MASTER'S THESIS

Course code: MKI210

Name: Markus Haugen

Effect of isolated and combined ingestion of Caffeine and Citrulline Malate on strength and power performance in strength-trained adults

- a randomized double-blind placebo-controlled crossover study

Date: 18.05.2022

Total number of pages: 37

NORD University

www.nord.no

MASTER'S THESIS

.....

_____

NORD University

www.nord.no

Contents

Abstract

Introduction: Caffeine is a highly popular er ergogenic supplements and researched a lot. Earlier research suggest that caffeine could increase maximal strength, power and muscular endurance and reduce rating of perceived exertion. CitMal has gained a lot of popularity last few years. This supplement is not as well researched as caffeine. CitMal can reduce post exercise soreness, increase number of repetitions, and give a small benefit on strength outcomes The aim of this study was to investigate a potential synergistic effect of caffeine and citruline malate as they are popular ergogenic supplements. **Method:** 35 resistance trained males and females (age: 23 ±3.2 years) received 6 mg/kg of caffeine and/or 12 grams of CitMal combined or in isolation before testing countermovement jump, maximal strength, and repetitions to failure (RTF) on squat and bench press. Perception of pain was rated after the RTF test. **Results:** No effect of supplementation in isolation and combined were found on the countermovement jump, one repetition maximum (1 RM) squat and pain perception. However, intake of Caffeine in isolation and combined with CitMal increased 1 RM bench press compared to placebo with 2.72% and 2.54%, respectively (ES Caffeine: 0.12/0.13; ES Caffeine & CitMal: 0.13/0.17). In addition, caffeine supplementation increased RTF by 18.66% for squat (ES:0.79/0.38) and by 9.46% for bench press (ES: 0.44/0.62). Similarly, ingestion of caffeine in combination with CitMal increased RTF by 18.60% for squat (ES:0.46/0.50) and by 9.30% for bench press (ES:0.52/0.11). No effect was observed with CitMal in isolation. **Conclusion:** Seven reported adverse events, of which 5 was in women. Both caffeine in isolation and combined with CitMal increased RTF and 1 RM bench press. No effect was observed in squat 1 RM, CMJ and pain perception for any of the supplements. The combination of supplements did not yield a performance benefit compared to only caffeine for any of the outcomes.

Introduction

Caffeine is a highly popular ergogenic supplement amongst recreational exercisers and athletes and is the most widely used legal drug in the world (Aguilar-Navarro et al., 2019). Previous research reveals that caffeine ingestion, usually in doses from 3 mg/kg to 6 mg/kg body weight (bw), can increase strength performance measured as maximal strength, power, and muscular endurance (Grgic, 2021; Grgic et al., 2019, 2020), together with reducing subjective ratings of perceived exertion (RPE) during exercise (Astorino et al., 2012; Doherty & Smith, 2005; Duncan et al. 2011; Grgic, 2021; Sawynok, 1998; Tarnopolsky, 2008). Two of the performance enhancing mechanisms of caffeine is thought to be the influence on adenosine receptor activity (i.e., central mechanisms), and excitation-contraction coupling (Gillum, 2013; Grgic et al., 2019; Mielgo-Ayuso et al., 2019; Trexler & Smith-Ryan, 2015). Caffeine has a similar molecular structure to adenosine where it can bind and act as an adenosine receptor antagonist. This leads to reduced pain and fatigue sensation, and increased readiness, which can lead to increased performance (Grgic, 2021). Excitation-contraction coupling (ECC) refers to electrical signals from the nervous system that releases calcium in the sarcoplasmic reticulum and results in muscle contraction (Calderón et al., 2014). However, this is currently only supported by in vitro studies and the dose required to see these effects in humans are believed to be 15- to 35- fold above reported physiological concentrations in humans, and normal dosages will assumably not lead to these peripheral effect (Neyroud et al., 2019). Thus, the central effect with the adenosine binding is likely the main cause of an ergogenic performance effect. Despite caffeine being widely researched as a stand-alone supplement, the effect of caffeine in combination with other supplements remains poorly understood.

Another supplement that has gained a lot of popularity in recent years is Citrulline Malate (L-Citrulline and malic acid). L- Citrulline is a non-essential amino acid that is primarily found in watermelon, cucumber and other melons (Figueroa et al., 2017). L-Citrulline serves as an precursor to L-Arginine (Rougé et al., 2007), where L-Citrulline is transported to the kidneys where it can be directly converted to L-Arginine (Windmueller & Spaeth, 1981). L-Arginine subsequently increases nitric oxide (NO) (Gonzalez & Trexler, 2020). One of the functions of NO is that it induces vasodilatation (expanding the blood vessels). Vasodilatation can affect exercise performance through reduced blood pressure, increased blood flow that may increase nutrient and oxygen delivery to the working muscle, and contribute to clearance of metabolic by-products (Gonzalez & Trexler, 2020). This could reduce the cost for ATP in a muscle

contraction, improve force production, improve calcium handling, and improved mitochondrial efficiency (Campos et al., 2018). Due to the low bioavailability of L-Arginine (Gonzalez & Trexler, 2020), supplementing with L-Citrulline is more efficient to increase L-Arginine in circulation, and it does so in a dose-dependent manner (Moinard et al., 2008). Thus, nitric oxide availability increases more after supplementing with L-Citrulline than L-Arginine directly (Bescós et al., 2009). Another benefit of L-Citrulline supplementation is that L-Arginine supplementation has shown to induce gastrointestinal issues at 13 grams (Grimble et al,. 2007), while L-Citrulline supplementation seems to be well-tolerated at doses up to 15 gram (Moinard et al., 2008).

Citrulline is often combined with malic acid as a supplement (Citrulline Malate [CitMal]). Supplementing with malic acid is proposed to increase the oxidative ATP production (Bendahan et al., 2002), and hypothesized to increase performance. However, the performance enhancing effects of malic acid in isolation is still unknown. Nevertheless, supplementing with CitMal can induce a small acute ergogenic effect on strength and power performance (Trexler et al., 2019), repetitions to failure (Vårvik et al., 2021), and reduced post-exercise rating of perceived exertion and muscle soreness (Rhim et al., 2020). Normally 8 grams of CitMal is used to affect acute performance (Vårvik et al., 2021), it remains to be investigated if a higher dose can cause more performance benefits (Gought et al,. 2021). The potential strength and power performance benefits of caffeine seems to be more potent than CitMal, and the available evidence of performance enhancing effects with CitMal supplementation is more mixed than caffeine (Gough et al. 2021.). Hence, the strength and power performance potential of CitMal is not yet clear and needs to be further explored in isolation and combined with other supplements.

The use of supplements containing a combination of various proposed ergogenic ingredients have increased in recent years for both athletes and recreational trainers (Maughan et al., 2007). As such, Caffeine and CitMal are often combined in a pre-made pre-workout supplement, or in a self-made pre-workout (Harty et al., 2018). Notably, there may be various interactions that hampers or attenuate performance when supplements are combined. As an example, the postulated main mechanism underlying the performance enhancing effects of CitMal is vasodilatation and consequently an increase in blood flow (Trexler et al., 2019a). Contrarily, caffeine can induce vasodilatation or vasoconstriction, depending on the dose and binding affinity (Higashi, 2019). When Caffeine binds to adenosine A2 receptors it can stimulate the production of nitric oxide, which subsequently induces vasodilatation and increased blood flow (Nowaczewska et al., 2020). On the contrary, binding to adenosine A1

receptor decreases nitric oxide release, which results in vasoconstriction and reductions in blood flow (Nowaczewska et al., 2020). The mechanisms underlying ergogenic effects of Caffeine and CitMal and the potential interactions between them remains to be elucidated, but co-ingestion could potentially both attenuate and hamper the performance enhancing effects of either supplement ingested in isolation. To the authors knowledge, no previous study has investigated the efficiency of Caffeine and CitMal combined to enhance strength and power performance.

Aims and hypotheses

The primary aim of this study was to compare the effect of 5 mg/kg per body mass of caffeine vs. 12 grams of Citrulline Malate vs. 5 mg/kg caffeine and 12 grams Citruline Malate combined, on maximal strength, repetitions to failure and countermovement jump performance in resistance trained males and females. In addition to examine the effect of these supplementations on pain perception after the repetitions to failure tests.

Due to potential synergistic effects of caffeine and CitMal supplementation, we hypothesized that co-ingestion of caffeine and CitMal would enhance strength and power measurements more than caffeine and CitMal ingested in isolation. We also hypothesized that caffeine would enhance maximal strength, repetitions to failure and countermovement jump performance more than placebo and CitMal in isolation, while CitMal would enhance the repetitions to failure tests compared to placebo.

Methods

Study design

A randomised, double-blind, placebo-controlled, crossover trial (Figure 1) was used to investigate the effect of caffeine and CitMal in isolation and combined on maximal strength, repetitions to failure, countermovement jump height and pain perception. Participants were familiarized to all procedures, were instructed to refrain from caffeine, alcohol and training 24-hours prior to every test session, which is deemed to be sufficient to avoid potential confounding by prior caffeine ingestion (Graham, 2001). All participants recorded a 24-hour diet log the day prior to testing and a weekly caffeine log. The food log was repeated at every trail to reduce variation in energy intake and hydration level. The participants attended four

test trials where they received either placebo (Fun Light zero calorie), 5 mg/kg caffeine, 12 grams of CitMal or the respective dosages of caffeine and CitMal combined, mixed in 500 mL non-caloric cordial. The supplementations at all four conditions were administered 60 minutes before initiation of the testing protocol. All test trials were separated by minimum 72 hours to ensure treatment washout and sufficient recovery. The order of supplementation at each of the cross-over trials were counterbalanced and randomized. Body composition was assessed with a Tanita bioelectrical impedance device (MC-780MA).

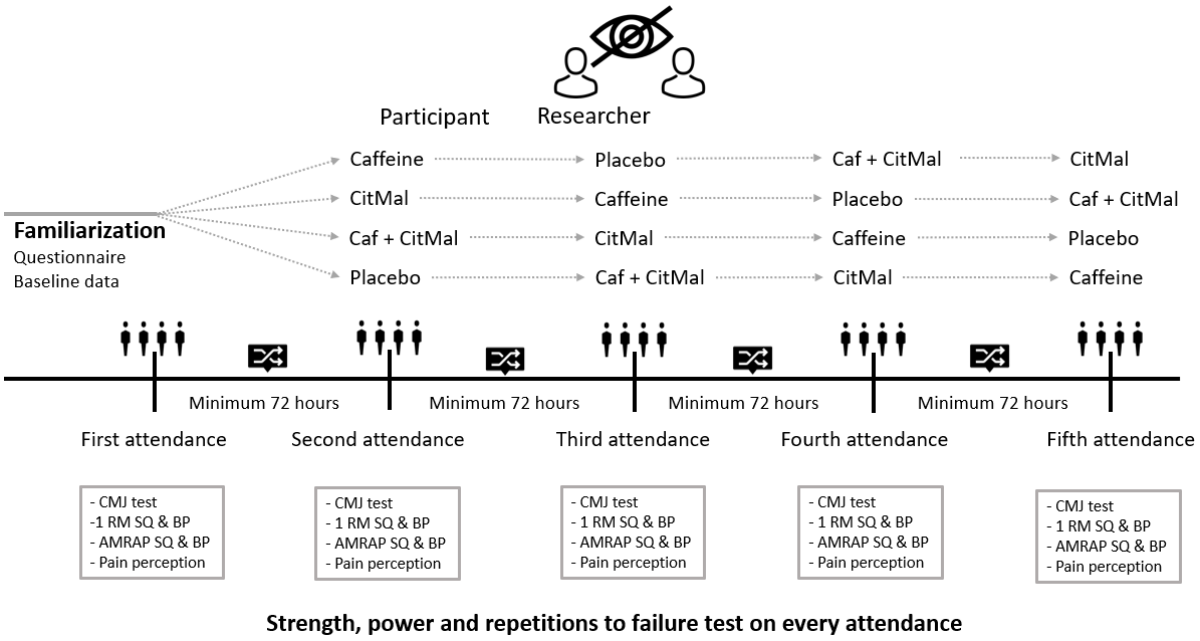

Figure 1 *Overview of the study design. CMJ = countermovement jump; RM = repetitions maximum; SQ = squat; BP = bench press; AMRAP = as many reps as possible; PP = pain perception*

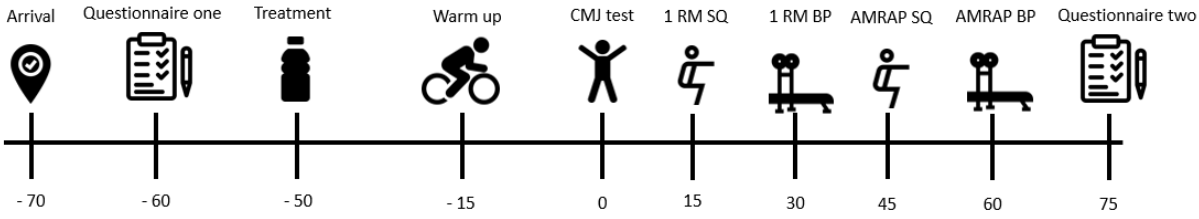

Figure 2 *Timeline of testday. Questionnaire one was only given on familiarization (personalia, weight, food log, caffeine log, training experience). Questionnaire two were question about treatment received. CMJ = countermovement jump; RM = repetition maximum; SQ = squat; BP = bench press; AMRAP = as many reps as possible*

Participants

40 healthy resistance trained males (n=20) and females (n=20) with no known medical condition and injuries were recruited. Resistance-trained individuals were recruited following these inclusion criteria: (a) 18-45 years old; (b) resistance trained for minimum 12 months and currently resistance training (> 2 session per week); (c) able to perform the barbell back squat and bench press with 120 and 100 % of body mass for males and 100 and 70 % of body mass for women, respectively; (d) familiar with back squat and bench press and training both minimum once a week. Participants were excluded if they were smoking, pregnant or lactating. Moreover, participants who knew they were adversely affected by caffeine and/or CitMal were excluded, used medicines and/or had recent injuries who could hamper the testing. Note, participants who could perform some parts of the testing were included, i.e., lower body injury who hindered maximum performance on the back squat, but not the bench press (n=4). Participants signed a written consent and completed a questionnaire about training experience. The study was performed in accordance with the Helsinki Declaration and approved by the Norwegian Center for Research Data (NSD) (project nr: 445723) and by the local ethics committee at the University of Agder (Kristiansand, Norway).

