

Does oral creatine supplementation improve strength? A meta-analysis

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KEY POINTS FOR CLINICIANS

- Oral creatine supplementation combined with resistance training increases maximal weight young men can lift.
- It is unknown whether this increase in strength translates into improvement in sports performance.
- Evidence in the existing literature is insufficient to draw conclusions about the effect of creatine in women or older individuals.
- Because no long-term studies have been performed on the safety of creatine supplementation, its use should not be universally recommended.

■ **OBJECTIVES** Oral creatine is the most widely used nutritional supplement among athletes. Our purpose was to investigate whether creatine supplementation increases maximal strength and power in healthy adults.

■ **STUDY DESIGN** Meta-analysis of existing literature.

■ **DATA SOURCES** We searched MEDLINE (1966–2000) and the Cochrane Controlled Trials Register (through June 2001) to locate relevant articles. We reviewed conference proceedings and bibliographies of identified studies. An expert in the field was contacted for sources of unpublished data. Randomized or matched placebo controlled trials comparing creatine supplementation with placebo in healthy adults were considered.

■ **OUTCOMES MEASURED** Presupplementation and postsupplementation change in maximal weight lifted, cycle ergometry sprint peak power, and isokinetic dynamometer peak torque were measured.

■ **RESULTS** Sixteen studies were identified for inclusion. The summary difference in maximum weight lifted was 6.85 kg (95% confidence interval [CI], 5.24–8.47) greater after creatine than placebo for bench press and 9.76 kg (95% CI, 3.37–16.15) greater for squats; there was no difference for arm curls. In 7 of 10 studies evaluating maximal weight lifted, subjects were young men (younger than 36 years) engaged in resistance training. There was no

difference in cycle ergometer or isokinetic dynamometer performance.

■ **CONCLUSIONS** Oral creatine supplementation combined with resistance training increases maximal weight lifted in young men. There is no evidence for improved performance in older individuals or women or for other types of strength and power exercises. Also, the safety of creatine remains unproven. Therefore, until these issues are addressed, its use cannot be universally recommended.

■ **KEY WORDS** Creatine; dietary supplements; meta-analysis. (*J Fam Pract* 2002; 51:945–952)

Creatine has gained widespread popularity during the past decade as a possible performance-enhancing agent among professional and recreational athletes. It is the most widely used performance-enhancing supplement among youth aged 10 to 17 years,¹ with 15% to 30% of high school athletes^{2,3} and 48% of male Division I college athletes⁴ reporting creatine use. Considered a nutritional supplement, it is not regulated by the United States Food and Drug Administration nor is it banned by the International Olympic Committee or National Collegiate Athletic Association. Because of the widespread use of creatine, primary care providers must be knowledgeable about its effectiveness and safety.

Oral creatine monohydrate increases skeletal muscle creatine concentration by 16% to 50%,⁵⁻⁷ but whether it is an effective ergogenic aid remains controversial. Multiple studies have investigated this question, but many have been small, often including fewer than 10 subjects, and results have been conflicting. Several reviews⁸⁻¹⁴ have addressed the effectiveness of creatine, but there has not been a systematic and comprehensive meta-analysis to resolve the uncertainties in the literature or to quantify the magnitude of the effect of creatine. To evaluate whether oral creatine supplementation

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improves strength and power in healthy adults, and further to quantify the effect, we performed a meta-analysis of randomized and matched controlled trials investigating creatine supplementation and strength.

METHODS

Search strategy

To identify possible studies for inclusion, 1 author (M.F.M.) searched the MEDLINE electronic database (1966–2000) using the terms “creatine supplementation” or “creatine” combined with “strength” or “power.” Another MEDLINE search (1966–2000) was independently conducted by another author (R.L.D.) using the term “creatine not kinase” combined with a previously published search strategy to comprehensively identify randomized clinical trials.¹⁵ We searched the Cochrane Controlled Trials Register using the term “creatine not kinase.” We manually reviewed bibliographies of identified studies, abstracts from American College of Sports Medicine annual meetings (1999 and 2000), and a reference list distributed by an expert on the subject at the annual meeting of the American Medical Society for Sports Medicine (2000). Titles and available abstracts were screened and relevant articles retrieved. An expert in the field was contacted for sources of unpublished data.

