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Creatine supplementation for patients with COPD receiving pulmonary rehabilitation: A systematic review and meta-analysis

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ABSTRACT

Background and objective: **Creatine improves muscle strength in exercising healthy individuals, and in patients with neuromuscular disease and heart failure. The aim of this study was to assess whether creatine supplementation improves pulmonary rehabilitation (PR) outcomes in patients with COPD.**

Methods: **A systematic review and meta-analysis was performed of randomized controlled trials published between January 1966 and February 2009 that evaluated the effect of creatine compared with placebo on exercise capacity, muscle strength and health-related quality of life (HR-QoL) in patients undergoing PR for COPD. The pooled estimates were expressed as mean differences (MD) or standardized mean differences (SMD).**

Results: **Four randomized controlled trials that included 151 patients were identified. There was no effect of creatine supplementation on exercise capacity (SMD –0.01, 95% CI: –0.42 to 0.22, $n = 151$). Creatine supplementation did not improve lower extremity muscle strength (SMD 0.03, 95% CI: –0.55 to 0.61, $n = 140$) or upper limb muscular strength (SMD 0.02, 95% CI: –0.33 to 0.38, $n = 128$) compared with placebo. Two studies ($n = 48$) assessed quality of life using the St. George's Respiratory Disease Questionnaire. There were no differences in HR-QoL according to domain or total scores. Overall, creatine appeared to be safe and was well tolerated. Quality assessment of the studies showed important limitations.**

Conclusions: **Creatine supplementation does not improve exercise capacity, muscle strength or HR-QoL in patients with COPD receiving PR. However, important limitations were identified in the quality of the available evidence, suggesting that further research is required in this area.**

Key words: chronic obstructive pulmonary disease, creatine, exercise, pulmonary rehabilitation.

SUMMARY AT A GLANCE

This meta-analysis explores the effect of creatine supplementation, in addition to pulmonary rehabilitation, on exercise capacity, muscle strength and quality of life in patients with COPD. There were no significant effects overall. Important limitations were identified in the quality of the available evidence, suggesting further research is needed.

INTRODUCTION

COPD is a systemic disease that is associated with significant morbidity and mortality. Several treatment interventions for COPD have been described,[1] including pulmonary rehabilitation. The benefits of pulmonary rehabilitation in patients with COPD are well established. A Cochrane systematic review that included 31 randomized control trials (RCT) showed that pulmonary rehabilitation relieves symptoms of dyspnoea and fatigue, improves emotional function and enhances patients' sense of control over their condition.[2] Pulmonary rehabilitation reduces the number of hospital days and other measures of health-care utilization, indicating that it is also cost-effective.[3–5] In a recent meta-analysis, patients with COPD exacerbations, who underwent pulmonary rehabilitation showed a reduction in the number of hospitalizations and mortality, and improved health-related quality of life (HR-QoL).[6] Several other studies have also shown that pulmonary rehabilitation improves muscle strength and exercise endurance in patients with COPD.[7–11]

Nutritional supplementation has been evaluated as an adjunct to pulmonary rehabilitation with varying results. An RCT evaluating a protein-rich diet in patients with COPD receiving pulmonary rehabilitation found no statistically significant benefit in terms of HR-QoL or exercise capacity.[12] Another RCT reported a small but non-significant benefit with the addition of a fat-rich diet compared with placebo, in patients receiving standard pulmonary rehabilitation.[13]

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Creatine is a widely available nutritional supplement. When phosphorylated, creatine forms a substrate for the generation of adenosine tri-phosphate, the basic unit for energy generation. Oral supplementation with creatine has been used to enhance gains in muscle function and mass. Long-term creatine supplementation enhances muscle strength during resistance training.[14] In addition, creatine supplementation increases lean tissue mass and improves leg strength, endurance and average power output during exercise training.[15] Oral creatine supplementation has also been shown to stimulate muscle hypertrophy during rehabilitation strength training.[16]

A meta-analysis by Kley and colleagues that included 12 RCT showed that short- and medium-term use of creatine improved muscle strength and was well tolerated in patients with muscular dystrophies.[17] Two other meta-analyses showed that oral supplementation with creatine was associated with increased lean body mass.[18,19] Supplemental creatine has also been shown to improve muscle strength in patients with heart failure.[20]

Small RCT of creatine supplementation in patients with COPD receiving pulmonary rehabilitation have been performed, although the results are conflicting. The purpose of this study was to systematically evaluate whether creatine supplementation is an effective adjunct to pulmonary rehabilitation in patients with COPD.