Table 1 *Participant characteristics for those who completed the study.*

	MEN (N=18)	**WOMAN (N=17)**	**ALL PARTICIPANTS (N=35)**	
	Mean ± SD	Mean ± SD	Mean ± SD	Range
AGE (YRS)	23.8 ± 3.4	22.1 ± 2.9	23 ± 3.2	18 - 30
HEIGHT (CM)	182.x ± 7.3**	166.1 ± 3.1	174.5 ± 9.9	160 - 200
BODY MASS (KG)	87.2 ± 12.5**	65.5 ± 5.6	76.9 ± 14.7	58.8 - 118.8
FAT-FREE MASS (KG)	67.4 ± 6.1**	46.3 ± 3.6	57.2 ± 11.8	39.8 - 80.3
FAT MASS (%)	18.2 ± 6.6*	25.1 ± 6.0	21.9 ± 7.1	9.9 - 35.1
RESISTANCE EXERCISE EXPERIENCE (YRS)	4.0 ± 2.2	4.7 ± 2.3	4.3 ± 2.3	1.0 - 10
SQUAT EXPERIENCE (YRS)	2.7 ± 2.2	3.1 ± 1.6	2.9 ± 1.9	1.0 - 9.5
BENCH PRESS EXPERIENCE (YRS)	3.0 ± 2.2	3.1 ± 1.8	3.1 ± 2.0	0.5 - 9.5
RE FREQUENCY (SESSIONS/WK)	4.6 ± 1.5	4.6 ± 1.5	4.6 ± 1.5	1 - 7
SELF-REPORTED 1 RM SQUAT (KG)	143.5 ± 38.3**	85.1 ± 19.9	115.9 ± 42.5	50 - 220
SELF-REPORTED 1 RM SQUAT (KG/BW)	1.6 ± 0.3*	1.3 ± 0.3	1.5 ± 0.4	0.7 - 2.4

SELF-REPORTED 1 RM BENCH PRESS (KG)	113.3 ± 28.1**	56.2 ± 11.3	86.3 ± 36.1	35 - 165
SELF-REPORTED 1 RM BENCH PRESS (KG/BW)	1.3 ± 0.3**	0.9 ± 0.2	1.1 ± 0.3	0.6 - 1.8
ENERGY (KCAL)	2616 ± 522**	1787 ± 365	2224 ± 614	1138 - 3858
PROTEIN (GR/DAY)	142 ± 41	110 ± 27	127 ± 38	70 - 210
CARBOHYDRATE (GR/DAY)	314 ± 75**	199 ± 60	260 ± 90	83 - 462
FAT (GR/DAY)	88 ± 28*	61 ± 22	75 ± 29	22 - 165
CAFFEINE (MG/DAY)	332 ± 126*	206 ± 124	273 ± 139	25 - 487
CAFFEINE (MG/KG/DAY)	3.8 ± 1.4	3.2 ± 2.x	3.5 ± 1.7	0.4 - 7.5
NUMBERS OF DAYS W CAFFEINE	6.4 ± 1.3	5.x ± 1.9	5.8 ± 1.8	1.5 - 7

* = indicates a significant difference between men and woman on a $p<0.05$ level, * = indicates a significant difference between men and woman on a $p<0.01$ level. 1 RM = 1 repetition maximum; MG/DAY = mg pr kg body weight pr day; GR/DAY = gram per day; KG/BW = kilogram pr kg body weight; RE = resistance exercise; Numbers of days w caffeine = numbers of days with caffeine consumption on the weekly log

Supplementation

The supplement conditions consisted of 5 mg/kg of caffeine as anhydrous powder (Caffeine, ReagentPlus, Sigma-Aldrich), 12 grams of Citrulline Malate powder with a ratio between L-Citrulline and Malate of 2:1 (Citrulline Malate, Trade Ingredients), the same dosages of Caffeine (5 mg/kg) and CitMal (12 grams) combined, or placebo (Fun Light© and water). All treatments were blended with 300 ml non-caloric Fun Light© and 200 ml water and had similar colour, taste, and volume. Participants were provided the drink in bottles 60 minutes prior to testing, and had to complete the drink within 1 minute to ensure all participants reached peak or close to peak plasma levels of caffeine and CitMal when the tests were initiated (Echeverri et al., 2010; Moinard et al., 2008) Bottles with supplements were shaken between every sip, and were instructed to drink all the liquid within three sips. The 60 min countdown started as soon the bottle was empty. An independent researcher who did not participate in other measurements or analysis randomized treatment order, mixed, and administered the treatments, and held the randomization of supplements until the end of the study. After every test, participants were asked which supplement they though they received. A standard question was given to all directly after the last repetitions to failure (RTF) test: “Which supplement do you think that you received? Placebo, only caffeine, both caffeine and citrulline malate, or only citrulline malate?”. The they had to respond within 10 seconds with no follow-up questions. They could guess the same supplement more than once but could not change earlier answers nor get to know earlier answers.

Adverse events

Participants were encouraged to contact the test leader if an event happened after they left the lab. An adverse event was problems that occurred from ingestion of treatment and throughout the test day. When an adverse events occurred, participant had to complete an *adverse events* protocol adopted from Pakulak et al., (2021) with a description of the event. The adverse event's relationship to the intervention (not related, unlikely, possibly, probably, definite), and how serious the adverse event was rated (life-threatening, required hospitalization, resulted in persistent disability, or non-serious), and its intensity (mild, moderate, severe, life threatening) were noted (Pakulak et al., 2021).

Measurements

Countermovement jump

The countermovement jump (CMJ) test was used to assess jump height (cm), maximal power (w), rate of force development (kN/s), and peak force (N/kg). Participants performed the CMJ on a force plate (Muscle lab, Ergotest Technology AS, Porsgrunn, Norway) with feet shoulder width apart and hands on the hips during the whole jump. Maximal vertical jumps were performed from an upright position with a self-selected dept. Feet had to be straight during the flight time because jump height was calculated with flight time. As a warm-up, the submaximal CMJ trials with approximately 50%, 75%, and 90% intensity were performed with 45 seconds breaks. Subsequently, participants rested 2 minutes before three maximal attempts were performed with 15 seconds between each attempt. Averages between all three jumps were used for statistical analysis.

1-repetition maximum

Participants completed a 1 RM test for both the squat and the bench press. The warm-up cConsisted of as many reps as preferred with the barbell, then 8 reps at 40% of estimated 1 RM, 6 reps at 60% of estimated 1 RM, 3 reps at 70% of estimated 1 RM and 2 reps at 80% of 1 RM (Gomo & Van Den Tillaar, 2016). After every successful 1 RM attempt, 4 minutes of rest were given, and the weight was increased with 0.25 kg to 5 kg (subjectively evaluated) until a final 1 RM was reached. Equipment used was a half rack (half rack easy 2.0, ata Group AS, Asker, Norway), calibrated (± 10 g) 20 kg barbell (ata Powerbar stainless steel 29mm, ata Group AS, Asker, Norway) and calibrated (± 10 g) plates from 0.25 kg to 50 kg (ata Powerlifting Steel Plate, ata Group AS, Asker, Norway). Participants had to perform the depth requirement set by International Powerlifting Federation (International Powerlifting Federation, 2021), which was

that the top surface at the hip joint should be below the knees in the bottom position. A test leader visually inspected the depth along with a rubber band that the participants could use as external feedback. Safety-pins as well as two experienced spotters were used under maximal attempts to ensure safety. In bench press, the elbows had to be fully extended at the completion of the lift to be an approved 1 RM. A pause on the chest at the bottom of the lift was not mandatory, but the shoes, butt and upper back had to be in touch with floor and bench throughout the lift. Stance width in the squat and grip width in the bench press were measured at familiarization, and participants had to adhere to it on all test trials. Equipment such as lifting belt, shoes, wrist wraps, knee sleeves and chalk were allowed, but participants had to use the self-selected equipment at all trials to ensure similar conditions.

Repetitions to failure and pain perception

Repetitions to failure were performed with 60% of the daily reached 1 RM (from measured 1 RM at each trial) for as many reps as possible (AMRAP). The repetitions were counted out loud from the test leader. No breaks were allowed between reps and commando was given from the test leader to ensure standardization between repetitions. Technical requirements were similar as the 1 RM tests. Failure was defined as not able to complete a full repetition without assistance or failing to keep up the standardized tempo set by the test leader on two repetitions. Meaning that the first repetition with too long pause (>1 sec) at the top resulted in a warning, and the next repetition pause between repetitions was deemed as repetition failure. Within 15 seconds of failure the participants had to rate their pain on a 11-point numerical rating scale (NRS) perceived pain score with the instructions that 0 points were equivalent to no pain and 10 points were their worst imaginable pain.

Statistical analyses

To check the normality, a Shapiro-wilk test was performed and the test revealed that the data were normally distributed, therefore, parametric tests were used. To assess trial differences in 1 RM, repetitions to failure, countermovement jump and pain perception, a one-way analysis of variance (ANOVA) with repeated measures (4 conditions) was conducted. If the assumption of sphericity was violated, the Greenhouse-Geisser adjustments of p-values are reported. When the ANOVA indicated a significant main effect or an interaction effect, the Sidak post hoc test was used. All results are presented as mean ± standard deviations or mean ± 95 % confidence interval. Effect sizes were evaluated with η_p^2 (partial eta squared), where <0.01 - 0.06 constitutes a small effect, 0.06 -0.14 a medium effect, and >0.14 a large effect. In addition, the effect size (*d*) was calculated for pairwise comparison according to Cohen

(Cohen, 1988). The magnitude of *d* was classified under the following thresholds, small ($0.2 \leq d \geq 0.5$), moderate ($0.5 \leq d \geq 0.8$), and large ($d \geq 0.8$). The alpha level of significance was set at $p<0.05$. Statistics were analyzed in SPSS version 27.0 (IBM Corp. Armonk, New York, USA).