Inclusion and exclusion criteria

Two reviewers independently assessed articles for inclusion. A third reviewer was consulted to resolve discrepancies. We used the following inclusion criteria: (1) the articles reported results of randomized or matched placebo-controlled trials investigating the effect of oral creatine supplementation on strength or power with or without concomitant resistance training; (2) the study subjects were healthy men or women older than 16 years with or without previous athletic training; and (3) the studies were published in any language. Given the general disagreement regarding the time required for muscle creatine concentration to return to presupplementation levels after discontinuing oral creatine,^{16–18} studies using a crossover design were excluded from the statistical analysis unless data from the first arm, before crossover, could be abstracted or obtained from the original investigator. Outcomes were measures of strength or power of any muscle group, including maximal weight lifted; peak power achieved in maximal (sprint) cycle ergometry; and peak knee flexion/extension torque in isokinetic dynamometer testing. Measurements of endurance, such as time to fatigue on cycle ergometer and number of repetitions achieved in submaximal weight lifting, were excluded. For studies reporting outcome per kilogram of body weight, we contacted investigators to obtain absolute outcome values and exclud-

ed studies if uncorrected data were not received. We also excluded articles that evaluated outcomes not investigated in at least 2 other studies. Finally, if we could not extract data in a usable form, we contacted investigators to obtain adequate data.

Quality assessment

Two independent reviewers appraised articles to determine methodological quality with respect to risk of bias under the following categories: method of randomization, allocation concealment, blinding, similarity of study groups, withdrawals and dropouts, and intention-to-treat analysis. Each study that met inclusion criteria was given a quality score, with a maximum possible score of 10, using a tool adapted from the Cochrane Handbook.¹⁹ The quality assessment data are presented but were not used to exclude or rank any study.

Data abstraction and statistical analysis

Two independent reviewers abstracted data, and a third reviewer resolved differences. For studies investigating multiple sprints, data from the first sprint only were included in statistical analysis because the first sprint is when peak power achievement is expected. A weighted mean difference (WMD) between creatine and placebo groups was calculated for each outcome using Review Manager 4.1 software (developed by The Cochrane Collaboration). A fixed effects model was used unless statistical heterogeneity was significant ($P < .05$), in which case a random effects model was used. Subanalyses were planned on several factors that were anticipated to be sources for variation, including (1) dose and duration of creatine administration, (2) concomitant resistance training, (3) different baseline level of physical training, (4) age, and (5) sex.

RESULTS

Description of studies

After reviewing titles and available abstracts of more than 500 articles, we retrieved 66 potentially relevant studies, 16 of which met inclusion criteria for the analysis.^{17,20–34} Characteristics of these studies are summarized in the Table. Included studies represented 20 discrete samples and 414 subjects. Two studies^{20,21} evaluated creatine supplementation in men older than 60 years, whereas all the others studied younger subjects (range, 18–36 years). Only 1 study included women.¹⁷ Creatine dosages were similar across included studies (typically 20 g/d for the first 4–7 days of supplementation and 5 g/d thereafter). Studies that evaluated maximal weight lifting performance were more likely to include adjuvant resistance training programs in their protocols than those that evaluated cycle ergometry sprint or isokinetic dynamometer

