SYSTEMATIC REVIEW

Acute Effects of Citrulline Supplementation on High-Intensity Strength and Power Performance: A Systematic Review and Meta-Analysis

Eric T. Trexler[1,2] · Adam M. Persky[3] · Eric D. Ryan[1,2] · Todd A. Schwartz[4] · Lee Stoner[1,2] · Abbie E. Smith-Ryan[1,2]

Abstract

Background Citrulline is an increasingly common dietary supplement that is thought to enhance exercise performance by increasing nitric oxide production. In the last 5 years, several studies have investigated the effects of citrulline supplements on strength and power outcomes, with mixed results reported. To date, the current authors are unaware of any attempts to systematically review this emerging body of literature.

Objective The current study sought to conduct a systematic review and meta-analysis of the literature describing the effects of citrulline supplementation on strength and power outcomes.

Methods A comprehensive, systematic search of three prominent research databases was performed to find peer-reviewed, English language, original research studies evaluating the effects of citrulline supplementation on indices of high-intensity exercise performance in healthy men and women. Outcomes included strength and power variables from performance tests involving multiple repetitive muscle actions of large muscle groups, consisting of either resistance training sets or sprints lasting 30 s or less. Tests involving isolated actions of small muscle groups or isolated attempts of single-jump tasks were not included for analysis due to differences in metabolic requirements. Studies were excluded from consideration if they lacked a placebo condition for comparison, were carried out in clinical populations, provided a citrulline dose of less than 3 g, provided the citrulline dose less than 30 min prior to exercise testing, or combined the citrulline ingredient with creatine, caffeine, nitrate, or other ergogenic ingredients.

Results Twelve studies, consisting of 13 total independent samples ($n = 198$ participants), met the inclusion criteria. Between-study variance, heterogeneity, and inconsistency across studies were low (Cochrane's $Q = 6.9$, $p = 0.86$; $\tau^2 = 0.0$ [0.0, 0.08], $I^2 = 0.0$ [0.0, 40.0]), and no funnel plot asymmetry was present. Results of the meta-analysis identified a significant benefit for citrulline compared to placebo treatments ($p = 0.036$), with a small pooled standardized mean difference (SMD; Hedges' G) of 0.20 (95% confidence interval 0.01–0.39).

Conclusion The effect size was small (0.20), and confidence intervals for each individual study crossed the line of null effect. However, the results may be relevant to high-level athletes, in which competitive outcomes are decided by small margins. Further research is encouraged to fully elucidate the effects of potential moderating study characteristics, such as the form of citrulline supplement, citrulline dose, sex, age, and strength versus power tasks.

✉ Abbie E. Smith-Ryan
abbsmith@email.unc.edu

1 Human Movement Science Curriculum, Department of Allied Health Sciences, University of North Carolina, Chapel Hill, NC, USA

2 Applied Physiology Laboratory, Department of Exercise and Sport Science, University of North Carolina-Chapel Hill, 312 Woollen, CB #8700, Chapel Hill, NC 27599, USA

3 Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA

4 Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA

1 Introduction

Nitric oxide (NO) is a gaseous signaling molecule with widespread effects on several physiological processes, most notably vasodilation to enhance delivery of oxygen and energy substrates to active musculature [1]. Additional actions include enhanced exercise efficiency, mitochondrial respiration, calcium handling in the sarcoplasmic reticulum, glucose uptake, and muscle fatigue [2]. Given the multifaceted role of NO in vasodilation and other exercise-related physiological processes, there is great interest in using citrulline supplementation to enhance endurance and high-intensity exercise performance. In the past decade,

Key Points

Results of the current meta-analysis indicate that citrulline supplementation increases performance of high-intensity strength and power tasks in comparison with placebo.

While the findings of the current meta-analysis indicate a statistically significant favorable effect of citrulline supplementation, the effect size is small (standardized mean difference $= 0.20$), and the body of literature is limited in size.

For high-level athletes in which margins of victory are small in magnitude, citrulline supplementation may impart meaningful effects for strength and power athletes.

several studies have investigated the effects of citrulline supplementation on strength and power outcomes, but mixed findings have been reported [3–12]. Furthermore, the exact mechanisms by which citrulline-based supplements may enhance performance are not fully understood. Citrulline's effects may be attributable to the effects of NO on blood flow, energy efficiency, and/or muscle function [2], but such supplements may also affect ammonia clearance and aerobic ATP production [10]. Meta-analytic techniques can be used to elucidate the ergogenic potential of citrulline supplementation, which would have important ramifications for athletes hoping to maximize strength and power performance.

Dietary supplement consumption is prevalent among US adults, with up to 53% of this population identifying as regular users [13]. NO precursors are a popular class of dietary supplements; given the effects of NO on a wide range of exercise-related physiological processes, NO precursor supplements are commonly marketed toward athletes and other active populations engaged in high-intensity exercise [14, 15]. As the direct precursor to NO production, preliminary studies investigated the effects of L-arginine supplementation on exercise outcomes. Select studies performed using untrained individuals showed ergogenic effects, but studies with trained participants have generally shown no significant effects [16]. For example, Liu et al. [17] studied the effect of 6 g of arginine per day for 3 days on intermittent cycling performance in trained judo athletes, with no ergogenic effect observed. Sunderland et al. [18] studied the effects of 4 weeks of L-arginine supplementation on maximal oxygen consumption (VO_{2max}) and ventilatory threshold in trained cyclists, with no effect of supplementation on either outcome. Notably, studies in trained athletes have shown that oral L-arginine does not significantly increase markers of systemic NO production [17, 19, 20], as bioavailability of

oral L-arginine supplementation is estimated to be approximately 60% [16].

