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Does Caffeine Added to Carbohydrate Provide Additional Ergogenic Benefit for Endurance?

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Context: Carbohydrate (CHO) and caffeine (CAF) both improve endurance performance. ***Purpose:*** To determine by systematic literature review coupled with meta-analysis whether CAF ingested with CHO (CHO+CAF) improves endurance performance more than CHO alone. ***Methods:*** Databases were searched using the keywords *caffeine, endurance, exercise, carbohydrate,* and *performance*. Criteria for inclusion were studies that used human subjects performing an endurance-exercise performance task and included both a CHO and CHO+CAF condition. Effect sizes (*ES*s) were calculated as the standardized mean difference. ***Results:*** Twenty-one studies met the criteria for analysis. *ES*s for individual studies ranged from –0.08 (trivial effect favoring CHO) to 1.01 (large effect favoring CHO+CAF). The overall *ES* equaled 0.26 (95% *CI* 0.15–0.38, $p < .001$), indicating that CHO+CAF provides a small but significant performance benefit over CHO. *ES* was not significantly ($p > .05$) related to CAF dose, exercise duration, or performance-assessment method. To determine whether *ES* of CHO+CAF vs. CHO was different than CAF compared with water (placebo), a subgroup meta-analysis compared 36 CAF vs. placebo studies against the 21 CHO+CAF vs. CHO studies. The overall *ES* for the former group of studies (*ES* = 0.51, 95% *CI* 0.40–0.61) was nearly 2-fold greater than in CHO+CAF vs. CHO studies ($p = .006$). ***Conclusions:*** CHO+CAF ingestion provides a significant but small effect to improve endurance performance compared with CHO alone. However, the magnitude of the performance benefit that CAF provides is less when added to CHO than when added to placebo.

Keywords: meta-analysis, performance, nutrition, supplement, fatigue

Nutritional ergogenic aids are commonly used by recreational and elite athletes as a method of improving performance during endurance competitions. Two ergogenic aids that have routinely been used by athletes and investigated over several decades are carbohydrate (CHO) and caffeine (CAF). It is well established that CHO ingestion during prolonged (≥1 hr), endurance exercise delays the onset of fatigue and improves exercise performance (Angus, Hargreaves, Dancey, & Febbraio, 2000; Below, Mora-Rodriguez, Gonzalez-Alonso, & Coyle, 1995; Coggan & Coyle, 1987; Coyle et al., 1983; Millard-Stafford, Sparling, Rosskopf, & DiCarlo, 1992; Sherman et al., 1989). The improvement observed in endurance-exercise performance has generally been attributed to the provision of an exogenous fuel source, increased rates of CHO oxidation, and maintenance of blood glucose to optimally supply the energy requirements for sustained high-intensity exercise (Coggan & Coyle, 1991; Coyle, 1992). Recent work has also suggested that CHO may improve endurance performance via central-nervous-system (CNS) activation (Carter, Jeukendrup, & Jones, 2004; Del Coso, Estevez, & Mora-Rodriguez, 2008).

The ergogenic effect of CAF during endurance exercise has also been examined extensively (Costill, Dalsky, & Fink, 1978; Graham & Spriet, 1991, 1995; Ivy, Costill, Fink, & Lower, 1979; Jackman, Wendling, Friars, & Graham, 1996). However, several possible mechanisms, not all directly linked to energy metabolism, could explain improved endurance with CAF. It was originally postulated that performance improvements were the result of a metabolic effect; specifically, CAF increased fat oxidation (Costill et al., 1978; Ivy et al., 1979), thereby reducing the reliance on muscle glycogen during exercise. Recent investigations have not validated this as the primary explanation for CAF's benefit (Cox et al., 2002; Graham, Helge, Maclean, Kiens, & Richter, 2000; Graham & Spriet, 1991; Jackman et al., 1996; Kovacs, Stegen, & Brouns, 1998). Alternative mechanisms have been proposed for the ergogenicity of CAF, including those related to CNS or peripheral actions on skeletal muscle. For example, adenosine-receptor antagonism (Davis et al., 2003) in the CNS may explain the decreased perception of effort often observed with CAF during exercise (Cole et al., 1996; Cox et al., 2002; Doherty & Smith, 2005; Jacobson, Febbraio, Arkinstall, & Hawley, 2001). Moreover, peripheral mechanisms such as improved skeletal-muscle force production may also underlie purported benefits (Lopes, Aubier, Jardim, Aranda, & Macklem, 1983; Meyers & Cafarelli, 2005). Because CHO ingestion enhances performance by supporting vital CHO metabolism and CAF potentially acts via alternative pathways (e.g., facilitating neuromuscular force production), it is tempting to speculate that CHO combined with CAF (CHO+CAF) might prove additive in

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augmenting endurance-exercise performance compared with CHO alone.