TABLE

Characteristics of included studies

Reference	No. subjects (sex)	Dose per day and duration	Training level	Weight training during study?	Outcome measurement	Quality score (out of 10)	Comparability of creatine & placebo groups at baseline*
Barnett 1996	17 (M)	280 mg/kg × 4 d	Active	No	CP	2.5	+
Cooke 1995	12 (M)	20 g × 5 d	Untrained	No	CP	2.5	+
Cooke 1997 [†]	80 (M)	20 g × 5 d	Trained or active	No	CP	2	+++
Dawson 1995 [‡]	18 (M), 22 (M)	20 g × 5 d	Active	No	CP	3	+++
Jones 1999	16 (M)	20 g × 5 d then 5 g × 10 wk	Trained	Yes	CM	3	+++
Stone 1999	20 (M)	0.22 g/kg × 35 d	Trained	Yes	CM, BP, S	4.5	+++
Kelly 1998	18 (M)	20 g × 5 d then 5 g × 26 d	Trained	Yes	3BP	2	—
Noonan 1998	39 (M)	20 g × 5 d then 300 mg/kg × 8 wk	Trained	Yes	BP	5.5	+++
Peeters 1999	35 (M)	20 g × 3 d then 10 g × 6 wk	Trained	Yes	BP	3	+++
Vandenbergh 1997	19 (F)	20 g × 4 d then 5 g × 10 wk	Untrained	Yes	BP, S	5	+++
Pearson 1999	16 (M)	5 g × 10 wk	Trained	Yes	BP, S, PT	3	+++
Volek 1999	19 (M)	25 g × 7 d then 5 g × 12 wk	Trained	Yes	BP, S	4.5	+++
Gilliam 2000	23 (M)	20 g × 5 d	Active but untrained	No	PT	2.5	+
Rawson 1999 [§]	20 (M)	20 g × 10 d then 4 g × 20 d	Untrained	No	AF, PT	4.5	+++
Rawson 2000 [§]	17 (M)	20 g × 5 d	Untrained	No	AF	3.5	+++
Becque 2000	23 (M)	20 g × 5 d then 2 g × 6 wk	Trained	Yes	AF	5	+

*Comparability between groups was assessed for age, anthropomorphic measurements, and strength outcomes. +++ = similar for all 3 characteristics; += similar for strength outcome measurements; — = not comparable at baseline for strength outcome.

[†]Four protocols with 20 subjects each evaluating the same strength outcome measurement reported in Cooke 1997.

[‡]Two separate experiments reported in Dawson 1995.

[§]Included subjects > 60 years old; in all others subjects were < 36 years old.

AF, 1 repetition maximum arm flexor strength; BP, 1 repetition maximum bench press strength; 3BP, 3 repetition maximum bench press strength; CM, cycle ergometer mean peak power; CP, cycle ergometer peak power; PT, isokinetic leg flexion/extension peak torque; S, 1 repetition maximum squat strength.

performance. None included cycle ergometry training.