METHODS

Objectives

The objectives of this systematic review and meta-analysis were to assess in patients with COPD receiving pulmonary rehabilitation:

- The effect of creatine supplementation on exercise capacity and peripheral muscle strength
- The effect of creatine supplementation on HR-QoL
- Any reported adverse effects related to creatine supplementation

Criteria for selecting studies for review

Randomized or quasi-randomized controlled trials of oral creatine supplementation in addition to pulmonary rehabilitation in patients with COPD were included. Studies were limited to those that included adult participants with COPD, based on standard criteria.[1] Study participants had to be enrolled in a pulmonary rehabilitation programme, although there were no limitations on the type of programme (inpatient vs outpatient), the duration of the programme or the type of treatment administered.

Method for the identification of studies

A comprehensive literature search was performed for articles published between January 1966 and February 2009, with no language restrictions. The literature search was limited to human studies indexed in The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PubMed, EMBASE and CINAHL, AMED, PEDro and the American College of Physicians (ACP) Journal Club. If a trial was included in the analysis and was indexed in the PubMed database, the 'Related Articles' option was utilized for further exploration of related studies. In addition, bibliographies and reference lists from the included primary studies were reviewed.

The search terms used were: (creatine OR cyclocreatine OR phosphocreatine) AND (respiratory rehabilitation OR pulmonary rehabilitation OR physical exercise OR physiotherapy OR exercise therapy OR rehabilitat* OR exercis* OR physical* OR train*) AND (COPD OR chronic obstructive pulmonary disease OR chronic obstructive lung disease OR chronic obstructive airway disease OR emphysema OR chronic airflow limitation OR chronic bronchitis).

Abstracts published in proceedings of international meetings were also reviewed, and included the conference proceedings of the American Thoracic Society and the European Respiratory Society. Finally, major trial registries were searched to identify ongoing studies.

Outcome measures

The primary outcome measures were exercise capacity, as measured by shuttle walking test, 6MWD or cardiopulmonary exercise test, and peripheral muscle strength. Secondary outcomes were HR-QoL, as measured by the St. George's Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Disease Questionnaire (CRQ), and adverse events attributable to creatine supplementation.

Measurement of exercise capacity was performed using several different testing modalities. The incremental shuttle walk test (ISWT) is a validated and reproducible method for assessing exercise capacity,[21] with a minimum clinically important improvement being defined as 47.5 m.[22] Other standardized measures of exercise capacity are the endurance shuttle walk tests (ESWT),[23] which provides an objective measurement of disability and allows direct comparison of patient performance,[21] and the 6MWD.[24] Oxygen saturation and dyspnoea severity were measured throughout the 6MWD, using an oximeter and the Borg scale,[25] respectively.

Measurements made on muscle groups were assessment of lower limb isokinetic force,[26] quadriceps force[27] or isometric maximum voluntary contractions. Muscle strength assessments also included upper limb isokinetic force and handgrip strength.

Assessment of HR-QoL is frequently performed using the validated SGRQ and CRQ. The SGRQ is repeatable, sensitive, and consists of three domains of symptoms, activity, and impacts on daily life, as well as a total score.[28] The minimally important difference for the SGRQ is a change of four units.[29] A higher score indicates a poor HR-QoL. The CRQ is also discriminatory and responsive in patients with chronic lung disease.[30] This questionnaire has four domains of

dyspnoea, fatigue, emotional function and mastery. A 0.5 unit increase per question has been established as a minimal clinically important difference indicating improvement in HR-QoL.[31]

Data collection and analysis

A combined list of articles was first created by both reviewers (F.A. and D.T.). Thereafter, the two authors reviewed the identified titles, abstracts and full publications independently. Disagreements were resolved by consensus. Weighted kappa statistics were calculated to assess inter-observer agreement,[32] using three categories of eligibility for each study in the systematic review (include, unclear, exclude).

Data were extracted independently by the two reviewers, and included all details of the studies (methods, participants, interventions, outcomes). All results were compiled into a table. If necessary, authors were contacted for further data or clarification of unresolved issues.

Assessment of study quality was performed using the Cochrane approach,[33] which assesses study quality based on six domains: methods used for sequence generation, allocation concealment, blinding, comprehensiveness of follow up of participants, selective reporting of results and other sources of bias. The latter may involve any important concerns about bias not addressed in the other domains. A risk of bias summary table was generated using the Review Manager software (RevMan version 5.0.20).

For continuous variables (ESWT, 6MWD, ISWT, muscle strength and HR-QoL scores) the mean difference (MD) or standardized mean difference (SMD) with 95% CI were calculated for each study. A random effect model was used for all analyses, to provide a pooled MD or SMD with 95% CI. SD were calculated using the formula: $SD = SE/\sqrt{n}$, where SE is the standard error obtained from the original data or mathematically derived from the sample size (n) and the original CI. When necessary, mean change scores and final measurements were combined in the same pooled estimates, in consultation with a biostatistician.

For dichotomous variables (adverse events) the OR with 95% CI for each study were calculated if applicable, using a random effect model.

