR, creatine; PL, placebo; CrM, Creatine Monohydrate; TR, training; SF-36, 36 item Short Form questionnaire; MMSE, Minimal Mental State Examination; BBCS, Brief Battery of Cognitive Screening; RNG, Random Number Generation; NRTFN, Number Recall Test Forward Number; NRTBN, Number Recall Test Backward Number; NRTFS, Number Recall Test Forward Spatial; NRTBS, Number Recall Test Backward Spatial; LTMT, Long Term Memory Test

S8- Details regarding **COPD variables.**

Endurance Shuttle Walking Test (ESWT)

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Deacon , 2008	68.2 (8.2)	CR=38 PL=42	CR=50% PL=74%	COPD	7	Creatine + Training	CrM=22g/d for 5d followed by 3.76g/d d	–	Lactose=24g/d for 5d followed by 4g/d during pulmonary rehabilitation	Pulmonary rehabilitation, 21 s/7w	**↑377.4 (257.7)s**	Both PL and CR groups significantly ($p<0.01$) increased ESWT. No significant differences between groups.
Faager, 2006	66.0 (6.0)	CR=13 PL=10	CR=46% PL=40%	COPD	8	Creatine + Training	CR?=0.3g/kg/d for 7d followed by 0.07g/kg/d	–	Glucose= ?	Pulmonary Rehabilitation, 2 s/w	**↑Pre:** 320.2 (202.4)s **Post:** 514.9(381.9)s	Both groups increased ESWT. The increased was significant ($p<0.01$) in CR group. No significant differences between groups.

Fat Free Mass (FFM)

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Deacon , 2008	68.2 (8.2)	CR=38 PL=42	CR=50% PL=74%	COPD	7	Creatine + Training	CrM=22g/d for 5d followed by 3.76g/d	–	Lactose=24g/d for 5d followed by 4g/d during pulmonary rehabilitation	Pulmonary rehabilitation, 21 s/7w	**↑ 0.9(1.6) kg**	Both PL and CR groups increased FFM. The increased was significant ($p<0.01$) in CR group. No significant differences between groups.
Fuld, 2005	61.7 (8.0)	CR=14 PL=11	?	COPD	12	Creatine + Training	CrM + glucose= 5g+35g 3xday for 14 days followed by 5g+35 1x/d	–	Glucose polymer= 40.7g 3xday for 14 days followed by 40.7g 1xday for 10 weeks	Pulmonary Rehabilitation, 2s/w	**↑2.0 (1.9) kg**	CR group significantly ($p<0.01$) increased FFM while PL group decreased it. The differences between groups are significant ($p<0.05$).

Fat Mass (FM)

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Effect on Cr group	Conclusions
Deacon , 2008	68.2 (8.2)	CR=38 PL=42	CR=50% PL=74%	COPD	7	Creatine + Training	CrM=22g/d for 5d followed by 3.76g/d	–	Lactose=24g/d for 5d followed by 4g/d during pulmonary rehabilitation	Pulmonary rehabilitation, 21 s/7w	↓	Both PL and CR groups decreased FM with no significant differences within or between groups.
Fuld, 2005	61.7 (8.0)	CR=14 PL=11	?	COPD	12	Creatine + Training	CrM + glucose= 5g+35g 3x/d for 14 days followed by 5g+35 1x/d	–	Glucose polymer= 40.7g 3xday for 14 days followed by 40.7g 1xday for 10 weeks	Pulmonary Rehabilitation, 2s/w	↓	Both groups decreased FM with no significant differences within or between groups.

CR, creatine; PL, placebo; PR, protein; CrM, Creatine Monohydrate; CHO, CrM-carbohydrate; COPD, Chronic Obstructive Pulmonary Disease