Methodological quality of included studies

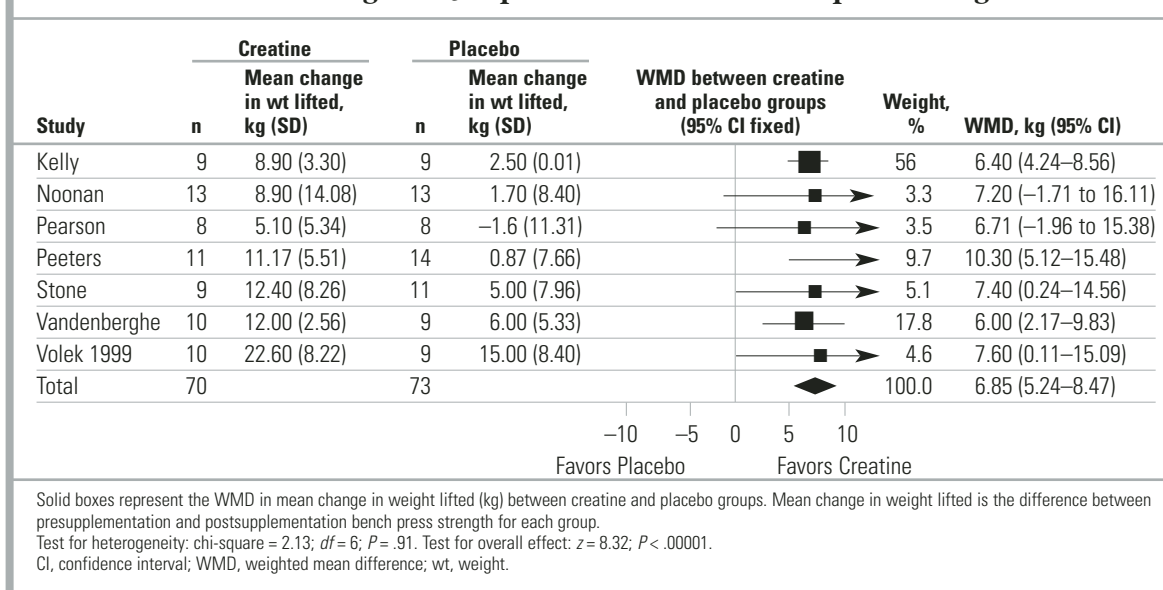
The methodological quality of studies was generally low (Table). The mean quality score was 3.5 ± 1.2 (mean ± SD) out of a possible 10 (range, 2–5.5). None of the studies identified the method of randomization used or specifically reported an intention-to-treat analysis. None specifically reported masking of outcome assessment. In general, these significant flaws in study design would tend to result in overestimation of the benefit of creatine supplementation.

Absolute strength

When 1- to 3-repetition maximum bench press strength measurements were statistically combined (they were homogeneous), the creatine supplementation group showed an absolute strength increase of 6.85 kg (95% confidence interval [CI], 5.24–8.47; n = 143) lifted per repetition greater than that seen with placebo alone (Figure 1). There was no additional advantage in strength performance after 9 to 12 weeks of supplementation (WMD = 6.6 kg; 95% CI, 3.5–9.5) compared with 4 to 8 weeks of supplementation (WMD = 6.6 kg; 95% CI, 4.8–8.4). Subanalysis for an interaction with resistance training, previous training level, age, or sex was not possible because all studies measuring bench press strength except one¹⁷ investigated creatine supple-

FIGURE 1

Studies assessing 1- to 3-repetition maximum bench press strength



mentation in previously trained young men who continued resistance training during supplementation. The 1 study in previously sedentary young women¹⁷ did find a trend toward increased bench press strength, although independently this change was not statistically significant.

There was no significant difference in 1-repetition maximum arm flexor strength with creatine supplementation (WMD = 1.53 kg; 95% CI, -1.07 to 4.13; *n* = 60; Figure 2). However, 2 trials^{20,21} of the 3 evaluating this outcome studied subjects older than 60 years and did not employ adjuvant weight training programs. The study that incorporated resistance training and evaluated younger subjects²² found a modest (29.9% vs 16.5%) improvement in 1-repetition maximum arm flexor

strength with creatine compared with placebo.

For 1-repetition maximum squat, creatine supplementation resulted in a strength increase of 9.76 kg (95% CI, 3.37–16.15; *n* = 74) greater than that of placebo (Figure 3). There was no advantage to longer-term supplementation (10.9 kg more than placebo [95% CI, 3.4–18.4] for 5–6 weeks compared with 10.4 kg [95% CI, 3.5–17.2] for 10–12 weeks). Again, in all but 1 study¹⁷ measuring squat performance, subjects were previously trained young men engaging in adjuvant resistance training programs, so subanalysis for other variables was not possible. For previously sedentary women, Vandenbergh et al¹⁷ found no difference at 5 weeks, but they did find a significant improvement in 1-repetition maximum squat performance