Statistical analyses, including creation of forest plots, were performed using the RevMan software. When appropriate, funnel plots were used to demonstrate the risk of publication bias. In addition, sources of heterogeneity were explored when applicable. This was done using a sensitivity analysis, in which a priori defined sources of heterogeneity served as explanatory variables. In addition, meta-regression was used to explore the sources of heterogeneity when applicable.

A list of possible sources of heterogeneity between studies was created prior to the analysis, including variability in the dose and duration of creatine supplementation, differences in the co-intervention (i.e. pulmonary rehabilitation programme), timing of collection of outcome measures and differences in study populations. In cases where statistical heterogeneity was encountered these items were explored using the Cochrane approach.[33]

RESULTS

The two reviewers conducted the literature search independently. The weighted kappa statistic for agreement was 0.80 with an SE of 0.09. The systematic search (Fig. 1) identified four RCTs, three published in peer-reviewed journals,[34–36] and one published as a conference abstract.[37] The characteristics of the included studies are summarized in Table 1. All participants in these studies received pulmonary rehabilitation during the intervention phase. As shown in Table 1, the intervention included an oral creatine supplement in varying doses, across the included primary studies. The duration of supplementation varied from 7 to 12 weeks. The placebo consisted of either glucose- or lactose-based supplements, except for one study in which the comparator was unclear.[37]

Overall, reporting of methods of randomization and concealment of allocation were unclear, indicating a high risk of bias. Blinding was adequate, indicating a low risk of bias. There was an adequate level of follow up and reporting of outcomes, except for one study (Fig. 2), indicating a low risk of bias. However, other methodological limitations that were identified across the included primary studies (outlined in Table 2) constituted a high risk of bias (Fig. 2).

Exercise capacity

Three studies assessed the effect of creatine supplementation on the ESWT,[34–36] while a fourth study assessed the effect on 6MWD.[37] Combining these four studies ($n = 151$) resulted in a pooled SMD of –0.01 (95% CI: –0.42 to 0.22), indicating no effect (Fig. 3a). Two studies ($n = 105$) evaluated the effect of creatine supplementation on ISWT distance and showed no difference between placebo and creatine with an MD of –3.15 m (95% CI: –32.6 to 26.3) (Fig. 3b).[34,36] A single study assessed the effect of creatine on maximal power output, as measured by cardiopulmonary exercise testing, but found no difference between creatine (mean change 8 W, SE 2) and placebo (mean change 10 W, SE 5).[37]

Muscle strength

Three studies ($n = 117$) assessed lower extremity muscle strength using quadriceps peak torque,[34–36] while a fourth study assessed muscle strength using quadriceps force.[37] When the results of these four studies were pooled ($n = 140$) the SMD was 0.03 (95% CI: –0.55 to 0.61), indicating no effect (Fig. 4a). One study reported quadriceps isometric strength and found a mean change (SD) of 19.60 (16.32) Nm in the creatine group compared with 23.10 (17.52) Nm in the placebo group (not significant).[34]