In contrast, oral supplementation with L-citrulline bypasses first-pass metabolism and enhances circulating L-arginine levels more effectively than oral L-arginine supplementation [21]. Citrulline can be recycled to produce L-arginine [16] without extensive pre-systemic degradation, thereby emerging as a promising target for NO precursor supplementation. A common form of citrulline supplementation is citrulline malate (CitMal), in which citrulline and malate are combined in ratios ranging from 1:1 to 2:1. A study in men with self-reported fatigue documented significant increases in aerobic adenosine triphosphate (ATP) production and phosphocreatine recovery during finger flexion exercise [22], while other research in trained cyclists showed an enhancement of post-exercise NO metabolite production following 6 g of CitMal supplementation [23]. In 2010, Perez-Guisado and Jakeman [10] conducted the first resistance training study with CitMal. A single 8-g dose of CitMal consumed 1 h before resistance exercise significantly enhanced the number of bench press repetitions performed over a 16-set training session.

A comprehensive review on NO precursor supplements was published by Bescos et al. [16] in 2012, with search results limited to publications from 2011 and before. At the time of its publication, citrulline research was in its infancy; only one study directly addressed the effects of citrulline supplementation on high-intensity strength or power outcomes [10], and the overall body of literature was too small to warrant a systematic review or meta-analysis. In the years since, this body of literature has grown considerably. For example, Wax et al. found CitMal to improve repetitions completed across multiple sets of lower-body exercise in male weightlifters [12], and also identified an improvement in upper-body resistance training performance in resistance-trained males [11]. Similarly, Glenn et al. documented strength and power improvements in female masters tennis players following acute (single-dose) CitMal consumption [8], along with upper- and lower-body repetitions completed by resistance-trained females [9]. In contrast, several other studies have shown no benefit of citrulline-based supplements. For example, Farney et al. [6] found no effect of CitMal supplementation on leg extension peak torque or peak power following circuit training, and repetitions completed during a 10-set leg extension protocol were not improved by acute CitMal supplementation [3].

While Bescos et al. [16] thoroughly reviewed the NO precursor supplement literature available as of 2011, a substantial number of studies investigating the effects of citrulline supplements on high-intensity strength and power outcomes have emerged in the years since. The results of individual studies have been mixed, with some reporting ergogenic effects [8–12] and some reporting null findings

[3–7]. Such ergogenic effects include increases in repetitions to fatigue (RTF) for bench press [9, 10], leg press [9], and multiple-exercise upper-body [11] and lower-body [12] resistance exercise protocols, in addition to improvements in handgrip strength and peak cycling power [8]. Based on the rapid emergence of several citrulline studies with equivocal findings, a systematic review to summarize the effects of citrulline supplements on strength and power outcomes is warranted.

1.1 Objective

Our objective was to perform a systematic review and meta-analysis of placebo-controlled trials evaluating the effects of acute citrulline supplementation on high-intensity exercise performance outcomes in healthy adults.

2 Methods

A systematic review and meta-analysis was conducted to evaluate the effects of citrulline supplementation on high-intensity exercise performance. The review was conducted and reported in accordance with guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [24].

2.1 Search Strategy

To identify suitable studies for the current review, literature searches of the PubMed/Medline, SPORTDiscus, and Web of Science databases were performed by a member of the research team (ETT). SPORTDiscus results were refined by source type ("academic journals"), and Web of Science results were refined by document type ("article"). The literature search included published records from the inception of each database through 14 August 2018. Searches included the following keywords as search terms: "citrulline," "citrulline malate," or "ʟ-citrulline"); in combination with "repetitions to fatigue," "resistance exercise," "resistance training," "strength," "strength training," "muscle strength," "muscular strength," "weight training," "weightlifting," "weight lifting," "muscular endurance," "one-repetition maximum," "one repetition maximum," "repetitions," "sprint," or "power."

2.2 Inclusion and Exclusion Criteria

Peer-reviewed, original research articles written in the English language were considered for inclusion; review articles and unpublished abstracts, theses, and dissertations were excluded. To be considered for inclusion, articles were required to be human experimental trials in healthy

populations, in which the effects of citrulline supplementation on high-intensity strength and power performance were compared to a placebo condition. Primary outcomes included indices of high-intensity exercise performance, including strength and power variables from performance tests involving multiple repetitive muscle actions of large muscle groups, consisting of either resistance training sets or sprints lasting 30 s or less. Tests involving isolated actions of small muscle groups (e.g., handgrip exercise with rest periods between attempts) or isolated attempts of single-jump tasks were not included for analysis, due to differences in metabolic requirements. Fatigue index outcomes reported as a reduction from peak strength or power were not included in the absence of raw values, as such outcomes may reflect low peak values (performance impairment) or fatigue reduction (performance improvement).

Studies were excluded from consideration if they lacked a placebo condition for comparison, were carried out in clinical populations, provided a citrulline dose of less than 3 g, provided the citrulline dose less than 30 min prior to exercise testing (to allow for sufficient absorption [21]), or combined the citrulline ingredient with creatine, caffeine, nitrate, or other ergogenic ingredients. Citrulline treatments mixed into juices containing antioxidants and other potentially bioactive phytochemicals were considered for inclusion if the study also included a comparator treatment of the same juice without citrulline added. For studies utilizing more than two treatment arms, the current meta-analysis only included comparisons between a citrulline-supplemented treatment beverage and an identical beverage lacking added citrulline.

2.3 Text Screening

Titles and abstracts of the initial search results were independently screened for relevance by two investigators (ETT and AES), based upon a priori inclusion and exclusion criteria. Following title and abstract screening, full texts were independently screened by the same two investigators to further evaluate congruence with inclusion and exclusion criteria, and to determine which studies warranted inclusion in the analysis. Any disagreements between reviewers were discussed until a consensus decision was reached.