To date, exercise-performance studies investigating CHO+CAF compared with CHO alone have produced mixed results. Some studies report significant performance improvements with CHO+CAF (Cox et al., 2002; Cureton et al., 2007; Kovacs et al., 1998), and others demonstrated no additional benefit (Hunter, St. Clair Gibson, Collins, Lambert, & Noakes, 2002; Sasaki, Maeda, Usui, & Ishiko, 1987; van Nieuwenhoven, Brouns, & Kovacs, 2005) beyond ingestion of CHO alone. The reason for equivocal results is unclear but might be the variety of experimental factors across the studies, such as subject characteristics, caffeine dose, or the test selected to evaluate exercise performance. Whether CHO+CAF significantly improves performance above CHO alone could be determined by conducting a rigorous systematic review of the literature coupled with a meta-analysis.

Therefore, our primary aim was to conduct a systematic review of the literature combined with meta-analysis to assess whether CHO+CAF provides an endurance-exercise performance benefit above CHO alone. Experimental factors (e.g., caffeine dose and other aspects of the test protocol to assess performance) that could account for the variability in standardized mean differences or effect size (*ES*s) among studies were also examined. Furthermore, to better understand whether the ergogenic effects of CHO and CAF are independent of each other (and thus potentially additive), we also examined whether the established magnitude of the ergogenic effect of CAF (compared with placebo control) for endurance is similar to that when CAF is combined with CHO, via systematic review and meta-analysis. If the *ES* of CAF is the same no matter what it is combined with, then it would seem that CAF's mechanism of action is independent of that of CHO (e.g., CHO facilitates metabolism, whereas CAF affects the neural or muscular systems). However, if the *ES* of CAF differs depending on whether it is added to CHO or placebo, this would suggest interaction or redundancy between the mechanisms of action for CAF and CHO (e.g., both influencing metabolism or CNS fatigue inhibition).

Methods

Identification of Studies for Inclusion

The databases of PubMed, SPORTDiscus, and ProQuest and conference proceedings from the American College of Sports Medicine annual meeting (from the past 19 years) were searched through April 2009. Our review used studies on human subjects with a crossover (within-subject) research design. The studies were required to contain an endurance-exercise bout that included a performance task (i.e., exercise time to fatigue, time to complete a set amount of work, or work completed in a set amount of time) and both a CHO and CHO+CAF condition. Our operational definition of endurance performance was that the exercise-performance test per se be at least 10 min in duration. However, the studies (Cureton et al., 2007; Eschbach et al., 2002; Ganio et al., 2007) with test duration of 10–15 min were preceded by a prolonged bout of submaximal exercise, so that the total exercise duration of the test protocol was on average for all studies 94.0 min and ranged from 19.6 to 250.4 min. For inclusion in the analysis, all study protocols had to use either preexercise ingestion of CHO and CHO+CAF within 90 min prior, ingestion during exercise, or both (preexercise ingestion and at some points during exercise). Investigations that were published in peer-reviewed journals were included, as well as those available as scientific conference proceedings, theses, or dissertations (in the case of one study by MacLeod, 2004) to avoid publication bias. Publication bias, as documented previously (Borenstein, Hedges, Higgins, & Rothstein, 2009), can occur because studies that report higher *ES*s are more likely to be published than those with low *ES*s; thus, this bias would be introduced into the meta-analysis if only published studies were included.

For the primary meta-analysis comparing CHO+CAF and CHO, the following keywords were used to search the data bases: *caffeine* and *carbohydrate* and (*performance* or *endurance* or *exercise*). In a supporting analysis to obtain the magnitude of the effect that CAF had compared with water (or placebo), the keywords *caffeine* and (*performance* or *endurance* or *exercise*) were used. Similar inclusion and exclusion criteria were used for the supporting analysis, with the exception that a placebo condition was used in place of a CHO condition. In addition, reference lists from related review articles on CAF were examined to further ensure that all relevant articles were included (Burke, 2008; Doherty & Smith, 2004, 2005; Ganio, Klau, Casa, Armstrong, & Maresh, 2009; Sökmen et al., 2008).