Results

35 participants, 18 males and 17 females (age: 23.0 ± 3.2 years, 174.5 ± 9.9 cm, 76.9 ± 14.7 kg [mean ± SD]) completed all four trials and were included in the analysis (Figure 3). Four participants dropped out due to injury sustained outside the experiment and one was lost to follow up

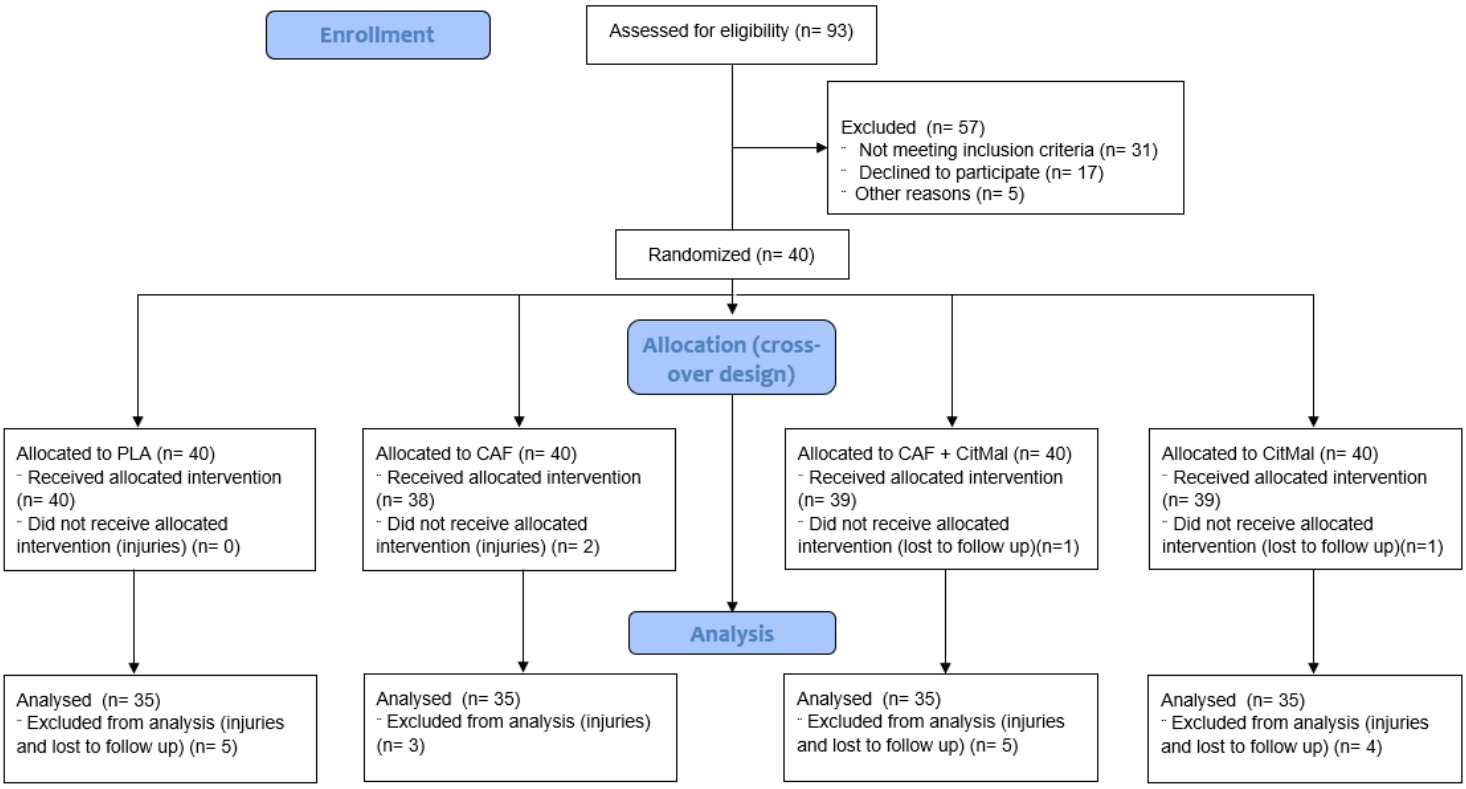

Figure 3 *Consort Flow Diagram for this within-subject trial. Diagram shows participant flow through each stage of the trial (enrolment, allocation, and analysis).*

Countermovement jump

No significant main effect was found for CMJ height, RFD, peak force, or peak power ($F < 0.59$, $p > 0.05$, $\eta^2 < 0.02$) (table 2 & Figure 6),

Table 2 Differences in countermovement jump between trials.

Condition	Compared to	Jump height (CM)		RFD (kN/s)		Force (N/kg)		Power (W/kg)	
		Mean 95% CI (LL, UL)	p-value	Mean 95% CI (LL, UL)	p-value	Mean 95% CI (LL, UL)	p-value	Mean 95% CI (LL, UL)	p-value
Placebo	Caffeine	-0.8 (-2.2, 0.6)	0.50	-0.0 (-1.2, 1.1)	1.00	-0.4 (-1.3, 0.6)	0.84	-0.1 (-0.5, 0.3)	0.94
	Caffeine + CitMal	-0.9 (-2.4, 0.6)	0.49	-1.2 (-4.8, 2.3)	0.91	-0.4 (14.6, 0.7)	0.87	-0.2 (-0.6, 0.2)	0.83
	CitMal	-0.4 (-1.6, 0.8)	0.94	0.3 (-0.8, 1.5)	0.95	0.2 (-0.7, 1.1)	0.98	-0.0 (-0.5, 0.4)	1.00
Caffeine	Placebo	0.8 (-0.6, 2.2)	0.50	0.0 (-1.1, 1.2)	1.0	0.4 (-0.6, 1.3)	0.84	0.1 (-0.3, 0.5)	0.94
	Caffeine + CitMal	-0.1 (-1.5, 1.3)	1.00	-1.2 (-4.6, 2.2)	0.91	-0.1 (-0.9, 0.8)	1.00	-0.0 (-0.4, 0.3)	1.00
	CitMal	0.4 (-1.2, 2.0)	0.56	0.4 (-0.8, 1.5)	0.93	0.6 (-0.2, 1.4)	0.19	0.1 (-0.3, 0.4)	0.99
Caffeine + CitMal	Placebo	0.9 (-0.6, 2.4)	0.49	1.2 (-2.3, 4.8)	0.91	0.4 (-0.7, 1.6)	0.87	0.2 (-0.2, 0.6)	0.83
	Caffeine	0.1 (-1.3, 1.5)	1.00	1.2 (-2.2, 4.6)	0.91	0.1 (-0.8, 0.9)	1.00	0.0 (-0.3, 0.4)	1.00
	CitMal	0.5 (-1.2, 2.2)	0.95	1.6 (-2.0, 5.2)	0.78	0.7 (-0.4, 1.8)	0.48	0.1 (-0.3, 0.6)	0.97
CitMal	Placebo	0.4 (-0.8, 1.6)	0.94	-0.3 (-1.5, 0.8)	0.95	-0.2 (-1.1, 0.7)	0.98	0.0 (-0.4, 0.5)	1.00
	Caffeine	-0.4 (-2.0, 1.2)	0.97	-0.4 (-1.5, 0.8)	0.93	-0.6 (-1.4, 0.2)	0.19	-0.1 (-0.4, 0.3)	0.99
	Caffeine + CitMal	-0.5 (-2.2, 1.2)	0.95	-1.6 (-5.2, 2.0)	0.78	-0.7 (-1.8, 0.4)	0.48	-0.1 (-0.6, 0.3)	0.97

CI = confidence interval; LL = lower limit (CI); UL = upper limit (CI); RFD = rate of force development.

Maximal strength

No significant main effect was revealed in 1 RM squat ($F < 1.95$, $p = 0.17$, $\eta^2 < 0.61$). A significant main effect was evident in 1 RM bench press a ($F < 4.56$, $p < 0.05$, $\eta^2 < 0.12$), where the Sidak post hock revealed ingestion of caffeine allowed participants to lift 2.72% more weight in 1 RM bench press than with placebo ($p \leq 0.01$). Furthermore, the combination of caffeine and CitMal allowed participants to lift 2.54% more weight in 1 RM bench press than with placebo ($p \leq 0.05$) (Table 3 & Figure 5).

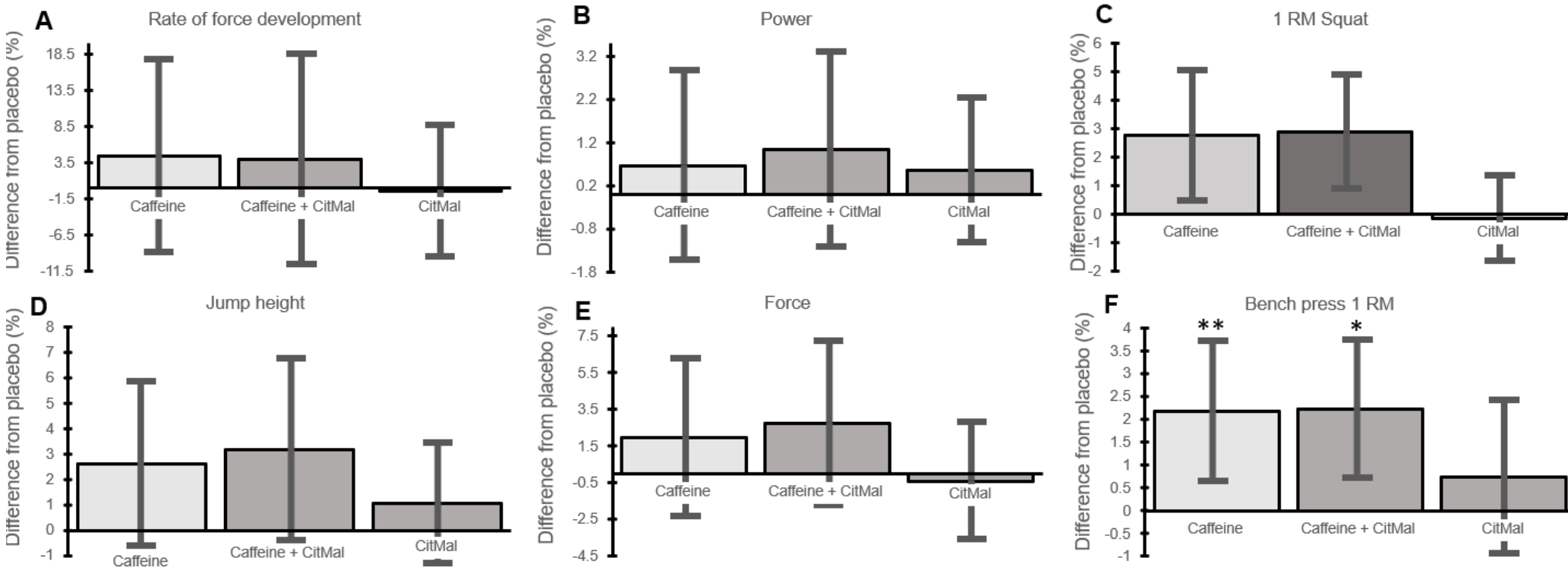

*Figure 4 Percentage difference compared to placebo. Mean ± 95%CI for (A) Rate of force development, (B) Power, (C) 1 RM Squat, (D), Jump height, (E) Force, and (F) Bench press 1 RM. 1 RM = 1 repetition maximum. * Indicates significant different from placebo ($p < 0.05$), and ** indicates significant differences from placebo ($p < 0.01$).*

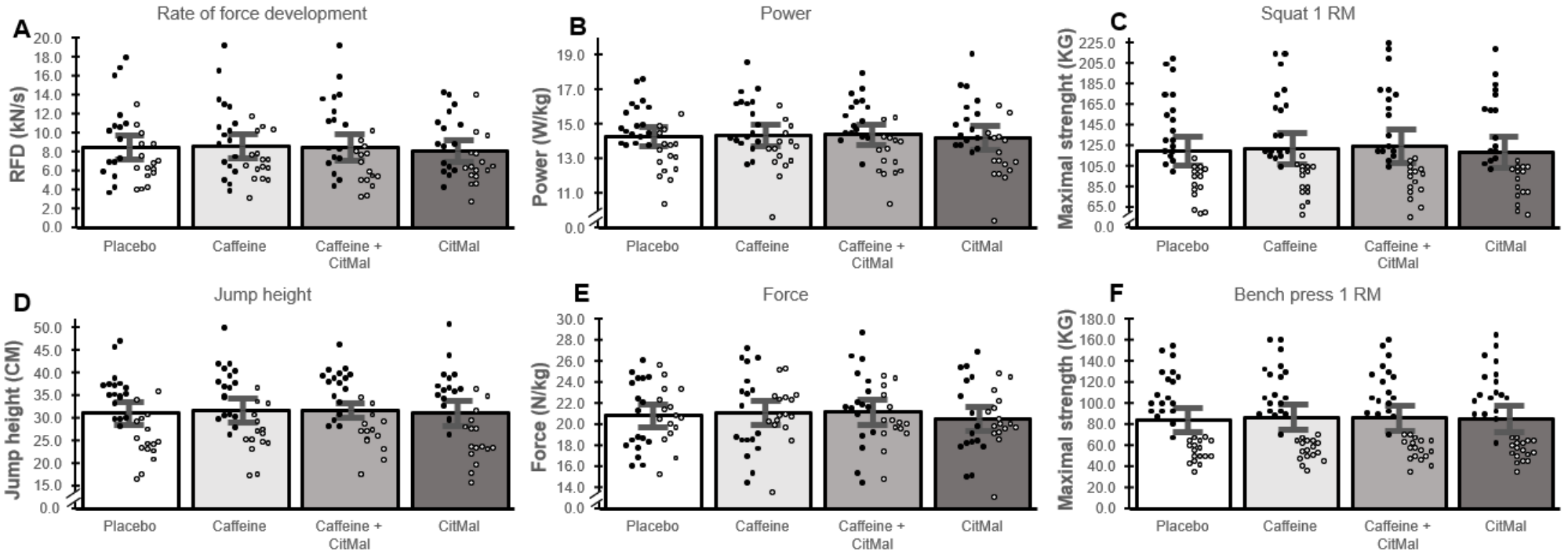

Figure 5 Group mean ± 95% confidence interval and individual data (black are men and white are women) for; (A) Rate of force development, (B) Power, (C) Squat 1 RM, (D) Jump height, (E) Force, and (F) Bench press 1 RM. 1 RM = 1 repetition maximum.