2.4 Data Extraction, Study Coding, and Quality Assessment

Studies were closely reviewed to extract group means, standard deviations, and sample sizes for outcome measures of interest. When values were plotted as figures, but not reported numerically in the text, values were estimated based on pixel count using calibrated images in ImageJ software (National Institutes of Health, Bethesda, MD, USA). Briefly, each figure was calibrated by measuring the number

of pixels between two known points on the vertical axis of the figure. Mean and standard deviation values were then estimated by measuring the pixel length of each plotted value in the figure, along with its associated error bar. For studies reporting multiple individual sets of a particular outcome, a summed overall value was calculated by summing the means of each set; an overall standard deviation was calculated by taking the square root of the summed variance from all of the individual sets. All extraction and coding were performed by ETT.

One study [5] included two experiments conducted in two separate samples; for the current meta-analysis, each sample was treated as an independent study, as discussed by Borenstein et al. [25]. For each measured outcome meeting inclusion criteria, standardized effect sizes were calculated as Hedges' G using the "metafor" package in R software (R Foundation for Statistical Computing, Vienna, Austria), yielding an effect size and an associated variance for each outcome. The SMD was used to determine the magnitude of the effect, where < 0.2 was defined as trivial, 0.2–0.3 as small, 0.4–0.8 as moderate, and > 0.8 as large [26, 27]. Most studies reported more than one outcome meeting study inclusion criteria; the method described by Borenstein [28] was used to compute a single, aggregated effect size estimate for each study, using the "MAd" package in R software. This aggregation method requires the estimation of the within-study correlation among outcome variables; while this was not reported in the studies analyzed, Baker and Nance [29] have previously published correlations between a representative collection of variables including both strength and power outcomes of both upper- and lower-body exercises. The mean of these correlation coefficients was calculated ($r = 0.70$) and used as a generalized estimate of within-study correlation among the variables of interest; a sensitivity analysis was performed, as described below.

All studies meeting inclusion criteria were carefully reviewed to document relevant study characteristics, which were tabulated in a spreadsheet (Microsoft Excel, Microsoft Corporation, Washington, DC, USA). Extracted information included study authors, year of publication, study design, dose and form of supplementation, timing of supplementation, participant sex, participant age, participant training status, inclusion and exclusion criteria for each trial, previsit guidelines, side effects, funding sources, and exercise outcomes. Exercise tasks were categorized based on type of outcome (strength or power), muscle groups utilized (upper body or lower body), and modality. For the purpose of categorizing training status, individuals were considered "resistance trained" (RT) if they engaged in regular resistance training at least twice a week, for at least 6 months preceding the trial; participants who were categorized as recreationally active, endurance-trained, or sport-trained were considered non-RT. For subgroup analyses, all study

characteristics were coded as binary variables (sex: males only vs. females included; training status: resistance trained vs. non-resistance trained; supplement form: citrulline malate vs. other (L-citrulline or L-citrulline + watermelon juice); musculature tested: lower body only vs. upper body included; type of exercise outcome: strength only vs. power outcomes included; modality of exercise: resistance exercise vs. cycle ergometry; funding source: industry funded or undisclosed funding vs. other). Included studies were qualitatively reviewed for risk of bias using the individual components of the Cochrane Risk of Bias Tool [30]. Domains of this tool include selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

2.5 Meta-Analysis

A meta-analysis using a random effects modeling approach was conducted using R software. Weighted estimation of standardized mean differences (SMD) across studies were pooled using the inverse variance method. The statistical heterogeneity across different trials in meta-analysis was assessed by the I^2 statistic [31], where $< 25\%$ indicates low risk of heterogeneity, 25–75% indicates moderate risk of heterogeneity, and $> 75\%$ indicates considerable risk of heterogeneity [31]. The I^2 statistic was calculated based upon the restricted maximum-likelihood estimator of τ^2. For included studies, standard errors were plotted against Hedges' G values to allow for visual evaluation of potential funnel plot asymmetry. Funnel plot asymmetry was further assessed using Egger's regression test [32], and Duval and Tweedie's Trim and Fill method [33]. Pooled effect point estimates are presented as SMDs, accompanied by the corresponding 95% confidence intervals (95% CIs; [lower bound–upper bound]).