FIGURE 2

Studies assessing 1-repetition maximum arm flexor strength

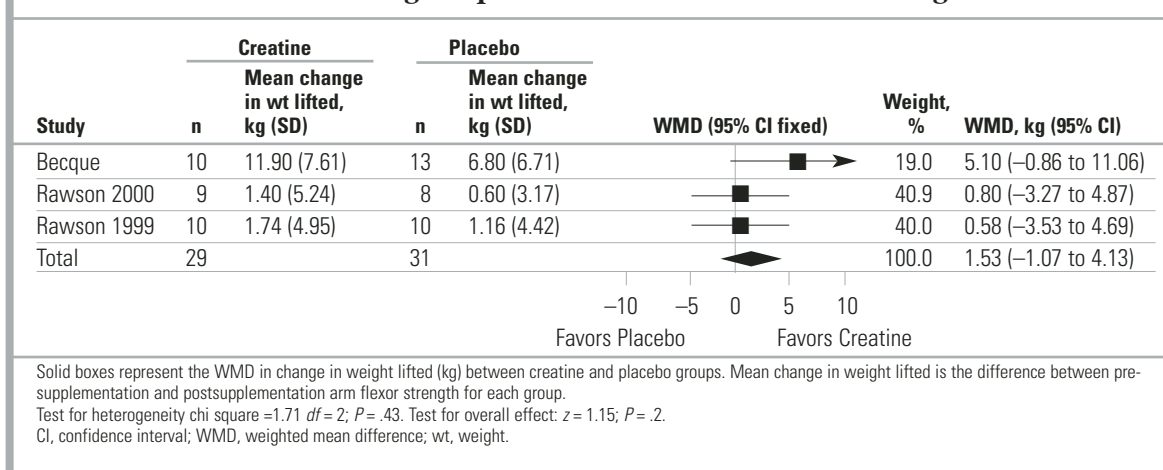
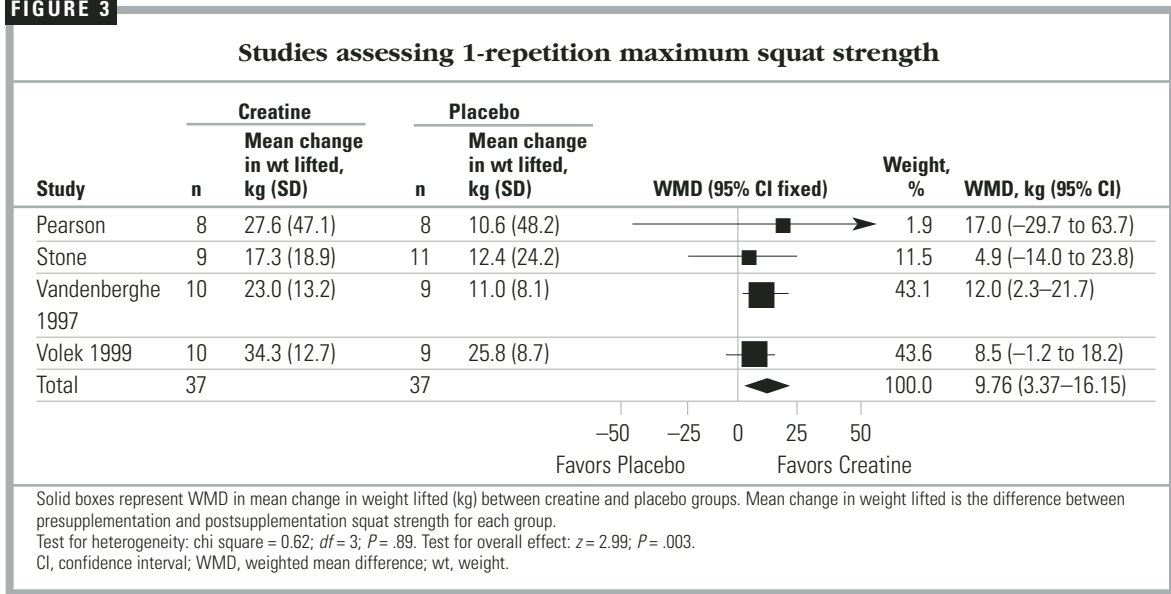