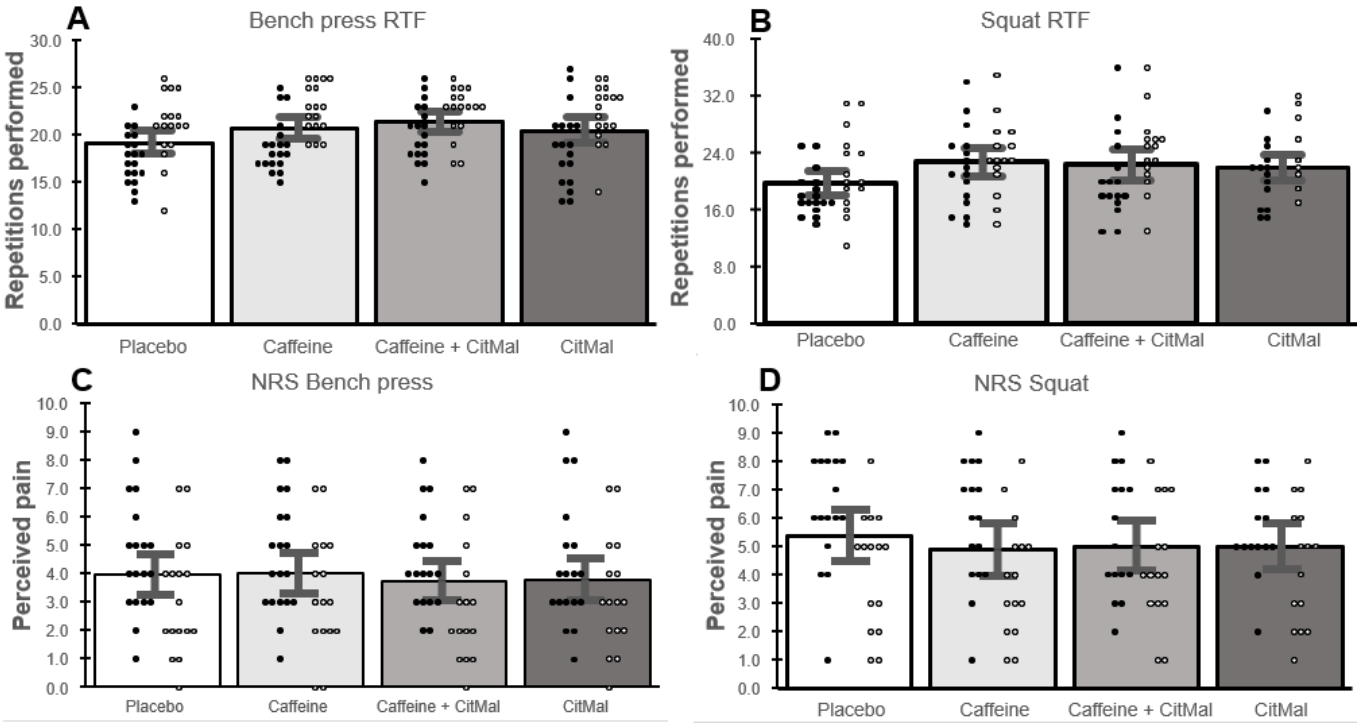

Figure 6 Group mean ± 95% confidence interval and individual data (black are men and white are women) for; (A) Bench press repetitions to failure, (B) Squat repetitions to failure, (C) Numerical rating scale (pain) bench press, and (D) Numerical rating scale (pain) for squat. NRS = numerical rating scale; RTF = repetitions to failure.

Repetitions to failure

A significant main effect occurred for AMRAP squat ($F < 5.40$, $p \leq 0.001$, $\eta^2 < 0.17$). The post hoc revealed that the caffeine condition completed 18.66% more repetitions than placebo condition ($p \leq 0.01$), and that the combination of caffeine and CitMal were better than placebo (18.60%) ($p \leq 0.05$). For bench press a significant main effect occurred for AMRAP ($F < 7.66$, $p \leq 0.001$, $\eta^2 < 0.18$). Sidak post hoc revealed a significant difference between placebo and caffeine in favor of caffeine (9.46%) ($p \leq 0.05$), and between placebo and caffeine and CitMal in favor of the latter group (9.30%) ($p \leq 0.001$).

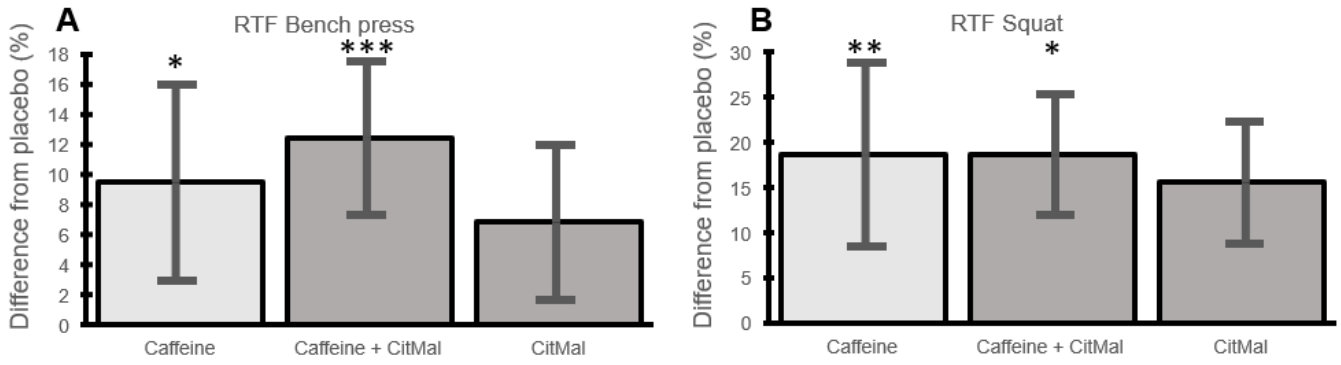

*Figure 7 Percentage difference compared to placebo. Mean ± 95% ± CI for (A) Repetitions to failure bench press, and (B) Repetitions to failure squat. * Indicates significant different from placebo (p < 0.05), ** indicates significant differences from placebo (p < 0.01), and *** indicates significant differences from placebo (p < 0.001).*

Table 3 Results from 1 RM and RTF test. P-value, lower- and upper 95% confidence interval. For 1 RM the mean difference are kilograms and for RTF the mean difference is number of repetitions.

Group	Compared with	1 RM Squat		1 RM Bench Press		RTF Squat		RTF Bench Press	
		Mean 95% CI (LL, UL)	p-value	Mean 95% CI (LL, UL)	p-value	Mean 95% CI (LL, UL)	p-value	Mean 95% CI (LL, UL)	p-value
Placebo	Caffeine	-2.4 (-4.9, 0.2)	0.07	-2.3 (-4.0, -0.5)	**<0.01****	-3.0 (-5.1, -0.9)	**<0.01****	-1.5 (-2.9, -0.0)	0.04*
	Caffeine + CitMal	-4.7 (-11.0, 1.5)	0.22	-1.8 (-3.6, -0.2)	0.02*	-2.5 (-4.8, -0.2)	**0.03***	-2.1 (-3.4, -0.8)	**<0.01*****
	CitMal	-2.6 (-9.1, 3.9)	0.84	-0.9 (-2.9, 1.2)	0.81	-1.9 (-4.0, -0.3)	0.12	-1.1 (-2.5, 0.3)	0.17
Caffeine	Placebo	2.4 (-0.2, 4.9)	0.07	2.3 (0.6, 4.0)	**<0.01****	3.0 (0.9, 5.1)	**<0.01****	1.5 (0.0, 2.9)	0.04*
	Caffeine + CitMal	-2.4 (-8.6, 3.9)	0.87	0.4 (-0.9, 1.8)	0.95	0.5 (-1.6, 2.7)	0.98	-0.7 (-1.8, 0.5)	0.49
	CitMal	-0.3 (7.3, 6.7)	1.00	1.4 (-0.9, 3.8)	0.46	1.2 (-1.1, 3.4)	0.63	0.4 (-1.3, 2.0)	0.99
Caffeine + CitMal	Placebo	4.7 (-1.5, 11.0)	0.22	1.9 (0.2, 3.6)	**0.02***	2.5 (0.2, 4.8)	0.03*	2.1 (0.8, 3.4)	**<0.01*****
	Caffeine	2.4 (-3.9, 8.6)	0.87	-0.4 (-1.8, 1.0)	0.95	-0.5 (-2.7, 1.6)	0.98	0.7 (-0.5, 1.8)	0.49
	CitMal	2.1 (-0.7, 4.9)	0.23	1.0 (-1.1, 3.1)	0.73	0.6 (-2.1, 3.4)	0.99	1.0 (-0.3, 2.4)	0.24
CitMal	Placebo	2.6 (-3.9, 9.1)	0.84	0.9 (-1.2, 2.9)	0.81	1.9 (-0.3, 4.0)	0.12	1.0 (-0.3, 2.5)	0.17

	Caffeine	0.3 (-6.7, 7.3)	1.00	-1.4 (-3.8, 0.9)	0.46	-1.2 (-3.4, 1.1)	0.63	-0.4 (-2.0, 1.3)	0.99
	Caffeine + CitMal	-2.1 (-4.9, 0.7)	0.23	-1.0 (-3.1, 1.1)	0.73	-0.6 (-3.4, 2.1)	0.99	-1.0 (-2.4, 0.3)	0.24

CI = confidence interval; LL = lower limit (CI); UL = upper limit (CI); RTF = repetitions to failure; RM = repetitions maximum
* Indicates a significant difference ($p \leq 0.05$), ** Indicates a significant difference ($p \leq 0.01$), *** Indicates a significant difference ($p \leq 0.001$)

Pain perception

The one-way within subjects ANOVA showed no significant main effect of condition on pain perception on the AMRAP test squat ($F=0.73$, $p = 0.54$, $\eta^2=0.26$) nor for the AMRAP test bench press ($F=0.96$, $p = 0.42$, $\eta^2=0.28$).

Table 4 pain perception (NRS) in the NRS test in the back squat and bench press.

Condition	**Compared with**	**NRS - Squat**		**NRS – Bench press**	
		Mean 95% CI (LL, UL)	p-value	Mean 95% CI (LL, UL)	p-value
Placebo	Caffeine	0.4 (-0.4, 1.2)	0.64	-0.1 (-0.9, 0.7)	0.99
	Caffeine + CitMal	0.3 (-0.5, 1.1)	0.91	0.2 (-0.5, 1.0)	0.95
	CitMal	0.3 (-0.7, 1.2)	0.98	0.2 (-0.4, 0.9)	0.87
Caffeine	Placebo	-0.4 (-1.2, 0.4)	0.64	0.1 (-0.7, 0.9)	0.99
	Caffeine + CitMal	-0.1 (-0.8, 0.6)	0.99	0.4 (-0.3, 1.0)	0.65
	CitMal	-0.1 (-1.0, 0.7)	0.99	0.3 (-0.4, 1.1)	0.76
Caffeine + CitMal	Placebo	-0.3 (-1.1, 0.5)	0.91	-0.2 (-1.0, 0.5)	0.95
	Caffeine	0.1 (-0.6, 0.8)	0.99	-0.4 (-1.0, 0.3)	0.65
	CitMal	-0.0 (-0.6, 0.5)	1.00	0.0 (-0.6, 0.6)	1.00
CitMal	Placebo	-0.3 (-1.2, 0.7)	0.98	-0.2 (-0.9, 0.4)	0.87
	Caffeine	0.1 (-0.7, 1.0)	0.99	-0.4 (-1.1, 0.4)	0.76
	Caffeine + CitMal	0.0 (-0.5, 0.6)	1.00	0.0 (-0.6, 0.6)	1.00

CI = confidence interval; LL = lower limit (CI); UL = upper limit (CI); NRS = numerical rating scale

Pairwise effect sizes (d)