Sensitivity analyses imputing $r = 0.5$ or $r = 1.0$ were conducted to assess the impact of the estimated correlation ($r = 0.70$) between dependent study outcomes through ensuring that findings were robust across a range of plausible correlation values [29]. To assess the effects of study characteristics on the pooled effect estimate, moderator effects were tested by fitting a random effects meta-regression model incorporating each coded study characteristic separately. Separate SMD estimates with corresponding 95% confidence intervals were constructed for each subgroup. Analyzed characteristics included sex of the sample, training status, citrulline form, musculature tested, type of exercise outcome tested, modality of exercise tested, and funding source, and were categorized as binary variables. All analyses were conducted by the same researcher (ETT), with all hypothesis tests conducted at the significance level of $\alpha = 0.05$.
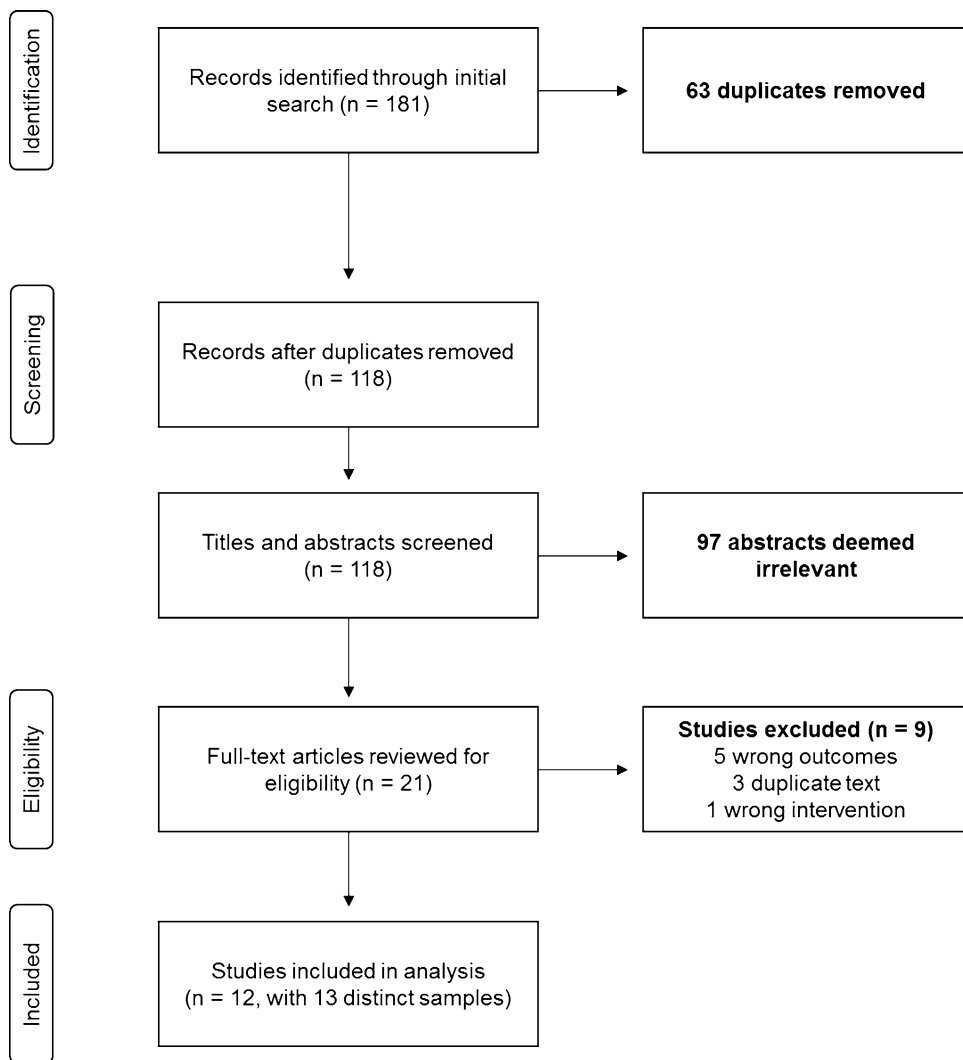
3 Results

3.1 Literature Search

The initial search yielded 181 total records, including 118 unique records and 63 duplicates. Title and abstract screening eliminated 97 irrelevant studies, resulting in 21 eligible studies for full-text screening. After full-text screening, 12 studies, consisting of 13 total independent samples (total n completing testing = 198), met the criteria for inclusion. The PRISMA flow diagram for the systematic review process is presented in Fig. 1.

Studies meeting inclusion criteria are summarized in Table 1. Studies were predominantly carried out in young adult populations; all sample means were between 20 and 30 years old, with one exception of 51 ± 9 years [8]. Citrulline malate (CitMal) was the most common form of supplementation (n studies = 10); the most common CitMal dosage was 8 g, with doses ranging from 6 to 12 g. Only one study using CitMal specifically reported the ratio of citrulline to malate, but independent laboratory analysis indicated that the labeled ratio overestimated the citrulline dose and underestimated the malate dose [3]. Other supplement forms included free-form L-citrulline and L-citrulline mixed into watermelon juice, with all studies supplying a citrulline dose of at least 3 g. Two studies included female-only samples, seven included male-only samples, and four contained a mixture of males and females. Supplements were typically provided 60 min prior to exercise, with one study providing the supplement 40 min prior [7] and another 120 min prior [5]. Eight studies evaluated strength outcomes only, two evaluated power outcomes only, and three evaluated both strength and power outcomes. Seven studies evaluated lower-body outcomes only, five evaluated upper-body outcomes only, and one study evaluated a combination of upper-body and lower-body tasks [9]. In all studies, supplementation was well tolerated, with one study reporting mild