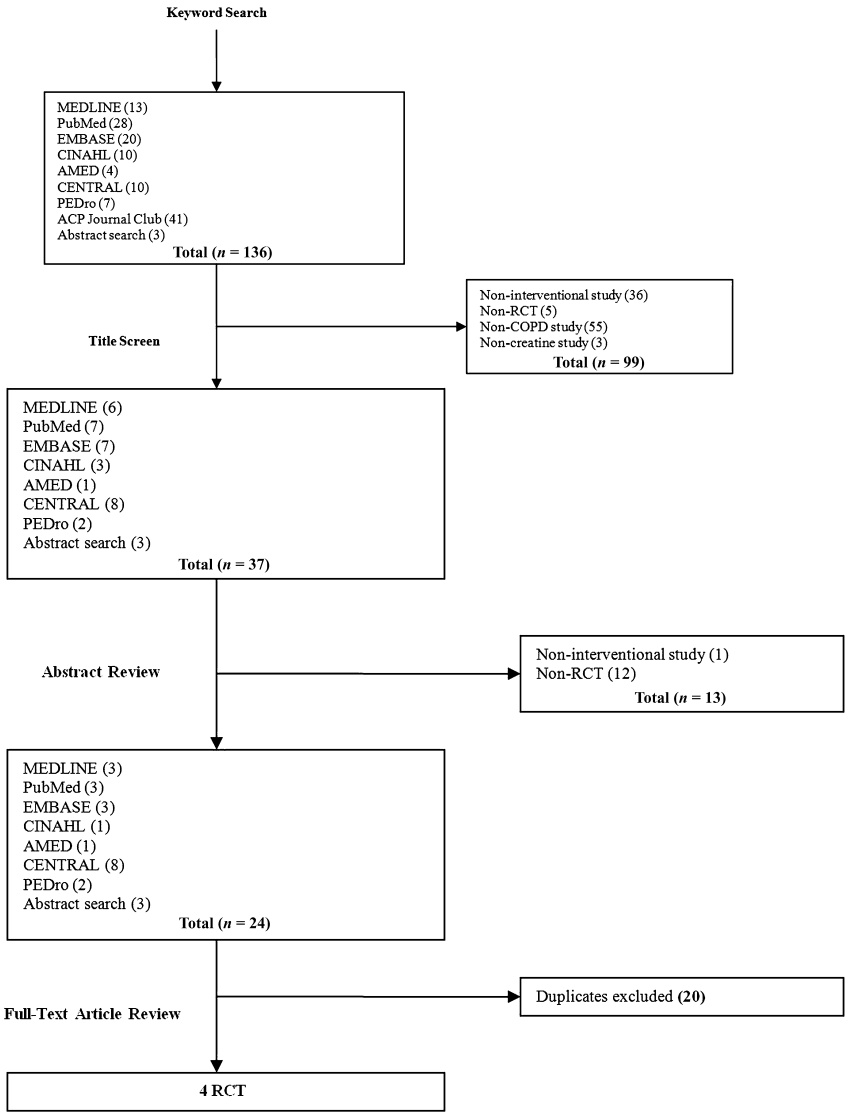


Figure 1 Search strategy for identification of published randomized controlled trials (RCT) of oral creatine supplementation in addition to pulmonary rehabilitation in patients with COPD.

Upper limb muscle strength measurements were reported as biceps and hand strength in three studies.[34–36] The results for these studies were pooled ($n = 128$) yielding a statistically non-significant SMD of 0.02 (95% CI: –0.33 to 0.38) (Fig. 4b).

Quality of life

Two studies ($n = 48$) assessed HR-QoL using the SGRQ.[35,36] The MD for total scores was –6.71 (95% CI: –13.98 to 0.46). The MD for the domains of symptoms, activity and impact were 3.17 (95% CI: –15.81 to 22.15), –10.17 (95% CI: –26.32 to 5.98) and –0.87 (95% CI: –9.76 to 8.02), respectively (Fig. 5a–d). These results indicated no statistically significant effect of creatine supplementation on HR-QoL. Deacon and colleagues assessed HR-QoL using the CRQ but found no benefit with creatine supplementation.[34] The CRQ domains did not show any significant changes: dyspnoea mean change –0.10 (95% CI: –0.52 to 0.32), fatigue mean change 0.00 (95% CI: –0.53 to 0.53), emotional mean change 0.00 (95% CI: –0.50 to 0.50) and mastery mean change 0.10 (95% CI: –0.40 to 0.60). The fourth study did not report effects on HR-QoL.[37]

Adverse events

There were only two deaths, which occurred in the control group in one study.[34] Two participants developed creatine supplement-related gastrointestinal upset and hair loss, resulting in the discontinuation of creatine supplementation.[34] Another study reported that two participants disliked the taste of the supplement, but did not report in which group they were.[36] The other two primary studies did not report any adverse events.[36,37] Given the infrequency of reported adverse effects and the incompleteness of these details, no further statistical analysis was conducted.

Table 1 Characteristics of the primary studies that were included in the meta-analysis (ordered by study ID)

	Deacon *et al.*[34]	Faager *et al.*[35]	Fuld *et al.*[36]	Gosselink *et al.*[37]
Publication	Journal: American Journal of Respiratory and Critical Care Medicine; Issue: 2008 Aug 1; 178 (3): 233–9.	Journal: International Journal of Chronic Obstructive Pulmonary Diseases; Issue: 2006; 1 (4): 445–53.	Journal: Thorax; Issue: 2005 Jul; 60 (7): 531–7.	Journal: American Journal of Respiratory and Critical Care Medicine [Abstracts]; 2003; 163: A961.
Funding source	British Lung Foundation grant	Unknown	Unknown	Fonds Voor Wetenschappelijk Onderzoek—Vlaanderen
Methods	Randomized parallel group trial	Randomized parallel group trial	Randomized parallel group trial	Randomized parallel group trial
Participants	100 COPD patients initially recruited. 80 patients (mean age 68 years, 62% men, FEV_1 44% predicted) completed study.	23 COPD patients (mean age 66 years, 43% men, FEV_1 43.1% predicted).	38 COPD patients (mean age 63 years, 60% men, FEV_1 45.5% predicted). 25 patients completed study.	26 COPD patients (mean age 64 years, 88% men, FEV_1 42% predicted). 23 patients completed study.
Interventions	Creatine: 22 g daily for 5 days then 3.76 g daily.	Creatine: 0.3 g/kg/day for 1 week, then 0.07 g/kg/day for 7 weeks	Creatine: with glucose polymer (5.7 g creatine monohydrate). 3 doses/day for 14 days, then once daily for 10 weeks.	Creatine: 5 g per dose, 4 doses/day for the first 5 days, then 1 dose/day for 12 weeks.
	Comparator: lactose	Comparator: glucose (unknown dose)	Comparator: glucose polymer only (40.7 g per dose, as for intervention)	Comparator: unknown
Pulmonary rehabilitation programme	Outpatient, 21 sessions in total over 7 weeks	60–75 min/session, 2 sessions/week for 8 weeks. Included exercise and non-exercise components (educational sessions). Included further home-based training.	1 h/session, 2 sessions/week, for 16 weeks. Included outpatient exercise and non-exercise components (educational and behavioural sessions). Included further home-based training.	Outpatient, 90 min/session, 3 sessions/week for 12 weeks. Included dynamic resistance training, treadmill walking, and cycle ergometry.
Outcomes	Shuttle walk test; CRQ; quadriceps (isokinetic and isometric), biceps and triceps peak torque; adverse events	Shuttle walk test; leg muscle strength and hand grip; SGRQ	Shuttle walk test; upper and lower body peak torque; SGRQ; adverse events	6MWD; quadriceps force, peak exercise capacity (workload)

CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St. George's Respiratory Questionnaire.

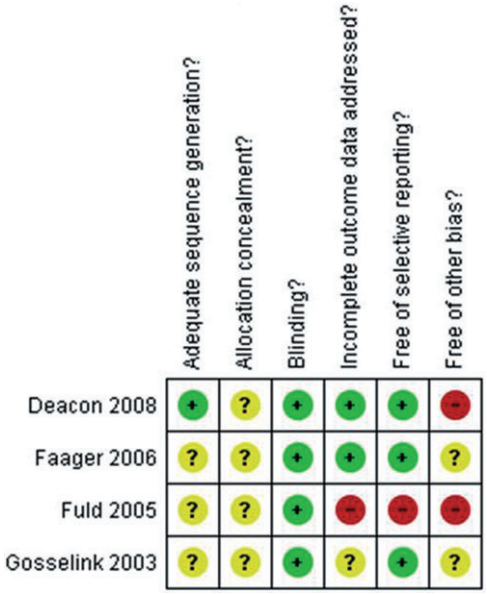


Figure 2 Summary of risk of bias showing the review authors' assessments of each risk of bias item for the primary studies included in the meta-analysis. Further details on the item 'Free of other bias' are provided in Table 2.

DISCUSSION

This systematic review and meta-analysis shows that creatine supplementation during pulmonary rehabilitation in patients with COPD does not improve exercise capacity, HR-QoL or muscle strength. The intervention was found to be safe, in general, with no significant adverse events.

This is the first comprehensive meta-analysis investigating the additive effect of creatine supplementation in COPD patients receiving pulmonary rehabilitation. A previous systematic review evaluated supplemental interventions in patients receiving pulmonary rehabilitation,[39,40] but only included one RCT assessing creatine supplementation.[37] A Cochrane review of nutritional supplementation for patients with stable COPD[40] included only one study that evaluated creatine.[36] Both of these rigorous systematic reviews were performed prior to the publication of the two most recent RCT, which were included in the present analysis.[34,35] The results from this meta-analysis also concur with the findings from two recent narrative reviews.[41,42]

The strengths of this overview and meta-analysis include the systematic and thorough search strategy employed and the detailed assessment of study quality. In addition, the systematic review involved independent data extraction for quality assessment and statistical analysis by the two reviewers, which has been shown in the past to result in lower overall error scores, compared with single data extraction.[43] Despite the systematic approach and strong statistical methodology used in this analysis there are important limitations that should be noted. In particular, this systematic review was limited by the small number of studies and the small cumulative sample size. Along with the small sample size, there were concerns regarding the methodological quality of the included primary studies. An important limitation that may affect validity and that was common to all the primary studies was the absence of intention-to-treat analyses. In most studies only participants who completed the trial were included in the final analysis. The small trials also had a potential risk of bias due to the unavailability of information about methods of randomization (except for one study[34]) and allocation concealment. As a result, the outcomes identified may be subject to a high risk of bias. An additional challenge that arose while preparing this review was dealing with different measures designed to assess the same outcome, for example, ESWT, ISWT and 6MWD to assess exercise capacity. This was overcome by using SMD, in which the treatment effect is computed by dividing the difference in means by the SD. Another important limitation is that it was necessary to combine changes in scores with final measurements in the analysis of SGRQ HR-QoL scores and muscle strength. Despite the potential concern regarding the combination of change in scores with final scores, the use of this method is widely accepted.[33] Similarly, it was not possible to combine the scores from the two measures of HR-QoL (i.e. CRQ and SGRQ) as these tools have different domains and the total scores and measures of dispersion were unavailable for the CRQ.