Table 5 Pairwise comparison for conditions

Outcome	Comparison	Cohen *d (pooled ES)*		Absolute mean difference (95% CI)
		Men	Woman	
1 RM Squat	Caffeine vs Placebo*	0.08	0.12	2.4 kg (0.5, 4.2)
	Caffeine vs Caffeine + CitMal	0.16	0.03	-2.5 kg (-6.9, 1.9)
	Caffeine vs CitMal	0.03	0.12	-0.3 kg (-5.3, 4.8)
	Caffeine + CitMal vs Placebo*	0.24	0.09	5.1 kg (0.6, 9.5)
	Caffeine + CitMal vs CitMal*	0.19	0.09	2.1 kg (0.1, 4.1)
	CitMal vs Placebo	0.05	0.01	2.6 kg (-2.1, 7.4)
1 RM Bench Press	Caffeine vs Placebo**	0.12	0.13	2.3 kg (1.0, 3.5)
	Caffeine vs Caffeine + CitMal	0.00	0.04	0.4 kg (-0.5, 1.4)
	Caffeine vs CitMal	0.03	0.07	1.4 kg (-0.3, 3.1)
	Caffeine + CitMal vs Placebo**	0.13	0.17	1.9 kg (0.7, 3.1)
	Caffeine + CitMal vs CitMal	0.03	0.11	1.0 kg (-0.5, 2.5)
	CitMal vs Placebo	0.09	0.06	0.9 kg (-0.6, 2.4)
AMRAP Squat	Caffeine vs Placebo***	0.79	0.38	2.9 kg (1.5, 4.3)
	Caffeine vs Caffeine + CitMal	0.24	0.13	0.8 kg (-0.7, 2.4)
	Caffeine vs CitMal	0.22	0.12	1.2 kg (-0.5, 2.8)
	Caffeine + CitMal vs Placebo**	0.46	0.50	2.4 kg (0.8, 4.0)
	Caffeine + CitMal vs CitMal	0.06	0.25	0.9 kg (-1.1, 2.8)
	CitMal vs Placebo*	0.65	0.28	1.9 kg (0.4, 3.4)
AMRAP Bench Press	Caffeine vs Placebo**	0.44	0.62	1.5 reps (0.7, 2.4)
	Caffeine vs Caffeine + CitMal**	0.52	0.11	-0.5 reps (-1.3, 0.2)
	Caffeine vs CitMal	0.00	0.21	0.4 reps (-0.7, 1.4)
	Caffeine + CitMal vs Placebo	0.96	0.51	2.0 reps (1.2, 3.0)
	Caffeine + CitMal vs CitMal	0.42	0.10	0.9 reps (-0.0, 1.8)
	CitMal vs Placebo	0.35	0.39	1.2 reps (0.3, 2.1)
Pain perception (NRS) - Squat	Caffeine vs Placebo**	0.28	0.14	-0.4 point (-0.9, 0.1)
	Caffeine vs Caffeine + CitMal**	0.09	0.24	-0.1 point (-0.5, 0.4)
	Caffeine vs CitMal	0.10	0.23	-0.1 point (-0.8, 0.5)
	Caffeine + CitMal vs Placebo	0.37	0.10	-0.3 point (-0.9, 0.2)
	Caffeine + CitMal vs CitMal	0.00	0.00	0.0 point (-0.4, 0.4)
	CitMal vs Placebo	0.43	0.09	-0.2 point (-0.9, 0.4)
Pain perception (NRS) – Bench Press	Caffeine vs Placebo**	0.00	0.10	0.0 point (-0.6, 0.6)
	Caffeine vs Caffeine + CitMal**	0.11	0.15	0.3 point (-0.1, 0.8)
	Caffeine vs CitMal	0.14	0.05	0.4 point (-0.2, 0.9)
	Caffeine + CitMal vs Placebo	0.10	0.05	-0.3 point (-0.8, 0.3)

	Caffeine + CitMal vs CitMal	0.05	0.10	0.0 point (-0.4, 0.4)
	CitMal vs Placebo	0.14	0.50	-0.2 point (-0.7, 0.2)

Abbreviations: 1 RM = 1 repetition maximum; CI = confidence interval. Significant differences between conditions are denoted by * (p<0.05), ** (p<0.01) and *** (p<0.001) (paired samples t-test)

Effectiveness of the blinding

Table 6 Percentage of correctly guessed treatment and ranked by how popular a guess was.

Received	Most guessed (%)	2nd most guessed	3rd most guessed	4th most guessed
Placebo	Placebo, 47.2%	Caffeine, 22.2%	CitMal, 19.4%	Caffeine + CitMal, 11.1%
Caffeine	Caffeine, 47.2%	CitMal, 22.2%	Placebo, 16.7%	Caffeine + CitMal, 13.9%
Caffeine + CitMal	CitMal, 34.3%	Caffeine + CitMal, 25.7%	Caffeine, 20.0%	Placebo, 20.0%
CitMal	Placebo, 40.0%	Caffeine, 22.9%	CitMal, 22.9%	Caffeine + CitMal, 14.3%

On average, participants correctly guessed 1.4 times out of possible 4. One woman guessed correctly with all four treatments.

Adverse events

Seven adverse events were reported. Six out of seven adverse events were reported as 'probably' when investigating the relationship to the supplements, and one participant was categorized as 'definite', one participant threw up 22 minutes after ingestion. Testing that day was terminated and successfully conducted another day. The six adverse events categorized as 'probably' were considered as 'non-serious. Three of the total six adverse events were categorized as 'mild', and four as 'moderate'. Notably, all seven adverse events were reported when participants received both caffeine and CitMal combined, and five out of the seven adverse events were reported by women.

Discussion

This is the first study to determine the effects co-ingestion of caffeine (5 mg/kg) and CitMal (12 gram) compared to either supplement in isolation or placebo. We hypothesized that co-ingestion of caffeine and CitMal would increase strength and power performance more than supplementing with caffeine and CitMal in isolation. However, no differences were detected in the countermovement jump test, nor for 1 RM squat. For 1 RM bench press a significant effect of the combination of caffeine and CitMal compared to placebo occurred.

We also hypothesized that supplementing with caffeine would enhance maximal strength and countermovement jump performance, and that supplementing with caffeine or CitMal alone would improve repetitions to failure and reduce pain perception, compared to placebo. We did not find any significant group effect of supplementing with caffeine alone for countermovement jump and strength performance. However, ingestion of caffeine lead to an increase in repetitions to failure test for both squat and bench press compared to placebo. No effect of supplementing with CitMal alone for RTF. Lastly, no effect of supplementing with CitMal or caffeine in isolation for pain perception.

Jump and power performance

Caffeine consumption alone and in combination with CitMal did not influence jump height in our study. The lack of effect following the supplementations on CMJ measurements is contrary to other research on caffeine (Grgic, 2021; Grgic & Mikulic, 2022), and CitMal (Trexler et al., 2019a). This is contrary to meta-analysis on caffeine's effect on jump height in team and combat sports (Diaz-Lara et al., 2022; Salinero et al., 2019; Tan et al., 2021) and in non-team based population (Grgic et al., 2018). The included studies in the respective meta-analysis used 3-6 mg/kg in all studies bar two who used 2mg/kg and 9 mg/kg. A potential benefit in jump test for the included participants in the "sports" meta-analysis are their athletic background. Especially in Tan et al., (2021) where the participant were basketball players. This analysis reached and ES of 0.19 (Glass Delta), Diaz-Lara et al. (2022) reached an ES of 0.38 and Salinero et al. (2019) reached an ES of 0.19. This is greater than the ES in this present study (0.05 for male and 0.21 for women). Participants in the studies included in the meta-analysis could be more familiar with general jumping and be more exposed to specific jumping training and testing which could reduce variation in jumping and increase performance due to better technique. The ES from the "non-sports" meta-analysis (Grgic et al., 2018) were 0.17 (Hedges

g) which is lower than the "sports" analysis, which could indicate lack of familiarity for the test. Participants in our study were not familiar with this type of testing either.

We found no effect of caffeine on rate of force development (RFD). Caffeine has shown an significant effect on RFD when tested during resistance exercise (Grgic & Mikulic, 2021), but no difference when recorded during CMJ test. Our results are in line with the results from Grgic & Mikulic meta-analysis (Grgic & Mikulic, 2021). Moreover, our ES were 0.02 and 0.04 for men and women on RFD, other studies ES for RFD on CMJ test were 0.25 (Bloms et al., 2016), 0.24 (Zbinden-Foncea et al., 2018) and 0.00 (Merino Fernández et al., 2021). Two of the compared studies used the same dosages as our study, 5mg/kg (Bloms et al., 2016; Zbinden-Foncea et al., 2018) and 3 mg/kg in the last study (Merino Fernández et al., 2021). None of the studies, and ours found a significant effect of the supplements. Other research indicates that there could be and dose-response relationship between caffeine and activities with short contraction time. A study from Pallares et al (2013) showed a dose-response relationship for power and mean propulsive velocity were performance increased from placebo to 3 mg/, to 6 mg/kg and with peak performance at 9 mg/kg (Pallarés et al., 2013). Our study and the other mentioned used a considerably lower dosage (3-5 mg/kg) which could explain the null findings. A proposed determinant for RFD is motor unit recruitment (Aagaard et al., 2002), and caffeine has improved motor unit recruitment in earlier studies (Black et al., 2015). In this study, motor unit recruitment of the knee extensor increased during maximal contractions with 5 mg/kg of caffeine compared to placebo (Black et al., 2015). A possible explanation for the discrepancy between that study and our study could be that CMJ test is more complex than a knee extensor test. As mentioned, the meta-analysis by Grgic & Mikulic found and effect of caffeine on RFD during resistance training as the study by Black et al (2015) mimics, but not CMJ as we used. Moreover, the daily caffeine consumption in Black et al (2015) were <40 mg/day and 272 mg/day in ours. It hypothesized that participants that are habituated to caffeine could respond different from non-habituated participants (Filip et al., 2020). Lastly, the test-retest reliability of RFD performed as CMJ is much less reliable than jump height with at coefficient of variation (CV) from 13% to 24% (Hori et al., 2009; Souza et al., 2020).

Contrary to our hypothesis, we did not find any effect of caffeine or caffeine in combination with CitMal for power. Unlike our study, most of the studies who explored caffeine's effect on power used dynamic strength exercises with different loads (percentage of 1 RM) instead of CMJ. Other studies who investigated this have used loads between 30% and 90% of 1 RM (Degrange et al., 2019; Venier et al., 2019; Wilk et al., 2019). In the study from Wilk et al.,

(2019) they gave participants, placebo, 3mg/kg, 6mg/kg and 9 mg/kg. They recorded peak power across three sets of bench press and none of the treatment groups achieved statistically significant better results with caffeine compared to placebo. However, a dose-response relationship between dosage and ES occurred and all dosage resulted in higher ES than our study (0.48, 0.72 and 0.77 vs. 0.07 male and 0.15 female). In Vernier et al (2019) they assessed mean power with isokinetic dynamometer. Participants received a gum containing 300mg caffeine which translates to 3.16 mg/kg (mean body mass of 83 kg). Ingestion of caffeine increased mean power in the knee extensors at an angular velocity of 60 °·s−1 and 180 °·s−1, but not in the knee flexors at the same velocity. The ES in this study were between 0.09 and 0.30. Degrange and colleagues (2019) gave participants 6 mg/kg of caffeine and tested mean power output in the back squat and bench press. They found a significant differences for both conditions with an ES of 0.24 in the bench press and 0.71 in the squat. Its hypothesized that percentage of 1 RM could influence the effect of caffeine, where the effect is more pronounced at a higher relative intensity (Grgic et al., 2018). In the dose-response study (Wilk et al., 2019) they used 50% of 1 RM, and failed to detect significant differences at 3mg/kg, 6mg/kg and 9 mg/kg, but Degrange et al., (2019) found a significant effect of 6 mg/kg on 80% of 1 RM in the bench press. This confirms the hypothesis regarding relative intensity and effect of caffeine. Our results are in line with that due to only using body weight. Another possible explanation for our null findings is the lack of standardized test time (Mora-Rodríguez et al., 2012).

We hypothesized that CitMal would not enhance jumping and power performance compared to placebo, nor would the combination of caffeine and CitMal enhance the performance more than caffeine in isolation. Our results confirmed that. The primary mechanism of CitMal are vasodilatation which could lead to improved blood (Gonzalez & Trexler, 2020). To enhance performance on CMJ test, rapid force production is necessary, as the main effect of CitMal is on prolonged exercises and performance benefit on short burst exercises should be trivial. This is confirmed in a meta-analysis from Trexler at al., (2019) who found and ES of 0.20 which is equivalent to small (Cohen, 1988), but they included a wide variety of power outcomes like squat, bench press and cycling.

Strength performance

In the present study, both caffeine alone and caffeine + CitMal increased maximal strength compared to placebo. The ergogenic effects of caffeine on maximal dynamic strength is well established (Grgic, 2021, 2022; Grgic et al., 2019). Earlier meta-analyses have demonstrated

effect sizes of 0.16-0.20 (Grgic, 2021, 2022; Grgic et al., 2019; Grgic, Grgic, et al., 2020) , which are somewhat in line with the present study who found an non-significant ES of 0.08 (men) and 0.12 (woman) for 1 RM squat, and 0.12 and 0.13 for 1 RM bench press. The ES in our study can be considered as "trivial". The mean change was 2.4 kg in the squat and 2.3 kg in the bench press. From practical perspective this could be considered as small. Those differences could be valuable for athletes in strength-based sports like powerlifting. Small increases could be the difference between medal or not. In our study, a few participants lifted above 200 kg in the squat and above 140 kg in the bench press. None of the lifters were competitive powerlifters, but such numbers are similar to numbers observed in national-level powerlifters (Bjørnsen et al., 2019).