Fig. 1 PRISMA diagram detailing systematic search and screening process

Table 1 Characteristics of studies included in the analysis

Study (first author, year)	Design	Age, years (mean±SD)	Sample size	Sex	Train-ing Status	Supplement form	Timing (min)	Modality	Strength or power	Upper- or lower-body exercise	Outcomes included
Wax, 2016 [11]	RDB	23.3±1.5	14	M	RT	8 g CitMal	60	RE	Strength	Upper	Repetitions (multiple exercises, multiple sets)
Wax, 2015 [12]	RDB	22.1±1.4	12	M	RT	8 g CitMal	60	RE	Strength	Lower	Repetitions (multiple exercises, multiple sets)
Perez-Guisado, 2010 [10]	RDB	29.8±7.6	41	M	RT	8 g CitMal	60	RE	Strength	Upper	Bench press repetitions (multiple sets)
Martinez-Sanchez, 2017 [39]	RDB	23.9±3.7	19	M	RT	3.3 g L-Citrulline in WMJ	60	RE	Mix	Lower	Peak and mean squat force and power
Gonzalez, 2017 [7]	RDB	21.4±1.6	12	M	RT	8 g CitMal	40	RE	Mix	Upper	Bench press repetitions, peak power, and mean power (multiple sets)
Glenn, 2017 [9]	RDB	23.0±3.0	15	F	RT	8 g CitMal	60	RE	Strength	Mix	Repetitions (multiple exercises, multiple sets)
Glenn, 2016 [8]	RDB	51±9.0	17	F	ST/ET	8 g CitMal	60	Cycling	Power	Lower	Relative peak power, anaerobic capacity
Farney, 2017 [6]	RSB	24.1±3.9	12	Mix	REC	8 g CitMal	60	RE	Mix	Lower	Repetitions (multiple exercises, multiple sets), peak leg extension torque and power before and after circuit training
da Silva, 2017 [42]	RDB	24.0±3.3	9	M	REC	6 g CitMal	60	RE	Strength	Lower	Repetitions (single set, multiple exercises, multiple days)
Cutrufello, 2015a [5]	RDB	20.8±1.3	10	Mix	ST/ET	6 g L-Citrulline	60	RE	Strength	Upper	Repetitions (multiple sets)
Cutrufello, 2015b [5]a	RDB	20.8±1.3	12	Mix	ST/ET	6 g L-Citrulline	120	RE	Strength	Upper	Repetitions (multiple sets)
Cunniffe, 2016 [4]	RDB	23.5±3.7	10	M	ST/ET	12 g CitMal	60	Cycling	Power	Lower	Peak and mean power (multiple sprints)
Chappell, 2018 [3]	RDB	23.7±2.4	15	Mix	RT	8 g CitMal	60	RE	Strength	Lower	Repetitions (multiple sets); isometric, concentric, and eccentric peak torque

SD standard deviation, *RDB* randomized, double-blinded, *RSB* randomized, single-blinded, *CitMal* citrulline malate, *M* male, *F* female, *RT* resistance trained, *REC* recreationally active, *ST* sport trained, *ET* endurance trained, *WMJ* watermelon juice, *min* minutes, *RE* resistance exercise

aCutrufello et al. [5] utilized two separate sub-samples, but provided descriptive information in aggregate

gastrointestinal (GI) discomfort in 15% of participants [10], and a nonsignificant trend for increased subjective ratings of GI discomfort in another study [4].

3.2 Risk of Bias

Risk of bias was generally deemed "low" for each component of the Cochrane Risk of Bias Tool. All studies were randomized controlled trials utilizing a flavor-matched placebo and a crossover design. All studies reported utilization of randomized sequence generation, although most lacked methodological detail with regard to how the sequences were generated. All studies reported double-blinded designs with one exception [6], in which only participants were blinded; this study resulted in a small SMD (0.03), which indicates a low likelihood that this single-blinded design led to biased outcomes in favor of the supplement condition. Treatment blinding was well documented, with placebo treatments matched with regard to flavor, smell, and appearance. Five studies further facilitated treatment concealment by requiring participants to consume the beverage while wearing nose clips to dull taste and smell sensitivity. Two studies asked participants to identify which treatment they received at each visit [8, 9]; in both cases, hypothesis testing indicated that subjects were unable to effectively identify the treatment received. Comparatively little detail was provided with regard to blinding of testers; 12 of 13 studies claimed to be double-blinded, with seven specifically stating that treatments were mixed and/or packaged by individuals who did not participate in testing.

Studies typically provided detailed pre-visit guidelines for participants, such as attention to dietary consistency the day before and day of testing, and abstinence from alcohol, caffeine, strenuous exercise, and other dietary supplements. Only one study lacked detail with regard to all of these factors [6], and one study instructed participants to maintain consistency with their dietary supplement intake rather than restricting supplementation altogether [3]. Of studies reporting detailed information pertaining to subject withdrawal, attrition was minimal and attributed to schedule constraints or reasons unrelated to the study. Evidence of reporting bias was minimal; some results were presented in graphical format only without numerical values provided, and some multi-set test outcomes were reported as a cumulative sum rather than individual set-by-set data. There were isolated cases in which data pertaining to pre-visit dietary habits and/or training habits were collected and not reported, but this lack of reporting is unlikely to bias the SMD estimate of such studies. Four studies reported that no funding was obtained, and three did not disclose funding information; of those disclosing the receipt of funding, two reported industry funding, with the others ($n = 4$) reporting combinations of government, foundation, and/or university funding.

3.3 Pooled Effect Estimate

Between-study variance, heterogeneity, and inconsistency across studies were low (Cochrane's $Q = 6.9$, $p = 0.86$; $\tau^2 = 0.0$ [0.0, 0.08], $I^2 = 0.0$ [0.0, 40.0]). Visual inspection of the funnel plot (Fig. 2) did not reveal substantial asymmetry, and Egger's regression test for funnel plot asymmetry yielded a nonsignificant result ($z = -0.34$, $p = 0.73$). The Duval and Tweedie Trim and Fill analysis identified no missing studies on either side of the plot.

Results of the meta-analysis identified a significant benefit of citrulline in comparison to placebo for measures of high-intensity strength and power performance ($p = 0.036$), with a small effect size (pooled SMD = 0.20 [0.01, 0.39]; Fig. 3). Sensitivity analyses indicated that this finding was robust with regard to imputed within-study correlation values of both $r = 0.5$ (SMD = 0.19 [0.02, 0.37], $p = 0.029$) and $r = 1.0$ (SMD = 0.20 [0.004, 0.405], $p = 0.045$) in the effect size aggregation computation.