In general, there was very little heterogeneity among the studies, arbitrarily defined as an I^2 statistic >45%. Given the small number of studies it was not possible to perform funnel plot, subgroup or sensitivity analyses. In addition, meta-regression was not performed due to the limited number of primary studies identified. A random effects model was used for all analyses regardless of the degree of heterogeneity. This method statistically minimizes the effects of heterogeneity and provides a more conservative estimate of treatment effect. Given the systematic and comprehensive approach adopted in this study, no risk of publication bias was anticipated.

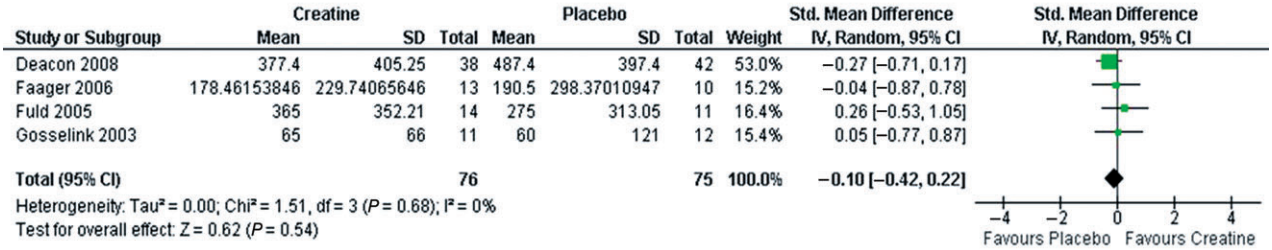
The effect of pulmonary rehabilitation in COPD has previously been established by several primary studies and meta-analyses.[2,7–11] The overall beneficial effect of pulmonary rehabilitation was confirmed again in the primary studies included in this meta-analysis. In the primary studies, both the intervention and control groups showed significant improvements in the outcomes of interest, when comparing the initial and final measurements. The current meta-analysis did not find any significant additive effect of creatine supplementation on pulmonary rehabilitation for COPD.

These results conflict with those from other studies assessing creatine supplementation in healthy individuals and patients with muscular dystrophy and heart failure. Studies evaluating creatine supplementation in healthy individuals have included both young[14] and elderly[15] participants. This suggests that the discrepancy between the present results and those for healthy subjects receiving creatine

Table 2 Risk of bias in the primary studies that were included in the meta-analysis

Item	Review authors' judgement (description)			
	Deacon *et al.*[34]	Faager *et al.*[35]	Fuld *et al.*[36]	Gosselink *et al.*[37]
1. Method of generating randomization	Adequate (computer-generated)	Unclear (not indicated)	Unclear (not indicated)	Unclear (author could not provide pertinent information)
2. Allocation concealment	Unclear (not described clearly even in trial registry[38])	Unclear (not indicated)	Unclear (not indicated)	Unclear (author could not provide pertinent information)
3. Blinding	Adequate (subjects, investigators and rehabilitation staff were blinded)	Adequate (described as double-blinded)	Adequate (described as double-blinded)	Adequate (described as double-blinded)
4. Follow up	Adequate (all patients were followed up closely in an attempt to measure the study outcomes)	Adequate (all patients were followed up closely in an attempt to measure the study outcomes)	Inadequate (around one-third of patients lost to follow up)	Unclear (author could not provide pertinent information)
5. Selective reporting	Adequate (reporting of outcomes was not biased)	Adequate (reporting of outcomes was not biased)	Inadequate (patients excluded from study for various reasons that were not specified a priori)	Unclear (author could not provide pertinent information)
6. Other	Comparative, intention-to-treat analysis not used (only patients who completed the study were included)	Calculation of sample size was not demonstrated	Only patients who completed the study were included in the analysis; no indication of analysis procedure (intention-to-treat analysis not used)	Unclear (author could not provide pertinent information)
7. Other			Required sample size was not achieved due to cost/time restraints; study was underpowered	

(a)