There are a few previous studies with similar caffeine supplementation dosages as the present study. Filip-Stachnik et al (2021) gave participants 6 mg/kg and reached an significant ES of 0.28 in the bench press, Grgic et al (2020) gave participants 2, 4 and 6 mg/kg and reached an non-significant ES of -0.03 (2mg/kg), 0.04 (4mg/kg), and 0.06 (6mg/kg) for bench press and 0.13 (2mg/kg), 0.07 (4mg/kg), and 0.06 (6mg/kg) for squat (Grgic et al., 2020), whereas Norum et al observed an ES of 0.18 (bench press) and 0.27 (squat). with 4 mg/kg of caffeine in trained females (Norum et al., 2020). Our results somewhat in line with previous results. The ES for men in our study were 0.08 and 0.12 for squat and bench press respectively. This corresponds well with the results form Grgic et al (2020) on both the 4mg/kg dosage and 6mg/kg dosage as both studies ES are considered as "trivial". The ES for women in our study were 0.12 and 0.13 for squat and bench press respectively. This is lower than the ES from Filip-Stachnik et al (2021) where the participants was women and performed bench press. Although, in the latter study the ES of 0.28 was with 6mg/kg of caffeine compared to our 5 mg/kg. In the same study, participants also received 3 mg/kg where the ES was 0.11 (Filip-Stachnik et al., 2021) which indicates that there could be an dose-response relationship. Grgic et al (2020) observed a dose-response relationship for bench press and caffeine consumption. Furthermore, women in Filip-Stachnik et al (2021) were classified as habitual caffeine consumers with an average caffeine consumption of 5.8 mg/kg pr day, which is far greater than 3.2 mg/kg pr day for women in our study. There is mixed research regarding habitual vs. non-habitual caffeine consumer (Grgic, 2021), but a limitation to this field is the discrepancy in classifying participants as habitual or non- habitual (Filip et al., 2020). Based on this we could only speculate if habituation affects results. Our results indicates that caffeine could lead to a small ergogenic effect for maximal strength.

CitMal alone did not influence maximal strength, which is in line with (Aguiar & Casonatto, 2021; Gough et al., 2021), but contrary to Trexler et al meta-analysis (2019). The body of evidence regarding CitMal, and maximal strength are sparse. A newly published meta-analysis (Aguiar & Casonatto, 2021) found no effect of CitMal supplementation on muscle strength (ES 0.17 for upper body and 0.06 for lower body). One should be careful with the interpretation due to low number of studies included (n=4). A possible explanation for the lack of effect from CitMal on maximal strength, could be that the ergogenic effect of CitMal is more advantageous on longer durations. It seems that CitMal`s effect have more metabolic- and less neural effects than caffeine. Acute maximal strength such as 1 RM are likely more dependent on neural factors (Del Vecchio et al., 2019), and may explain the null findings on strength from supplementing with CitMal. The present results indicates that caffeine enhance 1 RM performance, but CitMal alone does not. Moreover, contrary to our hypothesis the combination of caffeine and CitMal did not enhance maximal strength more than caffeine alone in the main analysis, but for the ES for Caffeine + CitMal vs. placebo were higher than caffeine vs. placebo for men in the squat, 0.24 vs 0.08. This could suggest that a combination could yield a benefit. Interestingly, our results that indicated a benefit in the lower limb muscle (squat) and not upper body muscles (bench press) is contrary to the sub-analysis from Aguiar & Casonatto (2021), they found a higher ES for upper body (0.17) than lower body (0.06), but only two studies were included in each analysis. The discrepancy could be explained with dosages, we used 12 grams of CitMal and the included studies in the meta-analysis used 2 to 8 grams and used isometric test compared to dynamic test in our study. We did not detect such differences in the main analysis nor for women.

Muscular endurance

Caffeine alone, and caffeine and CitMal co-ingested, improved repetitions to failure performance compared to placebo (ES male 0.79 and 0.44, ES woman 0.38 and 0.62 for caffeine alone and ES male 0.46 and 0.96, ES woman 0.50 and 0.51 for co-ingestion in the squat and bench press respectively). Those results confirm our hypothesis. Our ES for muscular endurance is higher than previous meta-analysis on the topic which recorded ES of 0.28 (Warren et al., 2010) and 0.25 (Grgic & Del Coso, 2021). The meta-analysis from Warren et al (2010) included a wide range of *muscular endurance* test, isometric contractions for as long as possible, maximum number of contractions or work done with peak force, and maximum number of contraction with isokinetic or isotonic resistance (Warren et al., 2010).

This does not translate perfect to our repetitions to failure test. If we compare our study to a few of the included studies with similar protocol they echo our results more than the meta-analysis. Astorino et al (2008) gave participants 6 mg/kg of caffeine and tested RTF on 60% of 1 RM in the bench press and leg press. The ES in that study were 0.36 and 0.12 for bench press and leg press respectively. Hudson et al (2008) gave participants 6 mg/kg of caffeine, and tested RTF test on leg extension on arm curl on a self-prescribed 10 RM weight. ES in this study ranged from 0.2 to 1.2 over the course of 4 sets of leg extension and between 0.12 and 0.59 for arm curl. Moreover, Williams and colleagues (2008) gave participants 300 mg of caffeine, which translates to an average consumption of 3.6 mg/kg before testing bench press and lat pulldown. RTF on both exercises were performed on 80% of their 1 RM, and the ES between placebo and caffeine were 0.82 for bench press and 0.62 for lat pulldown. The meta-analysis from Grgic and Del Coso (2021) were solely on women. Their main analysis reached an ES of 0.25 which lower than the results for women in our study. They performed sub-analysis of lower body (ES 0.43) and upper body (ES 0.20). Only the lower body analysis mimics our results (0.38). A challenge when comparing single studies to meta-analysis is the diversity in training/testing protocol and supplementation. Four of the included studies had quite similar protocol to this present study. Filip-Stachnik et al (2021) gave participants 6mg/kg and reached and ES of 0.33 on 50% of 1 RM bench press, Norum et al (2020) gave participants 4 mg/kg and reached an ES of 0.27 on 60% of 1 RM bench press, those results echoes ours. Furthermore, Goldstein et al (2010) used 6 mg/kg on 60% of 1 RM bench press and reached and ES of 0.02. A possible explanation or the discrepancy could be habituation to caffeine, this area is somewhat inconclusive (Grgic, 2021), but it could influence the results. In the Goldstein et al., (2010) 8 subjects consumed < 250 mg pr day and 7 consumed > 250 mg pr day. In our study 4 of the women consumed > 250 mg pr day and 12 < 250 mg day. This could indicate that the women from Goldstein et al (2010) were more habituated to caffeine than women in our study. Moreover, they only performed the bench press (Goldstein et al., 2010) compared to CMJ, squat and bench press in our study. This could indicate that the magnitude of effect is higher with more fatigue.

However, we did not detect an effect of CitMal alone on repetitions to failure performance. These findings are in contrast to a recent meta-analysis from (Vårvik et al., 2021), where they demonstrated that CitMal increased repetitions to failure with an average of 3 repetitions. However, some of the studies saw no differences (Vårvik et al., 2021). Supplementing with CitMal on repetitions to failure test are expected to yield a small benefit for repetitions to

failure, but smaller than supplementing with caffeine alone (Polito et al., 2016). The ES from Vårvik et al (2021) were 0.20 for the main analysis, 0.27 for lower and 0.17 for upper body. Our ES were 0.65 for men and 0.28 for women in the squat and 0.35 and 0.39 for men and women in the bench press. A plausible explanation for higher ES in our study could be the dosages. All included studies in the meta-analysis (Vårvik et al., 2021) used 8 grams of CitMal whereas we used 12 grams. In a dose-response study from Moinard and colleagues (2008) they saw a higher peak of citrulline concentration occur with ingestion of 15 grams compared to 10 grams (28.4% diff). One could speculate that a higher dose would yield a higher performance benefit. Moreover, they used only citrulline whereas we and the studies included in the meta-analysis used Citrulline and Malate. This highlights a bigger difference in pure Citrulline consumption and consequently citrulline concentration. Moreover, Moinard et al (2008) observed a rapid decline in performance independent of dosages (2, 5, 10, and 15 grams) which could indicate that a longer duration on the training/testing could need higher dosage to sustain adequate dosages for all exercises/tests. The difference between placebo and CitMal were 2.1 repetitions for squat and 1.3 for the bench press, this is supported by Vårvik et al. (2021) who could not detect a differences between CitMal and placebo in the sub-analysis for lower- and upper body. In further support of this, a previous a review from Trexler et al., (2019) also concluded that one should expect a small advantage when supplementing with CitMal. The results from the present study are somewhat in line with that, and the small difference could be explained by dosages as prolonged activities like RTF, the body are more dependent on the phosphagen system (PCr and ATP). The role of this system is to deliver energy substrate to working muscles. Therefore, it plausible to speculate that the performance enhancing effect of CitMal is improved PCr resynthesis, ATP production and increased blood flow (Bendahan et al., 2002; JM et al., 2020), and more could yield better resynthesis of PCr and ATP production.

We hypothesized that supplementing with caffeine and CitMal combined would enhance the ergogenic effect on repetitions to failure performance compared to ingesting each of them isolated. However, we could not detect a significant difference in the effect of caffeine compared to CitMal in repetitions to failure performance, but the effect sizes (*d*) were somewhat higher with caffeine alone (0.79 and 3.38 RTF squat, 0.44 and 0.62 RTF bench press) than CitMal alone (0.65 and 0.28 RTF squat, 0.35 and 0.39 RTF bench press). To the authors knowledge, no other studies have investigated the combination of Caffeine and CitMal. A potential synergistic effect could be caffeine's central effect and binding to the adenosine receptors which delays perceived fatigue and CitMal's effect on vasodilation and

blood flow. One should not rule out other potential and for the time being unknown mechanism. At this point this is only speculation and should be investigated directly to draw any meaningful conclusions.

Notably, a few studies have demonstrated relatively large effect on RTF- with Caffeine and CitMal together with other ingredients in multi-ingredient pre-workout supplements (Harty et al., 2018). Studies included in the review from Harty et al., (Harty et al., 2018) who included both caffeine and CitMal, reached effect sizes from 0.32 to 0.72 for the multi-ingredient pre-workout groups compared to placebo groups. These effect sizes are somewhat similar to repetition to failure effect sizes after supplementation CitMal and caffeine combined in present study (ES: 0.46-0.96). Little is still known about the interactions between ingredients in multi-ingredient supplement, and we did not observe an increase performance with CitMal, and caffeine combined, but a potential synergistic effect of CitMal and caffeine combined can still not be ruled out.

Pain perception

No effect on pain perception for caffeine, CitMal or caffeine and CitMal combined were observed in the present study. Previous research have demonstrated an effect of caffeine on pain perception with strength training and after a variety of other exercise modalities -(Myers et al., 1997)(Duncan et al., 2013; Ganio et al., 2011; Gliottoni & Motl, 2008)(Gliottoni & Motl, 2008) (Stadheim et al., 2015) (Maridakis et al., 2007). Moreover, the reduction in pain perception with caffeine is observed on a dose-dependent matter (Arazi et al., 2016; O'Connor et al., 2004). Our results disagree with (Arazi et al., 2016) who saw an significant effect of 5 mg/kg of caffeine on pain perception, but not on 2 mg/kg. Participants performed RTF on 60% of 1 RM leg press. Our results also disagree with Maridakis et al (2007) who saw lower pain intensity with caffeine after submaximal voluntary contractions. Participants received 5 mg/kg of caffeine. A possible explanation for the differences in results between the studies could be the training modalities. Caffeine is an adenosine antagonist and the release of adenosine is greater with inflammation, and eccentric training has shown to increase inflammation more than concentric training (Vincent et al., 2014). Therefore, type of muscle contraction could influence as people are stronger eccentric compared to concentric (Hollander et al., 2007). In our study, RTF were performed to concentric failure. Moreover, it is proposed that these effects of caffeine are mediated by a reduced afferent feedback (Kalmar

& Cafarelli, 2004), and blocking the adenosine receptor directly in the brain (Davis et al., 2003).

Adverse events

From a safety perspective, the co-ingestion of caffeine and CitMal could lead to gastrointestinal (GI) problems, especially for women. The reason for that may be the CitMal dose is relatively larger for woman than men when adjusted for body weight (0.14-gram pr kg for men and 0.18-gram pr kg for woman). Moinard et al (2008) experienced no adverse events with 15 grams of citrulline. In that study all participants were males and they ingested only citrulline. One could speculate that the combination of citrulline and malate may increase the risk of GI issues combined with potential sex differences. Ingestion of caffeine alone could also result in GI problems with the dose prescribed in this study (Souza et al., 2022). Moreover, only one participant (male) had regular experience with CitMal supplementation before the study.