Statistical Analysis

Data from each study were converted into the same format by calculating the standardized difference in means: $(M_{CAF} - M_{noCAF})/SD_{Pooled}$, where SD_{Pooled} is the pooled standard deviation (Borenstein et al., 2009) and was calculated as follows:

$$(SD^2_{noCAF} + SD^2_{CAF} - 2 \times r_{noCAF,CAF} \times SD_{noCAF} \times SD_{CAF})^{0.5}/[2 \times (1 - r_{noCAF,CAF})]^{0.5}$$

where $r_{no\ CAF,CAF}$ is the intertrial correlation between the no-CAF and CAF conditions. In seven studies, we were able to calculate $r_{no\ CAF,CAF}$ from the reported data (Bell, McLellan, & Sabiston, 2002; Eschbach et al., 2002; French, McNaughton, Davies, & Tristram, 1991; Graham & Spriet, 1991; MacLeod, 2004; Pasman, van Baak, Jeukendrup, & De Haan, 1995; Spriet et al., 1992), and in two instances $r_{no\ CAF,CAF}$ was obtained from the study authors (Cureton et al., 2007; Rehrer, Cusdin, & Deutsch, 1997). For studies for which we were not able to obtain intertrial correlations, we used the mean of the reported and obtained correlations ($r = .74$, $SD = .09$, range .62–.86 for CHO+CAF vs. CHO; $r = .86$, $SD = .12$, range .68–.99 for CAF vs. placebo). The Hedges correction (Hedges's *g*) was used to account for potential bias resulting from the small sample sizes used in the reviewed studies. To do this, the standardized mean difference and standard error were multiplied by the following correction factor (Borenstein et al., 2009): $1 - \{3/[4 \times (n_{noCAF,CAF} - 1)]\}$

In studies that reported more than one outcome, average *ES*s and their associated variances were used to calculate the meta-analyses' overall *ES*s. The overall *ES* was calculated using a random-effects model that accounts for true variation in effects occurring from study to study, as well as random error within a single study. The random-effects model was chosen over a fixed-effect model because experimental factors such as caffeine dose and test protocols to assess endurance performance had wide variation. An *ES* of zero would indicate that there is no difference between the two treatments, a negative *ES* would indicate that the condition without CAF yielded better performance, and a positive *ES* would indicate that the condition with CAF yielded better performance outcomes. The reference points developed by Cohen (1988) were used for interpretation, that is, that *ES*s of 0.2, 0.5, and 0.8 were considered small, moderate, and large, respectively.

To assess whether various experimental factors could explain the variation in *ES* observed among the studies, subgroup meta-analyses or metaregressions (method-of-moments model) were conducted. These analyses included metaregressions of continuous data—CAF dose, duration of the performance task, and subjects' fitness level (VO_{2max})—relative to study *ES*. Subgroup meta-analyses were used to examine the effects of categorical data: timing of CAF administration (e.g., before or during exercise), exercise mode (cycling vs. running), type of performance task (time to fatigue vs. fixed-endpoint task such as a time trial or work completed in fixed time), subjects' gender (men, women, or both), completion of an exercise bout before the performance event (yes or no), and published versus unpublished studies. Publication bias was also assessed by displaying the relationship between *ES*s of each study and standard error in a funnel plot combined with a trim-and-fill correction (Duval & Tweedie, 2000). Our group previously used these techniques in a meta-analysis (Warren, Park, Maresca, McKibans, & Millard-Stafford, 2010).

All calculations were made with the Comprehensive Meta Analysis, version 2.2 (Biostat, Englewood, NJ), software package. An α level of .05 was used for all analyses to indicate statistical significance.

Results

Study Characteristics for CHO+CAF Versus CHO Analysis

In all, 140 articles were identified for potential inclusion in the analysis. After reviewing the articles, 121 were eliminated as not meeting the inclusion criteria (e.g., an endurance performance task of at least 10 min and comparing both CHO and CHO+CAF conditions). Nineteen studies met the inclusion criteria (Table 1): thirteen peer-reviewed research articles (Bell & McLellan, 2002, 2003; Bell et al., 2002; Cox et al., 2002; Cureton et al., 2007; Hogervorst et al., 2008; Hulston & Jeukendrup, 2008; Hunter et al., 2002; Jacobson et al., 2001; Kovacs et al., 1998; Sasaki et al., 1987; Slivka et al., 2008; van Nieuwenhoven et al., 2005), five published abstracts from conference proceedings (Eschbach et al., 2002; Ganio et al., 2007; King et al., 2006; Rehrer et al., 1997; Smith et al., 2006), and one unpublished master's thesis (MacLeod, 2004). We included these well-designed scientific abstracts and thesis despite their tendency to influence the results toward a null finding. One research article (Cox et al., 2002) reported results from two independent studies, and another (Bell & McLellan, 2002) used two subgroups with different subjects (CAF users and nonusers). Thus, in all, 21 studies were used in the analysis.