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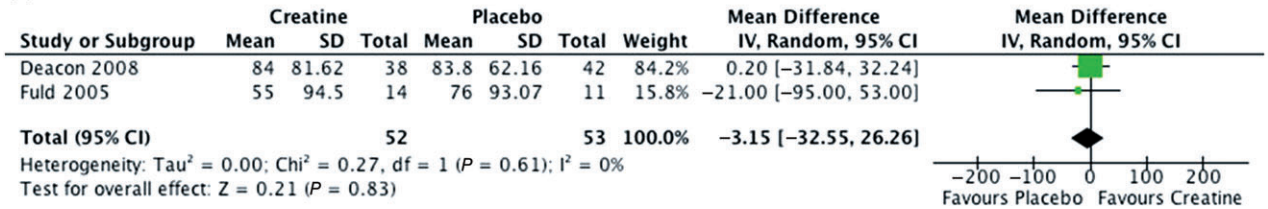
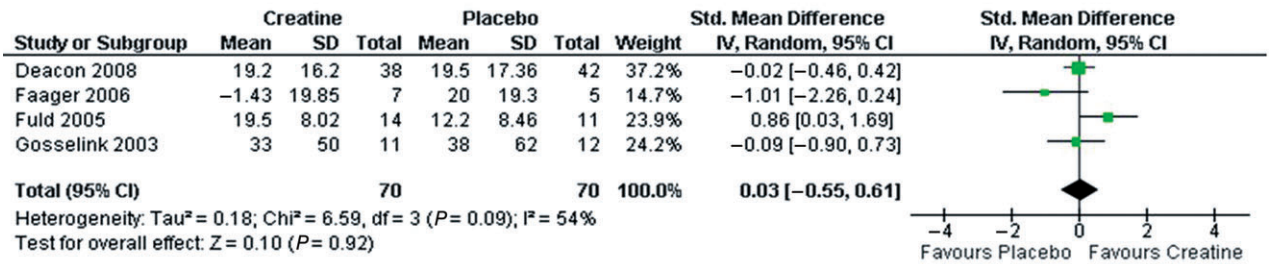


Figure 3 Forest plots for randomized controlled trials assessing the effect of creatine supplementation on exercise capacity in patients with COPD receiving pulmonary rehabilitation. Effect of creatine supplementation on (a) endurance shuttle walk test and 6MWD; and (b) incremental shuttle walk test.

(a)



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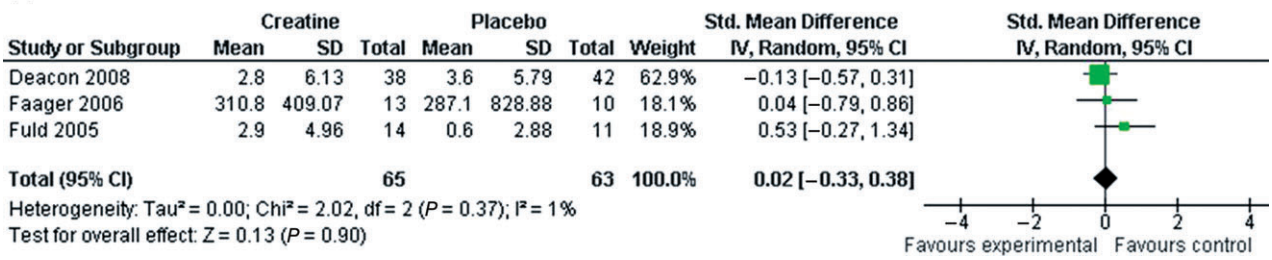

Figure 4 Forest plots for randomized controlled trials assessing the effect of creatine supplementation on limb strength in patients with COPD receiving pulmonary rehabilitation. Effect of creatine supplementation on (a) lower limb strength (quadriceps strength and quadriceps force); and (b) upper limb strength (biceps strength and handgrip).

supplementation is unrelated to age. In addition, the dose of supplement was similar among the primary studies included in this meta-analysis and the studies conducted in patients with muscular dystrophy and heart failure.[17,20] In two randomized controlled studies assessing the effect of creatine supplementation in patients with congestive heart failure there was a consistent improvement in muscle strength with both short-term (10 days)[20] and long-term (6 weeks)[44] supplementation. Favourable outcomes persisted as long as participants were receiving creatine supplements. Similar results have been reported for participants with myotonic dystrophy, although not for individuals with metabolic myopathies.[17] Therefore, these studies were similar in many ways to the primary studies included in this meta-analysis. However, unlike the studies evaluating the effect of creatine in patients with congestive heart failure and primary muscle disorders, all participants in the included primary studies received pulmonary