Limitations

One of the limitations of the present study were that we did not measure plasma concentrations of caffeine and citrulline after supplementation to the absorption rate and circulating levels of the supplementations alone and combined. Nevertheless, previous studies has shown that ingestion 60 min before testing is enough to reach peak plasma values of caffeine (Echeverri et al., 2010) and Citrulline (Moinard et al., 2008), with arginine showing peak values later (Moinard et al., 2008) which citrulline is converted to. The half-life of caffeine are 2.5 to 4.5 hours (Echeverri et al., 2010) and around 1 hour for Citrulline. Alle testing were completed within 2 hours from ingestion. Secondly, we did not measure possible mediators of the supplements that could have given more insight into the potential interactions between them, such as vasoconstriction and vasodilatation. Thirdly, the majority of participants in the present study were classified as moderate caffeine consumers (n= 11) , and some were classified as low- (n= 9) and high (n= 15) caffeine consumers (Filip et al., 2020). It is possible that habitual intakes of caffeine influence the ergogenic effects (Evans et al., 2018), but the literature is somewhat ambiguous on this topic (de Souza Gonçalves et al., 2017; Evans et al., 2018; Lara et al., 2019).

Conclusions

This present study demonstrated that the ingestion of 5mg/kg of caffeine alone or combined with 12 grams of CitMal improved maximal strength, but there were no additional effects of combining the supplementations. Supplementing with caffeine alone or together with CitMal did also both improve repetitions to failure performance, but there was no enhanced synergistic effect. CitMal alone did not enhance any of our measurements. Five of seven adverse events in the present study were found in women when supplementing with caffeine and CitMal combined, thus future studies should investigate potential interaction effect with blood flow measurement, look at genders differences and if there are sex differences. The result could indicate that women should exclude or reduce the dosage of CitMal in combination with caffeine to mitigate GI issues. All participants included in this present study were resistance trained and therefor our results could be generalized to similar population. Moreover, the sample included nearly 50/50 distribution between men and woman so the results could be generalized to both sexes.

References

Aagaard, P., Simonsen, E. B., Andersen, J. L., Magnusson, P., & Dyhre-Poulsen, P. (2002). Increased rate of force development and neural drive of human skeletal muscle following resistance training. *Journal of Applied Physiology*, *93*(4), 1318–1326. https://doi.org/10.1152/japplphysiol.00283.2002

Aguiar, A. F., & Casonatto, J. (2021). Effects of Citrulline Malate Supplementation on Muscle Strength in Resistance-Trained Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Dietary Supplements*, *0*(0), 1–19. https://doi.org/10.1080/19390211.2021.1939473

Aguilar-Navarro, M., Muñoz, G., Salinero, J. J., Muñoz-Guerra, J., Fernández-álvarez, M., Plata, M. D. M., & Del Coso, J. (2019). Urine caffeine concentration in doping control samples from 2004 to 2015. *Nutrients*, *11*(2). https://doi.org/10.3390/nu11020286

Arazi, H., Hoseinihaji, M., & Eghbali, E. (2016). The effects of different doses of caffeine on performance, rating of perceived exertion and pain perception in teenagers female karate athletes. *Brazilian Journal of Pharmaceutical Sciences*, *52*(4), 685–692. https://doi.org/10.1590/s1984-82502016000400012

Astorino, T. A., Rohmann, R. L., & Firth, K. (2008). Effect of caffeine ingestion on one-repetition maximum muscular strength. *European Journal of Applied Physiology*, *102*(2), 127–132. https://doi.org/10.1007/s00421-007-0557-x

Bendahan, D., Mattei, J. P., Ghattas, B., Confort-Gouny, S., Le Guern, M. E., & Cozzone, P. J. (2002). Citrulline/malate promotes aerobic energy production in human exercising muscle. *British Journal of Sports Medicine*, *36*(4), 282–289. https://doi.org/10.1136/bjsm.36.4.282

BjØrnsen, T., Wernbom, M., Kirketeig, A., Paulsen, Gø., SamnØy, L., BÆkken, L., Cameron-Smith, D., Berntsen, S., & Raastad, T. (2019). Type 1 Muscle Fiber Hypertrophy after Blood Flow-restricted Training in Powerlifters. *Medicine and Science in Sports and Exercise*, *51*(2), 288–298. https://doi.org/10.1249/MSS.0000000000001775

Black, C. D., Waddell, D. E., & Gonglach, A. R. (2015). Caffeine's Ergogenic Effects on Cycling: Neuromuscular and Perceptual Factors. *Medicine and Science in Sports and Exercise*, *47*(6), 1145–1158. https://doi.org/10.1249/MSS.0000000000000513

Bloms, L. P., Fitzgerald, J. S., Short, M. W., & Whitehead, J. R. (2016). The Effects of Caffeine on Vertical Jump Height and Execution in Collegiate Athletes. *Journal of Strength and Conditioning Research*, *30*(7), 1855–1861. https://doi.org/10.1519/JSC.0000000000001280

Calderón, J. C., Bolaños, P., & Caputo, C. (2014). The excitation-contraction coupling mechanism in skeletal muscle. In *Biophysical Reviews* (Vol. 6, Issue 1, pp. 133–160). https://doi.org/10.1007/s12551-013-0135-x

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd Ed). Routledge. https://doi.org/10.4324/9780203771587

Davis, J. M., Zhao, Z., Stock, H. S., Mehl, K. A., Buggy, J., & Hand, G. A. (2003). Central nervous system effects of caffeine and adenosine on fatigue. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *284*(2), R399-404. https://doi.org/10.1152/ajpregu.00386.2002

de Souza Gonçalves, L., de Salles Painelli, V., Yamaguchi, G., de Oliveira, L. F., Saunders, B., da Silva, R. P., Maciel, E., Artioli, G. G., Roschel, H., & Gualano, B. (2017). Dispelling the myth that habitual caffeine consumption influences the performance response to acute caffeine supplementation. *Journal of Applied Physiology*, *123*(1), 213–220. https://doi.org/10.1152/japplphysiol.00260.2017

de Souza, J. G., Del Coso, J., Fonseca, F. de S., Silva, B. V. C., de Souza, D. B., da Silva Gianoni, R. L., Filip-Stachnik, A., Serrão, J. C., & Claudino, J. G. (2022). Risk or benefit? Side effects of caffeine supplementation in sport: a systematic review. In *European Journal of Nutrition*. https://doi.org/10.1007/s00394-022-02874-3

Degrange, T. D., Jackson, W. A., Williams, T. D., Rebecca, R., Marshall, M. R., & Ballmann, C. G. (2019). Acute Caffeine Ingestion Increases Velocity and Power in Upper and Lower Body Free-Weight Resistance Exercises. *International Journal of Exercise Science*, *12*(2), 1289–1289.

Del Vecchio, A., Casolo, A., Negro, F., Scorcelletti, M., Bazzucchi, I., Enoka, R., Felici, F., & Farina, D. (2019). The increase in muscle force after 4 weeks of strength training is mediated by adaptations in motor unit recruitment and rate coding. *Journal of Physiology*, *597*(7), 1873–1887. https://doi.org/10.1113/JP277250

Diaz-Lara, J., Grgic, J., Detanico, D., Botella, J., Jiménez, S. L., & Del Coso, J. (2022). Effects of acute caffeine intake on combat sports performance: A systematic review and meta-analysis. *Critical Reviews in Food Science and Nutrition*, *0*(0), 1–16. https://doi.org/10.1080/10408398.2022.2068499

Duncan, M. J., Stanley, M., Parkhouse, N., Cook, K., & Smith, M. (2013). Acute caffeine ingestion enhances strength performance and reduces perceived exertion and muscle pain perception during resistance exercise. *European Journal of Sport Science*, *13*(4), 392–399. https://doi.org/10.1080/17461391.2011.635811

Echeverri, D., Montes, F. R., Cabrera, M., Galán, A., & Prieto, A. (2010). Caffeine's vascular

mechanisms of action. *International Journal of Vascular Medicine*, *2010*(March 2016). https://doi.org/10.1155/2010/834060

Evans, M., Tierney, P., Gray, N., Hawe, G., Macken, M., & Egan, B. (2018). Acute Ingestion of Caffeinated Chewing Gum Improves Repeated Sprint Performance of Team Sport Athletes With Low Habitual Caffeine Consumption. *International Journal of Sport Nutrition and Exercise Metabolism*, *28*(3), 221–227. https://doi.org/10.1123/ijsnem.2017-0217

Figueroa, A., Wong, A., Jaime, S. J., & Gonzales, J. U. (2017). Influence of L-citrulline and watermelon supplementation on vascular function and exercise performance. *Current Opinion in Clinical Nutrition and Metabolic Care*, *20*(1), 92–98. https://doi.org/10.1097/MCO.0000000000000340

Filip-Stachnik, A., Wilk, M., Krzysztofik, M., Lulińska, E., Tufano, J. J., Zajac, A., Stastny, P., & Del Coso, J. (2021). The effects of different doses of caffeine on maximal strength and strength-endurance in women habituated to caffeine. *Journal of the International Society of Sports Nutrition*, *18*(1). https://doi.org/10.1186/s12970-021-00421-9

Filip, A., Wilk, M., Krzysztofik, M., & Del Coso, J. (2020). Inconsistency in the ergogenic effect of caffeine in athletes who regularly consume caffeine: Is it due to the disparity in the criteria that defines habitual caffeine intake? *Nutrients*, *12*(4), 1087. https://doi.org/10.3390/nu12041087

Ganio, M. S., Johnson, E. C., Lopez, R. M., Stearns, R. L., Emmanuel, H., Anderson, J. M., Casa, D. J., Maresh, C. M., Volek, J. S., & Armstrong, L. E. (2011). Caffeine lowers muscle pain during exercise in hot but not cool environments. *Physiology and Behavior*, *102*(3–4), 429–435. https://doi.org/10.1016/j.physbeh.2010.12.005

Gliottoni, R. C., & Motl, R. W. (2008). Effect of caffeine on leg-muscle pain during intense cycling exercise: possible role of anxiety sensitivity. *International Journal of Sport Nutrition and Exercise Metabolism*, *18*(2), 103–115. https://doi.org/10.1123/ijsnem.18.2.103

Goldstein, E., Jacobs, P. L., Whitehurst, M., Penhollow, T., & Antonio, J. (2010). Caffeine enhances upper body strength in resistance-trained women. *Journal of the International Society of Sports Nutrition*, *7*(1), 1–6. https://doi.org/10.1186/1550-2783-7-18

Gomo, O., & Van Den Tillaar, R. (2016). The effects of grip width on sticking region in bench press. *Journal of Sports Sciences*, *34*(3), 232–238. https://doi.org/10.1080/02640414.2015.1046395

Gonzalez, A. M., & Trexler, E. T. (2020). Effects of Citrulline Supplementation on Exercise Performance in Humans. *Journal of Strength and Conditioning Research*, *34*(5), 1480–1495. www.nsca.com

Gough, L. A., Sparks, · S Andy, Mcnaughton, L. R., Matthew, ·, Higgins, F., Newbury, J. W., Trexler, E., Faghy, M. A., & Bridge, C. A. (n.d.). A critical review of citrulline malate supplementation and exercise performance. *European Journal of Applied Physiology*, *3*. https://doi.org/10.1007/s00421-021-04774-6

Gough, L. A., Sparks, S. A., McNaughton, L. R., Higgins, M. F., Newbury, J. W., Trexler, E., Faghy, M. A., & Bridge, C. A. (2021). A critical review of citrulline malate supplementation and exercise performance. In *European Journal of Applied Physiology* (Issue 3). https://doi.org/10.1007/s00421-021-04774-6

Graham, T. E. (2001). Caffeine and exercise: metabolism, endurance and performance. / Cafeine et exercice: metabolisme, endurance et performance. *Sports Medicine*, *31*(11), 785–807. http://articles.sirc.ca/search.cfm?id=S-791474%5Cnhttp://search.ebscohost.com/login.aspx?direct=true&db=s3h&AN=SPHS-791474&site=ehost-live%5Cnhttp://www.adis.com

Grgic, J. (2021). Effects of Caffeine on Resistance Exercise: A Review of Recent Research. In *Sports Medicine*. Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s40279-021-01521-x

Grgic, J. (2022). Exploring the minimum ergogenic dose of caffeine on resistance exercise performance: a meta-analytical approach. *Nutrition*, *97*, 111604. https://doi.org/10.1016/j.nut.2022.111604

Grgic, J., & Del Coso, J. (2021). Ergogenic effects of acute caffeine intake on muscular endurance and muscular strength in women: A meta-analysis. *International Journal of Environmental Research and Public Health*, *18*(11). https://doi.org/10.3390/ijerph18115773

Grgic, J., Grgic, I., Pickering, C., Schoenfeld, B. J., Bishop, D. J., & Pedisic, Z. (2020). Wake up and smell the coffee: caffeine supplementation and exercise performance-an umbrella review of 21 published meta-analyses. *Br J Sports Med*, *54*, 681–688. https://doi.org/10.1136/bjsports-2018-100278