FIGURE 3

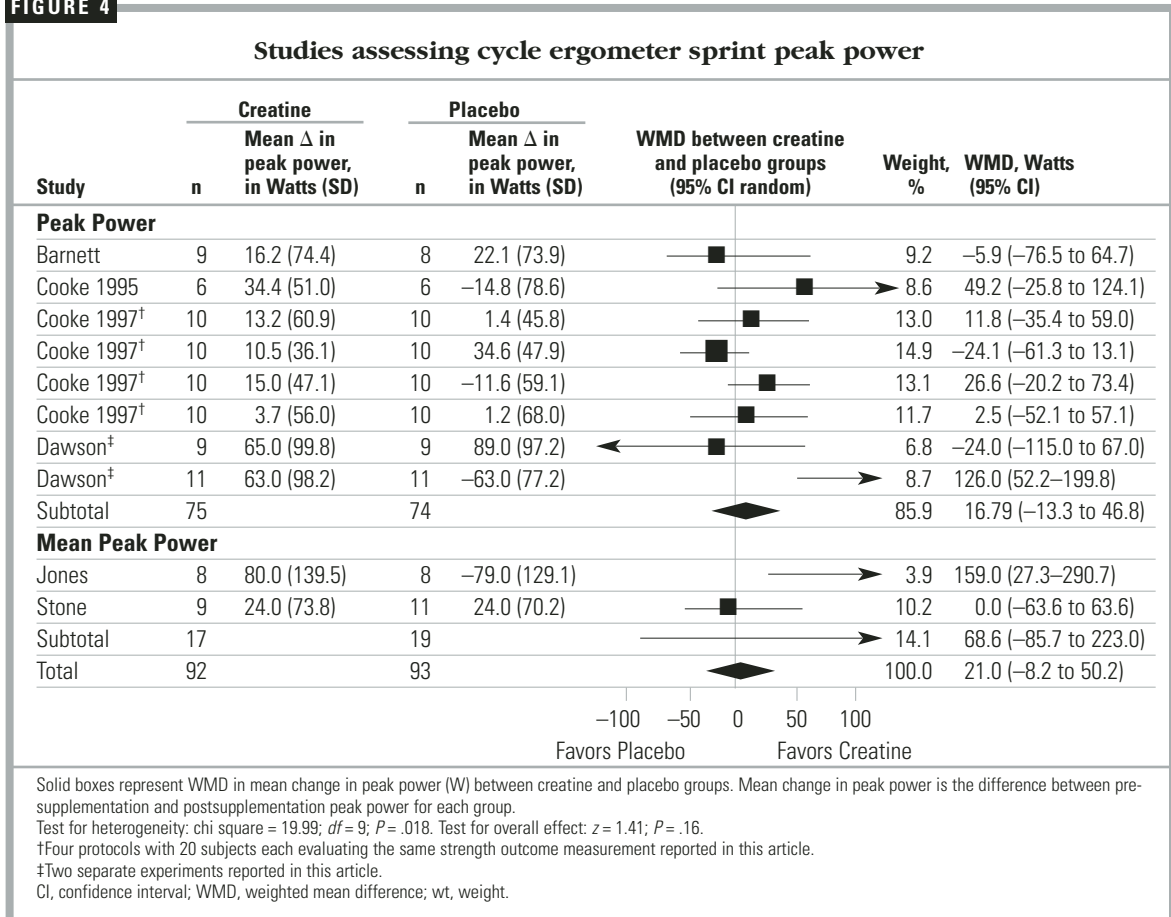


with creatine supplementation at 10 weeks. Tests for heterogeneity were nonsignificant for all absolute strength variables.

To evaluate for publication bias, we examined funnel plots of each of the 3 absolute strength out-

comes (bench press, arm flexor, and squat exercises). No evidence of publication bias was demonstrated. Figure W1 (available on the JFP Web site: <http://www.jfponline.com>) depicts a composite funnel plot of all 3 outcomes using a standardized

FIGURE 4



mean difference to allow comparison between these 3 different outcomes.