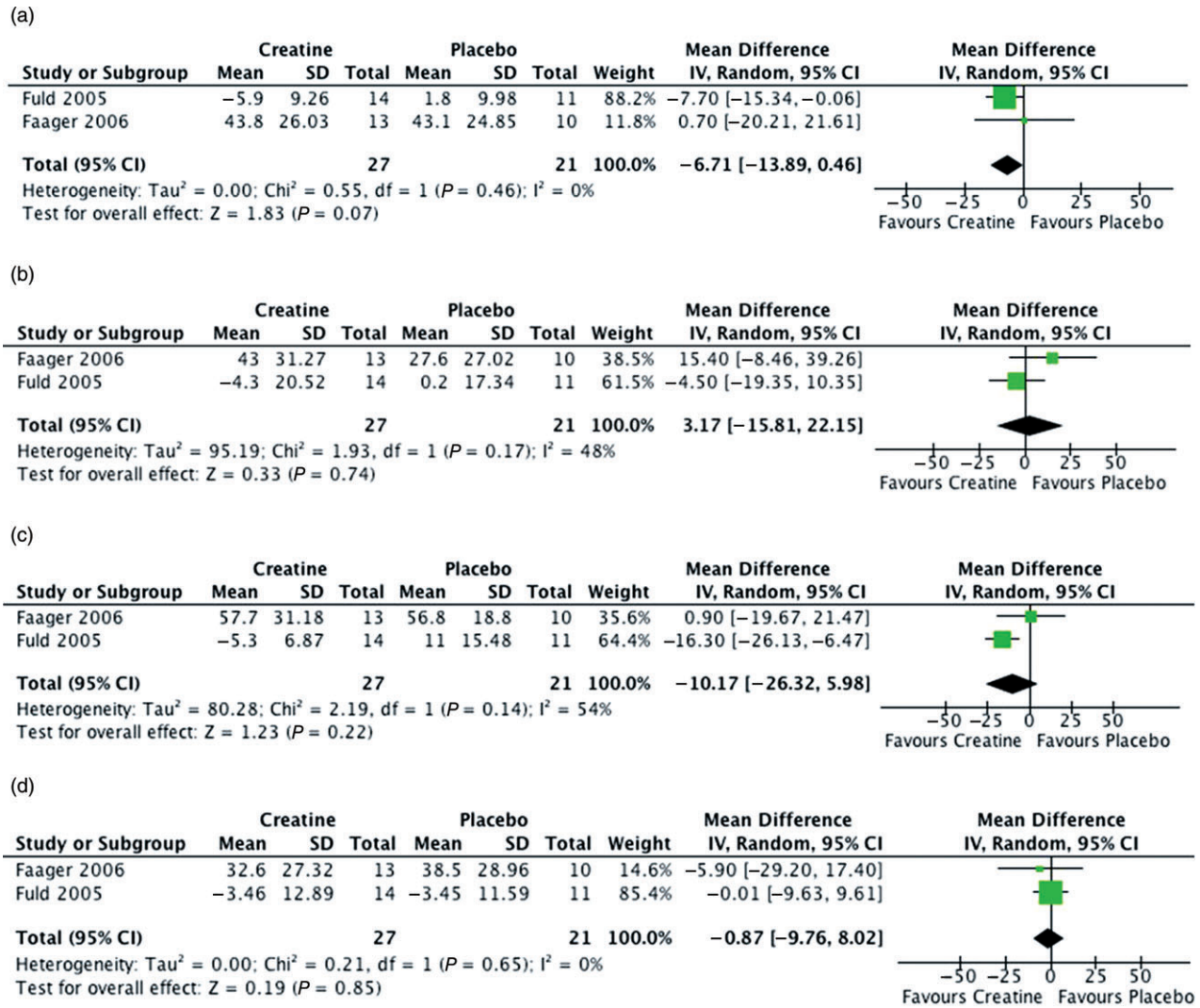

Figure 5 Forest plots for randomized controlled trials assessing the effect of creatine supplementation on quality of life in patients with COPD receiving pulmonary rehabilitation. Effect of creatine supplementation on (a) St. George's Respiratory Questionnaire (SGRQ) total score; (b) SGRQ symptoms domain; (c) SGRQ activity domain; and (d) SGRQ impacts on daily life domain.

rehabilitation during the intervention period. Therefore, it is possible that the lack of an observed effect of creatine supplementation in this meta-analysis was due to the relatively greater effect of pulmonary rehabilitation on muscle strength and exercise capacity. It is uncertain whether the use of creatine supplementation would be beneficial in patients with COPD who are not receiving pulmonary rehabilitation, either because they do not have access or are unable to participate. This area may require further research.

Consistent with other literature in the area, this systematic review suggests that creatine supplementation is safe with few possible side-effects. Potential side-effects include water retention, muscle pain and occasional cramps.[41] Although a statistical analysis of adverse events could not be performed due to their infrequency, a summary of the findings indicated that creatine supplementation was well tolerated in this population.

Creatine supplementation when added to pulmonary rehabilitation does not improve exercise capacity, muscle strength or quality of life in patients with COPD. Creatine was found to be safe, in general, with no reported serious adverse events. Based on the findings from this systematic review creatine supplementation cannot be recommended as an adjunct to pulmonary rehabilitation. However, limitations in the quality of the available studies suggest that further research is needed in this area. An adequately powered and methodologically rigorous study using a computer-generated randomization scheme and strict allocation concealment, with sample size calculation and intent to treat analysis, may provide a more valid indication of the effectiveness of creatine supplementation in COPD patients receiving pulmonary rehabilitation. In addition, the use of a more responsive outcome measure for exercise capacity such as cycle endurance time[45–47] may increase the

likelihood of being able to assess whether there is any benefit in adding creatine supplementation to pulmonary rehabilitation in patients with COPD.

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