Grgic, J., & Mikulic, P. (2021). Effects of caffeine on rate of force development: A meta-analysis. *Scandinavian Journal of Medicine and Science in Sports*, *August*, 1–10. https://doi.org/10.1111/sms.14109

Grgic, J., & Mikulic, P. (2022). Effects of caffeine on rate of force development: A meta-analysis. *Scandinavian Journal of Medicine and Science in Sports*, *32*(4), 644–653. https://doi.org/10.1111/sms.14109

Grgic, J., Mikulic, P., Schoenfeld, B. J., David, ·, Bishop, J., & Pedisic, Z. (2019). The Influence of Caffeine Supplementation on Resistance Exercise: A Review Key Points. *Sports Medicine*, *49*, 17–30. https://doi.org/10.1007/s40279-018-0997-y

Grgic, J., Sabol, F., Venier, S., Mikulic, I., Bratkovic, N., Schoenfeld, B. J., Pickering, C., Bishop, D. J., Pedisic, Z., & Mikulic, P. (2020). What dose of caffeine to use: Acute effects of 3 doses of caffeine on muscle endurance and strength. *International Journal of Sports Physiology and Performance*, *15*(4), 470–477. https://doi.org/10.1123/ijspp.2019-0433

Grgic, J., Trexler, E. T., Lazinica, B., & Pedisic, Z. (2018). Effects of caffeine intake on muscle strength and power: a systematic review and meta-analysis. *Journal of the International Society of Sports Nutrition*, *15*(1), 104–125. https://doi.org/10.1186/s12970-018-0216-0

Grimble, G. K. (2007). Adverse gastrointestinal effects of arginine and related amino acids. *Journal of Nutrition*, *137*(6), 1693S-1701S. https://doi.org/10.1093/jn/137.6.1693s

Harty, P. S., Zabriskie, H. A., Erickson, J. L., Molling, P. E., Kerksick, C. M., & Jagim, A. R. (2018). Multi-ingredient pre-workout supplements, safety implications, and performance outcomes: A brief review. In *Journal of the International Society of Sports Nutrition* (Vol. 15, Issue 1, p. 41). https://doi.org/10.1186/s12970-018-0247-6

Hollander, D. B., Kraemer, R. R., Kilpatrick, M. W., Ramadan, Z. G., Reeves, G. V, Francois, M., Hebert, E. P., & Tryniecki, J. L. (2007). Maximal eccentric and concentric strength discrepancies between young men and women for dynamic resistance exercise. *Journal of Strength and Conditioning Research*, *21*(1), 34–40. https://doi.org/10.1519/R-18725.1

Hori, N., Newton, R. U., Kawamori, N., McGuigan, M. R., Kraemer, W. J., & Nosaka, K. (2009). Reliability of Performance Measurements Derived From Ground Reaction Force Data During Countermovement Jump and the Influence of Sampling Frequency. *Journal of Strength and Conditioning Research*, *23*(3), 874–882. https://doi.org/10.1519/JSC.0b013e3181a00ca2

Hudson, G. M., Green, J. M., Bishop, P. A., & Richardson, M. T. (2008). Effects of Caffeine and Aspirin

on Light Resistance Training Performance, Perceived Exertion, and Pain Perception. *Journal of Strength and Conditioning Research*, *22*(6), 1950–1957. https://doi.org/10.1519/JSC.0b013e31818219cb

International Powerlifting Federation. (2021). *Technical Rules book*. 18. http://www.powerlifting-ipf.com/fileadmin/ipf/data/rules/technical-rules/english/2015_V2_IPF_Technical_Rules_Book_2015_classic_rules_in_back_section.pdf

JM, R., J, G., & M, G. (2020). Acute effects of Nitrosigine® and citrulline malate on vasodilation in young adults. In *Journal of the International Society of Sports Nutrition* (Vol. 17, Issue 1, p. 12). https://pubmed.ncbi.nlm.nih.gov/32093766/

Kalmar, J. M., & Cafarelli, E. (2004). Caffeine: A valuable tool to study central fatigue in humans? *Exercise and Sport Sciences Reviews*, *32*(4), 143–147. https://doi.org/10.1097/00003677-200410000-00004

Lara, B., Ruiz-Moreno, C., Salinero, J. J., & Del Coso, J. (2019). Time course of tolerance to the performance benefits of caffeine. *PloS One*, *14*(1), e0210275. https://doi.org/10.1371/journal.pone.0210275

Maridakis, V., O'Connor, P. J., Dudley, G. A., & McCully, K. K. (2007). Caffeine Attenuates Delayed-Onset Muscle Pain and Force Loss Following Eccentric Exercise. *Journal of Pain*, *8*(3), 237–243. https://doi.org/10.1016/j.jpain.2006.08.006

Merino Fernández, M., Ruiz-Moreno, C., Giráldez-Costas, V., Gonzalez-Millán, C., Matos-Duarte, M., Gutiérrez-Hellín, J., & González-García, J. (2021). Caffeine doses of 3 mg/kg increase unilateral and bilateral vertical jump outcomes in elite traditional Jiu-Jitsu athletes. *Nutrients*, *13*(5). https://doi.org/10.3390/nu13051705

Moinard, C., Nicolis, I., Neveux, N., Darquy, S., Bénazeth, S., & Cynober, L. (2008). Dose-ranging effects of citrulline administration on plasma amino acids and hormonal patterns in healthy subjects: The Citrudose pharmacokinetic study. *British Journal of Nutrition*, *99*(4), 855–862. https://doi.org/10.1017/S0007114507841110

Mora-Rodríguez, R., Pallarés, J. G., López-Samanes, Á., Ortega, J. F., & Fernández-Elías, V. E. (2012). Caffeine ingestion reverses the circadian rhythm effects on neuromuscular performance in highly resistance-trained men. *PLoS ONE*, *7*(4). https://doi.org/10.1371/journal.pone.0033807

Myers, D. E., Shaikh, Z., & Zullo, T. G. (1997). Hypoalgesic effect of caffeine in experimental ischemic muscle contraction pain. *Headache*, *37*(10), 654–658. https://doi.org/10.1046/j.1526-4610.1997.3710654.x

Neyroud, D., Cheng, A. J., Donnelly, C., Bourdillon, N., Gassner, A. L., Geiser, L., Rudaz, S., Kayser, B., Westerblad, H., & Place, N. (2019). Toxic doses of caffeine are needed to increase skeletal muscle contractility. *American Journal of Physiology - Cell Physiology*, *316*(2), C246–C251. https://doi.org/10.1152/ajpcell.00269.2018

Norum, M., Risvang, L. C., Bjørnsen, T., Dimitriou, L., Rønning, P. O., Bjørgen, M., & Raastad, T. (2020). Caffeine increases strength and power performance in resistance-trained females during early follicular phase. *Scandinavian Journal of Medicine and Science in Sports*, *30*(11), 2116–2129. https://doi.org/10.1111/sms.13776

Nowaczewska, M., Wiciński, M., & Kaźmierczak, W. (2020). The Ambiguous Role of Caffeine in Migraine Headache: From Trigger to Treatment. *Nutrients*, *12*(8), 2259. https://doi.org/10.3390/nu12082259

O'Connor, P. J., Motl, R. W., Broglio, S. P., & Ely, M. R. (2004). Dose-dependent effect of caffeine on

reducing leg muscle pain during cycling exercise is unrelated to systolic blood pressure. *Pain*, *109*(3), 291–298. https://doi.org/10.1016/j.pain.2004.01.017

Pakulak, A., Candow, D. G., Totosy de Zepetnek, J., Forbes, S. C., & Basta, D. (2021). Effects of Creatine and Caffeine Supplementation During Resistance Training on Body Composition, Strength, Endurance, Rating of Perceived Exertion and Fatigue in Trained Young Adults. *Journal of Dietary Supplements*. https://doi.org/10.1080/19390211.2021.1904085

Pallarés, J. G., Fernández-Elías, V. E., Ortega, J. F., Muñoz, G., Muñoz-Guerra, J., & Mora-Rodríguez, R. (2013). Neuromuscular responses to incremental caffeine doses: Performance and side effects. *Medicine and Science in Sports and Exercise*, *45*(11), 2184–2192. https://doi.org/10.1249/MSS.0b013e31829a6672

Polito, M. D., Souza, D. B., Casonatto, J., & Farinatti, P. (2016). Acute effect of caffeine consumption on isotonic muscular strength and endurance: A systematic review and meta-analysis. *Science and Sports*, *31*(3), 119–128. https://doi.org/10.1016/j.scispo.2016.01.006

Salinero, J. J., Lara, B., & Del Coso, J. (2019). Effects of acute ingestion of caffeine on team sports performance: a systematic review and meta-analysis. *Research in Sports Medicine*, *27*(2), 238–256. https://doi.org/10.1080/15438627.2018.1552146

Souza, A. A., Bottaro, M., Rocha Junior, V. A., Lage, V., Tufano, J. J., & Vieira, A. (2020). Reliability and test-retest agreement of mechanical variables obtained during countermovement jump. *International Journal of Exercise Science*, *13*(4), 6–17.

Stadheim, H. K., Nossum, E. M., Olsen, R., Spencer, M., & Jensen, J. (2015). Caffeine improves performance in double poling during acute exposure to 2,000-m altitude. *Journal of Applied Physiology*, *119*(12), 1501–1509. https://doi.org/10.1152/japplphysiol.00509.2015

Tan, Z. Sen, Sim, A., Kawabata, M., & Burns, S. F. (2021). A Systematic Review of the Effects of Caffeine on Basketball Performance Outcomes. *Biology*, *11*(1), 17. https://doi.org/10.3390/biology11010017

Trexler, E. T., Persky, A. M., Ryan, E. D., Schwartz, T. A., Stoner, L., & Smith-Ryan, A. E. (2019a). Acute Effects of Citrulline Supplementation on High-Intensity Strength and Power Performance: A Systematic Review and Meta-Analysis. In *Sports Medicine* (Vol. 49, pp. 707–718). https://doi.org/10.1007/s40279-019-01091-z

Trexler, E. T., Persky, A. M., Ryan, E. D., Schwartz, T. A., Stoner, L., & Smith-Ryan, A. E. (2019b). Acute Effects of Citrulline Supplementation on High-Intensity Strength and Power Performance: A Systematic Review and Meta-Analysis. In *Sports Medicine* (Vol. 49, Issue 5, pp. 707–718). https://doi.org/10.1007/s40279-019-01091-z

Vårvik, F. T., Bjørnsen, T., & Gonzalez, A. M. (2021). Acute effect of citrulline malate on repetition performance during strength training: A systematic review and meta-analysis. In *International Journal of Sport Nutrition and Exercise Metabolism* (Vol. 31, Issue 4, pp. 350–358). https://doi.org/10.1123/IJSNEM.2020-0295

Venier, S., Grgic, J., & Mikulic, P. (2019). Acute enhancement of jump performance, muscle strength, and power in resistance-trained men after consumption of caffeinated chewing gum. *International Journal of Sports Physiology and Performance*, *14*(10), 1415–1421. https://doi.org/10.1123/ijspp.2019-0098

Vincent, H. K., Percival, S., Creasy, R., Alexis, D., Seay, A. N., Laura Ann, Z., MacMillan, M., & Vincent, K. R. (2014). Acute Effects of Enhanced Eccentric and Concentric Resistance Exercise on Metabolism and Inflammation. *Journal of Novel Physiotherapies*, *4*(2).

https://doi.org/10.4172/2165-7025.1000200

Warren, G. L., Park, N. D., Maresca, R. D., Mckibans, K. I., & MILLARD-STAFFORD, M. L. (2010). Effect of Caffeine Ingestion on Muscular Strength and Endurance. *Medicine & Science in Sports & Exercise*, *42*(7), 1375–1387. https://doi.org/10.1249/MSS.0b013e3181cabbd8

Wilk, M., Filip, A., Krzysztofik, M., Maszczyk, A., & Zajac, A. (2019). The acute effect of various doses of caffeine on power output and velocity during the bench press exercise among athletes habitually using caffeine. In *Nutrients* (Vol. 11, Issue 7). https://doi.org/10.3390/nu11071465

Williams, A. D., Cribb, P. J., Cooke, M. B., & Hayes, A. (2008). The effect of ephedra and caffeine on maximal strength and power in resistance-trained athletes. *Journal of Strength and Conditioning Research*, *22*(2), 464–470. https://doi.org/10.1519/JSC.0b013e3181660320

Windmueller, H. G., & Spaeth, A. E. (1981). Source and fate of circulating citrulline. *American Journal of Physiology - Endocrinology and Metabolism*, *4*(6), 473–480. https://doi.org/10.1152/ajpendo.1981.241.6.e473

Zbinden-Foncea, H., Rada, I., Gomez, J., Kokaly, M., Stellingwerff, T., Deldicque, L., & Peñailillo, L. (2018). Effects of caffeine on countermovement-jump performance variables in elite male volleyball players. *International Journal of Sports Physiology and Performance*, *13*(2), 145–150. https://doi.org/10.1123/ijspp.2016-0705