3.4 Subgroup Analysis

Hypothesis testing yielded nonsignificant moderation effects by sex ($p = 0.72$), training status ($p = 0.88$), supplement form ($p = 0.71$), musculature tested ($p = 0.73$), type of exercise outcome ($p = 0.19$), modality of exercise ($p = 0.82$), or funding source ($p = 0.77$). Standardized mean differences for subgroups are presented in Table 2. In the absence of statistically significant moderation effects, these group-specific SMDs are exploratory in nature, and should
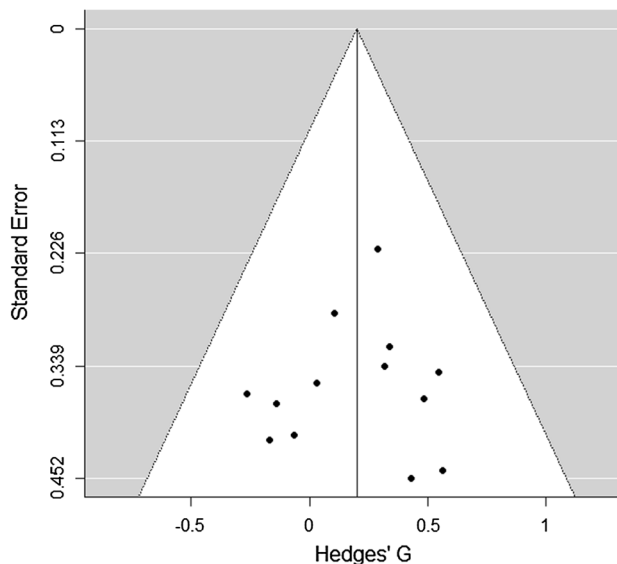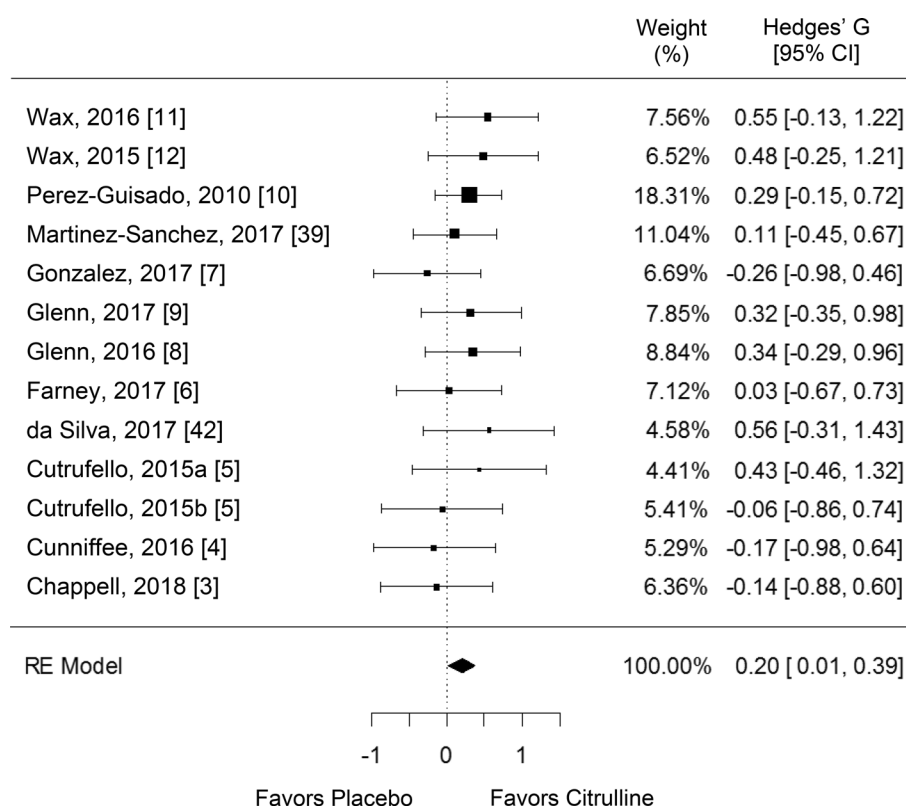

Fig. 2 Funnel plot (standard error vs. Hedges' *G*) for studies meeting inclusion criteria

Fig. 3 Forest plot of studies meeting inclusion criteria. *CI* confidence interval, *RE model* random effects model

	Weight (%)	Hedges' G [95% CI]
Wax, 2016 [11]	7.56%	0.55 [-0.13, 1.22]
Wax, 2015 [12]	6.52%	0.48 [-0.25, 1.21]
Perez-Guisado, 2010 [10]	18.31%	0.29 [-0.15, 0.72]
Martinez-Sanchez, 2017 [39]	11.04%	0.11 [-0.45, 0.67]
Gonzalez, 2017 [7]	6.69%	-0.26 [-0.98, 0.46]
Glenn, 2017 [9]	7.85%	0.32 [-0.35, 0.98]
Glenn, 2016 [8]	8.84%	0.34 [-0.29, 0.96]
Farney, 2017 [6]	7.12%	0.03 [-0.67, 0.73]
da Silva, 2017 [42]	4.58%	0.56 [-0.31, 1.43]
Cutrufello, 2015a [5]	4.41%	0.43 [-0.46, 1.32]
Cutrufello, 2015b [5]	5.41%	-0.06 [-0.86, 0.74]
Cunniffee, 2016 [4]	5.29%	-0.17 [-0.98, 0.64]
Chappell, 2018 [3]	6.36%	-0.14 [-0.88, 0.60]
RE Model	100.00%	0.20 [0.01, 0.39]

-1   0   1

Favors Placebo   Favors Citrulline

be interpreted for the purpose of forming hypotheses rather than conclusions.

4 Discussion

The current systematic review and meta-analysis sought to summarize the existing literature evaluating the effects of citrulline supplementation on high-intensity strength and power outcomes. Thirteen independent samples met inclusion criteria, with a total pooled sample size of $n = 198$. Results of the meta-analysis indicate that citrulline supplementation confers a significant benefit on strength and power outcomes in comparison to placebo, with a pooled standardized mean difference (Hedges' *G*) of 0.20 [0.01, 0.39]. This effect size is small, but may impart meaningful benefits for athletes in which competitive success is determined by small margins of victory.