Cycle ergometer peak power

Creatine supplementation had no effect on peak power production during cycle ergometry sprint (Figure 4). Results among studies were widely variable (test for heterogeneity $P = .035$), so a random effects model was used to pool data. The summary weighted mean difference of 16.79 W (95% CI, -13.26 to 46.84; $n = 149$) was insignificant, both statistically (test for overall effect $P = .3$) and clinically, because this represents approximately a 1% change greater than baseline. Two studies^{23,24} looked at mean peak power across a series of 15- to 30-second sprints and found inconsistent results, with a summary weighted mean difference of 68.61 W (95% CI, -85.74 to 222.97; $n = 36$). Of note, for the 2 studies^{24,25} that demonstrated improved performance with creatine, the difference was accentuated by an unexplained but pronounced worsening of performance after supplementation in the placebo groups.

Dynamometer peak torque

Only 3 studies^{21,26,27} evaluated peak torque, and all used slightly different outcome assessments. One study²⁶ reported average peak torque across 30 isokinetic leg flexion/extension contractions; 1 study²¹ reported the sum of peak torque across 5 sets of 30 isokinetic leg flexion/extension contractions; and 1 study²⁷ gave peak torque data for isokinetic leg extension but did not describe precisely how peak torque was determined. There was no difference between creatine and placebo for isokinetic leg flexion/extension peak torque using a standardized mean difference to account for variations in measurement of this outcome. Tests for heterogeneity were nonsignificant for this outcome ($P = .19$).

Adverse effects

Four studies commented on short-term adverse effects of creatine supplementation. Three studies^{17,23,28} found no difference between creatine and placebo. One study²¹ reported gastrointestinal upset, rash, or headache in 3 subjects taking creatine and no adverse effects in subjects taking placebo. None of these studies was designed to evaluate long-term adverse effects of creatine supplementation, and there were no reports of longer-term follow up.

DISCUSSION

This is the first study to report quantitatively the effect of creatine supplementation on strength performance from meta-analysis of the existing literature. We found that oral creatine supplementation improves maximal resistance exercise performance in previously trained young men. There is insufficient evidence that creatine improves other meas-

ures of strength, such as cycle ergometry sprint peak power or isokinetic dynamometer peak torque, or that creatine improves strength in women or older individuals. The effect of creatine on endurance, submaximal exercise, or actual "on-field" athletic performance was not addressed.

Creatine's ergogenic properties may result from allowing increased work during training and decreasing recovery time. If so, creatine must be combined with adjuvant training to increase strength and power. Only studies investigating maximal weight-lifting performance incorporated resistance-training programs specific to the outcome being measured. Three studies included weight training but investigated non-weight-lifting outcomes,^{23,24,27} and only 1 study²⁴ found a benefit from creatine supplementation. It is unclear whether the lack of effect for non-weight-lifting outcomes means that creatine is not beneficial unless combined with specific adjuvant training or that creatine simply is not ergogenic for outcomes other than maximal weight lifted.

This meta-analysis has some limitations. Our definition of strength included only "pure strength" or "power" measurements to allow statistical comparisons between similar outcomes. Because muscle strength is related to muscle endurance, researchers may define strength differently. It is not obvious at what point an exercise becomes a test of endurance and not just strength, but there is a physiologic basis for believing that creatine supplementation would more markedly improve performance in maximal or shorter duration exercises (ie, requiring strength and not endurance). The inclusion criteria for this project were determined before study review and selection and were applied consistently across all studies.

The quality and design of identified studies was another limitation. Most were small and did not fully delineate their randomization or blinding strategies. Multiple variations in study protocols made combining results of different studies somewhat problematic. Unfortunately, meta-regression or subanalysis for variables such as concurrent resistance training, previous training level, age, and sex were not possible because too few studies evaluated these variables independently of one another. Almost all of the studies finding a benefit of creatine supplementation were in young, previously trained men who engaged in resistance training concomitantly with supplementation, and the outcome measured was maximal weight lifted. Those studies not finding a difference were generally of less highly trained or older individuals, did not include resistance training, and more often investigated outcomes other than maximal weight lifted. This meta-analysis identifies that it is impossible to conclude from the existing literature which combination of variables is necessary to see a benefit of creatine supplementation.