S9- Details regarding **Parkinson variables.**

Parkinson Variables

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Outcomes	Conclusions
Bender, 2008	60 (9.4)	CR=40 PL=20	CR=71 % PL=78 %	Parkinson Disease	96	Creatine	Cr=20g/d for 6d followed by 2g/d for 6m and 4g/d	–	?	–	**Total striatal 123I-FP-CIT uptake**	Both groups decreased Total striatal 123I-FP-CIT uptake without significant differences within or between groups
											SPECT variableS	No overall treatment effect
											UPDRS scores	Both groups increased UPDRS scores without significant differences within or between groups
											Agonist dose	Both groups significant($p<0.05$) increased agonist dose. No significant differences between groups
											Levodopa dose	Both groups increased levodopa doses without significant differences within or between groups
Hass, 2007	68.1(3 .8)	CR=10 PL=10	85%	Parkinson Disease	12	Creatine + Training	CrM= 20g for the first 5d followed by 5g/d	–	Lactose Monohydrate= 20g for the first 5d followed by 5g/d	Resistance Training=2 sessions/w	**UPDRS total**	Cr group significant ($p<0.05$) decreased UPDRS total while PL group significantly ($p<0.05$) increased
											UPDRS mental	Both groups significantly ($p<0.05$) decreased UPDRS mental
											UPDRS ADL	Both groups significantly ($p<0.05$) decreased UPDRS ADL
											UPDRS motor	Cr group significant ($p<0.05$) decreased UPDRS motor while PL group significantly ($p<0.05$) increased

CR, creatine; PL, placebo; CrM, Creatine Monohydrate; UPDRS, Unified Parkinson's Disease Rating Scale, ADL, Activity of Daily Living

S10- Details regarding **Safety Issues.**

Renal function

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/ week)	Outcomes	Effect on Cr group	Conclusions
Brose, 2003	68.7 (4.8)	CR=14 PL=14	CR=57 % PL=50 %	Older adults	14	Creatine + Training	CrM+dextrose= 5g+2g/d	–	Dextrose= 7g/d	Resistance, 3 s/w	Plasma creatinine	↑**Pre:** 111.4(24.4)μmol/L **Post:** 1262(33.4)μmol/L	CR group significantly ($p<0.05$) increased plasma creatinine, while PL group decreased. No significant differences between groups.
											Urine Creatine	↑**Pre:** 0.9(0.4)mg/mL **Post:** 1.0(0.4)mg/mL	CR group significantly ($p<0.05$) increased urine creatine, while PL group had no changes. No significant differences between groups.
											Urine Creatinine	↑	Both groups increased urine creatinine without significant differences within or between groups.
											Urine Cr:Crn ratio	↑**Pre:** 0.89(0.73) **Post:** 2.13(1.97)	Cr group significantly ($p<0.05$) increased Cr:Crn ratio, while PL group decreased. No significant differences between groups.
Cañete, 2006	68 (4)	CR=10 PL=6	0%	Older Women	1	Creatine	CrM=0,3 g/kg x3/d for 7d	–	Powdered Cellulose= 0.3g/Kg x3/d	–	Plasma creatinine	0	Both CR and PL groups presented no changes on plasma Creatinine.
											Plasma urea	0	Both groups presented no changes on plasma urea.
Collins, 2016	70.33 (?)	CR+PR= 9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	Plasma creatinine	↑	CR+PR increased plasma creatinine while PR group had no changes. No significant differences within or between groups..
											Plasma urea	↑	Both CR+PR and PR groups increased plasma urea with no significant differences within or between groups
Gotshalk, 2002	65.4(1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3g/Kg	–	Cellulose powder=0.3 g/kg	–	Plasma creatinine	↑ **Pre:** 89.4(15.7)μmol/l **Post:** 97.9(17.8)μmol/l	CR group significantly ($p<0.05$) increased plasma creatinine while PL group decreased. No significant changes between groups.
											BUN	0	Both groups presented no changes on plasma BUN.
Gotshalk, 2008	63.3 (1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Cellulose powder=?	–	Plasma creatinine	↑	Both CR and PL groups increased plasma creatinine with no significant differences within or between groups
											BUN	↓	Both groups decreased BUN with no significant differences within or between groups