4.1 Interpretation of Study Results

The current body of literature successfully navigates potential hurdles that would contraindicate meta-analytic procedures. Statistical indices related to among-study variance, heterogeneity, and inconsistency across studies were all favorable for pooled analysis, and indices related to risk of bias were generally low. Results of funnel plot analyses

Table 2 Subgroup analyses

Subgroups	*n* studies	SMD	95% CI	*p* value
Sex				
Male-only	7	0.23	− 0.01 to 0.47	0.06
Females included	6	0.16	− 0.14 to 0.45	0.29
Training status				
RT	7	0.21	− 0.02 to 0.44	0.08
Non-RT	6	0.18	− 0.13 to 0.49	0.26
Citrulline form				
Citrulline malate	10	0.22	0.01 to 0.43	**0.04**
Other	3	0.13	− 0.28 to 0.54	0.53
Musculature tested				
Lower-body only	7	0.17	− 0.10 to 0.43	0.21
Upper-body included	6	0.23	− 0.03 to 0.49	0.08
Type of exercise outcome				
Strength only	8	0.30	0.06 to 0.54	**0.01**
Power included	5	0.04	− 0.25 to 0.34	0.77
Modality of exercise				
Resistance exercise	11	0.21	0.01 to 0.41	**0.04**
Cycle ergometry	2	0.15	− 0.35 to 0.64	0.56
Funding source				
Industry/undisclosed	5	0.23	− 0.04 to 0.50	0.10
Other	8	0.17	− 0.08 to 0.43	0.19

Bold *p* values indicate statistical significance ($p < 0.05$)

n studies number of studies, *SMD* standardized mean difference (Hedges' *G*), *95% CI* 95% confidence interval, *RT* resistance trained

indicated that the body of literature did not exhibit meaningful risk of publication bias or small-study effects. Finally, the studies meeting inclusion criteria reported outcome measurements of strength and power that imposed similar physiological and metabolic demands, thereby allowing for standardization of effects via transformation to Hedges' G values. Taken together, characteristics of the existing literature indicate that calculation of a pooled effect size point estimate is appropriate, thereby enhancing confidence in the pooled effect estimate of SMD = 0.20. This effect size is small, but comparable to other ergogenic dietary supplements. For example, creatine has been shown to exert moderate effects on upper-body exercise (SMD = 0.42), and small effects on lower-body exercise (SMD = 0.21) [34]. Similarly, caffeine exerts effects of similar magnitude on both strength (SMD = 0.20) and power (SMD = 0.17) performance [35]. In a recent meta-analysis investigating the effects of various supplements on short-duration (45 s to 8 min) exercise tasks [36], moderate effect sizes were reported for caffeine (SMD = 0.41) and bicarbonate (SMD = 0.40), whereas trivial effect sizes were reported for nitrate (SMD = 0.19) and beta-alanine (SMD = 0.17).

Despite the similarities between studies, a number of distinct study characteristics warrant exploration. Due to a small number of studies per subgroup, hypotheses tests of moderating effects may be underpowered and should be interpreted cautiously. Hypothesis testing identified no significant moderating effects of sex, training status, supplement form, musculature tested, type of exercise outcome, modality of exercise, or funding source. Sex-based comparisons yielded reasonably similar effect estimates between studies with male samples ($n = 7$) and studies with female or mixed-sex ($n = 6$) samples (SMD = 0.23 and 0.16, respectively). For example, Glenn et al. have documented ergogenic effects of CitMal in female masters athletes [8] and resistance-trained females [9], whereas similar results have been reported in male samples by Perez-Guisado and Jakeman [10] and Wax et al. [11, 12]. Minor differences existed between studies of varying training status, musculature tested, modality of exercise, and funding source, with SMD estimates varying by no more than 0.06 between subgroups.

Of the studies included in the meta-analysis, eight reported strength outcomes only, whereas five studies reported power outcomes or a mixture of strength and power outcomes. While hypothesis testing did not identify a significant moderating effect, SMD estimates differed substantially in studies including strength outcomes only (SMD = 0.30) in comparison to studies including power outcomes (SMD = 0.04). While many sports rely on sport-specific application of both strength and power, there are distinctions that separate the two constructs from one another. Strength pertains to the development of high forces, whereas power pertains to the rapid generation of force per unit time [37]. When evaluating the effects of citrulline supplements on physical tasks with varying demands, it is important to consider the multiple mechanisms by which citrulline supplements may impart ergogenic effects. Citrulline supplements may confer ergogenic effects by either enhancing NO production or facilitating ammonia clearance [10], and supplement forms containing malate may also affect exercise via aerobic ATP production, and even systemic effects on acid-base balance [38]. Furthermore, the physiological effects of NO are multifaceted, with the potential to influence blood flow, exercise efficiency, mitochondrial respiration, calcium handling in the sarcoplasmic reticulum, glucose uptake, and muscle fatigue [2]. Of the literature included in the current analysis, strength outcomes often involved greater overall external loads (such as resistance training repetitions with 80% of one-repetition maximum [10]) in comparison to power tasks (such as cycling against a resistance of 7.5% of bodyweight [8]). In addition, strength tests often included open-ended tasks in which repetitions were completed until failure [9–12], whereas power tasks often included fixed-endpoint tasks in which individuals were challenged to complete as much work as possible in a fixed timeframe [4, 8]. Given the multifaceted mechanisms that may dictate the ergogenic effect of citrulline supplementation, distinctions pertaining to the physiological demands and testing characteristics of strength versus power tasks may contribute to the observed difference in SMD estimates.