More information is needed on the safety of creatine supplementation. Although a recent review³⁵ reported no significant short-term adverse effects, no adequate long-term studies have been conducted. Two retrospective trials^{36,37} reported no adverse effects from longer-term (up to 5 years) creatine supplementation; however, neither study was randomized, blinded, or controlled, and neither had sufficient statistical power to detect uncommon adverse effects. Additionally, the designs of these studies precluded the possibility of detecting serious adverse effects such as death or disability. There have been case reports of renal dysfunction due to creatine³⁸⁻⁴⁰ and, as of 1998, the Food and Drug Administration had received 32 adverse event reports including seizures, myopathy, rhabdomyolysis, cardiac arrhythmia, and death.⁴¹

Given the popularity of nutritional supplements among all levels of athletes, clinicians cannot avoid questions about the effectiveness and safety of creatine supplementation. This meta-analysis demonstrated that oral creatine does improve performance during maximal resistance exercises in young men. However, we found no benefit for outcomes other than maximal weight lifted, suggesting that creatine may not improve actual performance in more complex movements requiring strength, speed, and coordination of multiple muscle groups. Studies investigating the effect of creatine in actual athletic performance are lacking.

Several important questions remain to be answered about creatine. What are the effects for women and older individuals? Is resistance training necessary to see strength performance improvement? Are these improvements in strength accompanied by improved athletic performance? How long do the effects of creatine remain after discontinuing supplementation? Most importantly, what is the long-term safety profile of creatine? Without further research to answer these questions, we cannot support the use of creatine supplementation for performance enhancement despite evidence for a positive impact on some components of strength.

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CORRECTIONS

On page 868 of the October issue a name was misspelled; the correct name is Brian S. Alper.

In the table appearing on page 877 of the October issue, the entry for Fosamax inadvertently combined prevention and treatment dosages. The corrected entry is shown below.

Drug therapy for prevention and treatment of postmenopausal osteoporosis			
Drug (trade name)	Indication and dosage	Possible side effects (% of patients)	Cost per month*
Calcium and vitamin D (generic, Tums, Citracal, and others)	Prevention and treatment: 1200-1500 mg/day calcium and 800 IU/day vitamin D	Nausea, dyspepsia (uncommon), constipation (10%)	\$5 (both)
Estrogen† (Premarin, Ogen, Estrace, Estraderm, and others)	Prevention: 0.625 mg/day conjugated equine estrogen or the equivalent; 0.3 mg/day may be effective	Nausea, breast tenderness, vaginal bleeding, mood alterations, headache, bloating	\$14-\$28
Alendronate (Fosamax)	Prevention: 5 mg/day or 35 mg/week Treatment: 10 mg/day or 70 mg/wk	Nausea, dyspepsia, esophageal irritation	\$67
Risedronate (Actonel)	Prevention and treatment: 5 mg/day or 35 mg/week	Abdominal pain, nausea, diarrhea	\$67
Raloxifene (Evista)	Treatment: 60 mg/day	Hot flashes (6%), leg cramps (3%)	\$70
Calcitonin nasal spray (Miacalcin)	Treatment: 200 IU/day (1 spray in 1 nostril per day)	Rhinitis (5%), epistaxis, sinusitis	\$66

*Average wholesale cost to the pharmacy for 30 days of therapy; (Drug Topics Red Book. Montvale, NJ; Medical Economics Co., Inc, 2002.)
 †Women with a uterus need to take a progestin such as medroxyprogesterone acetate (Provera \$30/month, generic \$9/month) or a combination estrogen/progestin product (Prempro \$33/month, FemHRT \$26/month).