Liver function

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Outcomes	Effect on Cr group	Conclusions
Cañete 2006	68(4)	CR=10 PL=6	0%	Older Women	1	Creatine	CrM=0,3g/kg x3/d for 7d	–	Powdered Cellulose =0.3G/Kg x3/d for 7d	–	Albumin	0	CR group had no changes on plasma albumin and PL increased. No significant differences within or between groups.
											AST	0	CR group had no changes on AST while PL decreased. No significant differences within or between groups.
											ALT	0	Cr group had no changes on ALT while PL decreased. No significant differences within or between groups.
											GGT	↓	CR group decreased GGT while PL group increased. No significant differences within or between groups.
Collins, 2016	70.33(?)	CR+PR=9 PR=7	?	Older adults	14	Creatine + Protein + Training	?	?	?	Resistance, 2s/w	Bilirrubin	↓	Both CR+PR and PR groups decreased plasma Brb with no significant differences within or between groups.
											AST	↓	Both CR+PR and PR groups decreased AST with no significant differences within or between groups.
											ALT	↑	Both CR+PR and PR groups increased AST with no significant differences within or between groups.
											GGT	↓	CR+PR group increased GGT while PR group decreased. No significant differences within or between groups.
											ALP	↑	CR+PR group increased ALP while PL group decreased. No significant differences within or between groups.
Gotshalk, 2002	65.4(1.5)	CR=10 PL=8	100 %	Older Men	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder= 0.3g/kg	–	AST	↓	Cr group decreased AST while PL group increased. No significant differences within or between groups.
											ALT	↓	Both groups decreased ALT with no significant differences within or between groups.
											GGT	↓	CR group decreased GGT while PL group increased. No significant differences within or between groups.
											Albumin	↓	CR group decreased plasma albumin while PL group increased. No significant differences within or between groups.

Gotshalk , 2008	63.3(1.2)	CR=15 PL=12	0%	Older Women	1	Creatine	CrM=0.3 g/kg/d	–	Celulose powder= ?	–	AST	↓	Cr group decreased AST while PL group increased. No significant differences within or between groups.
											ALT	↑	Cr group increased ALT while PL group decreased. No significant differences within or between groups.
											GGT	↑	Cr group increased GGT while PL group decreased. No significant differences within or between groups.

Reported Adverse effects

Study	Mean age (SD)	Sample size	% males	Population	Duration (weeks)	Intervention	Creatine (dose per day)	Proteins (dose per day)	Placebo (dose per day)	Exercise type, Duration (sessions/week)	Adverse effect reported	Number of reports on Cr group	Number of reports on CPL group
Brose 2003	68.7 (4.8)	CR=14 PL=14	CR=57% PL=50%	Older adults	14	Creatine + Training	CrM+dextrose=5g+2g/d	–	Dextrose=7g/d	Resistance, 3 s/w	Gastrointestinal distress	1	1
Candow, 2008	65.6 (2.7)	CrP=10 CR=12 PL=12	100%	Older Men	10	Creatine + Protein + Training	CrM= 0.1 g/kg/D	Protein= 0.3 g/kg/d	Chocolate and Cherry-flavored sucrose powder =1.2 g/kg	Resistance 3s/w	Muscle soreness and stiffness	1	2
Chrusch , 2001	70.4 (1.6)	CR=16 PL=14	100%	Older Men	12	Creatine + Training	Cr=0.3 g/kg/d for the first 5 d followed by 0.07 g/kg	–	Sucrose Fluor Mixture=0.3g/d first 5d followed by 0.07g/d	Resistance, 3s/w	Loose stool, muscle cramping, muscle pull or strain.	(+++)	(+)
Gotshalk , 2002	65.4 (1.5)	CR=10 PL=8	100%	Older Men	1	Creatine	CrM= 0.3G/KG	–	Celulose powder=0.3 g/kg	–	"There were no significant differences between groups in blood pressure and Likert scores for muscle cramps, gastrointestinal distress, and well-being"	?	?
Rawson , E.S. et al 1999	66.7 (1.9)	?	100%	Older Men	4	Creatine	CrM + dextrose= 20g+28g/d during 10 days, followed by 4g+6.8g	–	Dextrose= 25g/d for 10d followed by 20g	–	Gastrointestinal disconfort	1	0
											Skin rash	1	0
											Muscle cramping of the plantar flexors	1	0

CR, creatine; PL, placebo; CrM, Creatine Monohydrate; PR, Protein; BUN, Blood Urea Nitrogen, AST. Aspartate Transaminase, ALT, Alanine Aminotransferase; GGT, Gamma-glutamyl transferase, ALP, Alkaline phosphatase;