Modest differences in SMD estimates were also observed between studies utilizing the CitMal form of supplementation in comparison to other forms of citrulline (ten studies vs. three; SMD = 0.22 vs. 0.13). However, given the low number of studies using alternate forms of citrulline ($n = 3$), these values should be interpreted cautiously. These studies reported individual SMDs of 0.43 [5], 0.11 [39], and −0.06 [5]. As such, the pooled estimate describing these studies summarized a wide range of heterogeneous effect estimates; as more studies assessing alternate forms of citrulline supplements become available, this point estimate may become more refined. Nonetheless, an independent or synergistic ergogenic effect of malate cannot be ruled out. Malate contributes to aerobic ATP production as a tricarboxylic acid (TCA) cycle intermediate and a major component of the malate-aspartate shuttle mechanism, and may influence acid-base balance by promoting systemic alkalosis [38]. There is evidence of enhanced physical stamina following oral L-malate supplementation in mice completing a swimming task [40], but a human trial found no effect of an oral solution containing malate, succinate, and pyridoxine-alpha-ketoglutarate on cycling performance or recovery [41]. At this point in time, there is insufficient literature documenting the effects of alternate citrulline forms on strength and

power outcomes to infer reduced efficacy in comparison to CitMal supplementation.

In addition to variability in supplement form, this body of literature features variable estimated citrulline dosages ranging from approximately 3–6 g. Unfortunately, the use of meta-regression or other quantitative techniques to evaluate dose-response relationships are precluded by unclear reporting. Of the available literature investigating citrulline malate, only one study clearly reported the supplement ratio of citrulline to malate within the manuscript [3]. This study also tested the observed ratio of citrulline to malate; while the product was advertised as a 2:1 ratio, analysis revealed a ratio of 1.11:1. Five separate brands of CitMal products with purported 2:1 ratios were independently tested, with observed values ranging from 1.11:1 to 1.92:1. To describe the relationship between citrulline dose and exercise response, it is critical for supplement manufacturers to consistently meet label claims, and investigators are encouraged to verify supplement content via independent analysis when possible. Investigators are also encouraged to more clearly identify funding sources, as multiple individual studies failed to disclose any statement regarding internal or external project funding. However, the observed funnel plot symmetry is not consistent with publication bias that could potentially arise from external funding pressures, and studies that included industry funding or failed to disclose funding did not report substantially different SMD values in comparison to other studies (SMD = 0.23 vs. 0.17, respectively). Publication bias may also arise from reluctance of journals to publish null findings, but funnel plot analyses for the current body of literature are not consistent with substantial publication bias or small-study effects.

4.2 Limitations

Results of the current analysis must be interpreted within the context of its limitations. When study results involve different test protocols and outcome measurements, aggregation of results requires conversion to a standardized effect size unit. This aggregation assumes that the outcomes represent effects that are similar enough to warrant combination. The current analysis mitigated this limitation by employing strict criteria to ensure that included outcomes reflected strength and power tasks with similar physiological and metabolic demands. Due to a low number of studies per subgroup, hypothesis tests evaluating moderating effects between subgroups possessed relatively low statistical power. As a result, subgroup-specific SMDs have been provided, which may inform the design of future citrulline supplementation trials and allow for readers to make preliminary inferences about how these variables may influence outcomes. Finally, the current analysis identified a statistically significant effect favoring citrulline supplementation over placebo, but it

should be noted that the 95% confidence interval of this SMD ranges from 0.01 to 0.39. As more literature becomes available, this point estimate may change in magnitude and precision, and even a small shift toward the null could reverse the statistical decision to reject the null hypothesis. As such, additional double-blinded, randomized, placebo-controlled interventions would be helpful in assessing the effects of citrulline supplements on high-intensity strength and power outcomes, with the goal of continuing to enhance the validity and precision of its effect size point estimate.

4.3 Recommendations

The body of citrulline supplementation research is rapidly growing, and more research is required to fully elucidate its effects on strength and power performance. More randomized trials are needed to resolve a number of research questions that persist. Notably, further research is encouraged to investigate apparently discrepant outcomes in strength versus power tasks. More studies using female samples are warranted, and studies utilizing mixed-sex samples should report sex-specific results to allow further exploration of potential sex differences. Additional studies are needed to evaluate citrulline sources other than CitMal, to determine whether malate is an independent and/or synergistic contributor to ergogenic outcomes in the CitMal literature. In addition, studies should provide specific citrulline to malate ratios to allow for quantification of the citrulline dose, and verify labeled dosages with independent analysis when possible. Finally, there is a need for citrulline research in older populations. Only one study [8] meeting inclusion criteria featured a sample with a mean age above 30 years; supplements enhancing strength and power may have important clinical applications in the management of sarcopenia.

5 Conclusion

The effects of citrulline supplementation on high-intensity strength and power outcomes have been studied extensively in recent years. While only one paper meeting inclusion criteria was available prior to 2015 [10], there is now sufficient published evidence to warrant meta-analytic techniques to summarize the literature. Results of the current analysis indicate that citrulline supplementation confers a significant performance benefit for high-intensity strength and power tasks in comparison to placebo, with a pooled SMD of 0.20 [0.01, 0.39]. The effect size was small (0.20), but may be relevant to high-level athletes, in which competitive outcomes are decided by small margins [36]. As the literature currently stands, subgroup analyses are limited by the low number of studies per category. As such, further research is encouraged to fully elucidate the effects of potential moderating study

characteristics, such as form of citrulline supplement, citrulline dose, sex, age, and strength versus power tasks.

Compliance with Ethical Standards

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