The doses of both CAF and CHO were quite variable among these studies (as indicated in Table 1) and not reported in two studies (Bell et al., 2002; MacLeod, 2004). CAF dose in the CHO+CAF versus CHO meta-analysis ranged from 1.3 to 10.8 mg/kg body weight (median = 5 mg/kg). CHO dose ingested across the duration of exercise ranged from 23.1 to 113.6 g/hr of exercise (median 56.4 g/hr). Subjects in four studies did not consume the CHO and CAF at the same time points: CAF was consumed either 3 hr before beginning exercise (Eschbach et al., 2002), 1 hr before beginning exercise (Rehrer et al., 1997), or 1 hr before and during exercise (Cox Studies A and B; Cox et al., 2002). The CAF was ingested in the form of a capsule (Bell & McLellan, 2002, 2003; Bell et al., 2002; Cox et al., 2002; Eschbach et al., 2002; Hunter et al., 2002; Jacobson et al., 2001; Rehrer et al., 1997; Slivka et al., 2008), dissolved in a drink (Cureton et al., 2007; Ganio et al., 2007; Hulston & Jeukendrup, 2008; King et al., 2006; Kovacs et al., 1998; MacLeod, 2004; Sasaki et al., 1987; van Nieuwenhoven et al., 2005), or contained in a performance bar (Hogervorst et al., 2008). Only three studies used a CHO condition that contained only CHO (plus flavoring; MacLeod, 2004; Rehrer et al., 1997; Sasaki et al., 1987). In most of the other studies, the CHO condition was a sports drink with electrolytes (Bell & McLellan, 2002, 2003; Cox et al., 2002; Cureton et al., 2007; Eschbach et al., 2002; Ganio et al., 2007; Hunter et al., 2002; King et al., 2006; Kovacs et al., 1998; Smith et al., 2006; van Nieuwenhoven et al., 2005). Two studies included in the analysis (Cureton et al., 2007; Ganio et al., 2007) used slightly different CHO-drink concentrations (~1%) between the CHO and CHO+CAF study conditions; however, both were commercially available sports drinks, and CHO doses were within a range previously determined to be ergogenic (Coyle, 1992; Coyle et al., 1983). The CHO+CAF in those two studies also included small amounts of other ingredients (e.g., taurine, carnitine) that are not currently known to be ergogenic at the levels consumed. The 21 studies yielded a total of 333 subjects, with 93% being men. The median number of subjects in a study was 11. Subjects were well trained, with mean VO_{2max} ranging among the studies from 51 to 71 $ml \cdot kg^{-1} \cdot min^{-1}$. The average percentage performance difference reported in the studies (last column in Table 1) suggests that CHO+CAF might result in a 6% performance improvement versus CHO.

Table 1 Summary of the Studies Included in the CHO Versus CHO+CAF Meta-Analysis Listed in Chronological Order

Study	*N* (M/F)	VO_{2max} (ml · kg^{-1} · min^{-1})	CAF dose (mg/kg)	CHO dose (g/hr)	EM	Performance task	% Change in performance vs. CHO
Sasaki et al., 1987	5 (5/0)	62.7	6.2	52.9	TR	Run until exhaustion at 80% VO_{2max}	–2.6
Rehrer et al., 1997	15 (15/0)	63	4.2	60.0	CE	Total work completed in 30 min	–0.4
Kovacs et al., 1998	15 (15/0)	NR	2.1, 3.2, or 4.5	74.8	CE	Time to complete a set amount of work (T[J] = 0.75 × W_{max} × 3,600)	3.5
Jacobson et al., 2001	8 (8/0)	65.2	6.0	67.9	CE	Time trial to complete 7 kJ/kg of work	4.3
Bell & McLellan, 2003	12 (10/2)	57.5	4.0	NR	TR	10-km treadmill run	1.7
Cox et al., 2002 (Study A)	12 (12/0)	66.4	1.3 or 6.0	74.8 or 60.4	CE	Time trial to complete 7 kJ/kg of work	3.3
Cox et al., 2002 (Study B)	8 (8/0)	71.2	1.9	113.6 or 84.0	CE	Time trial to complete 7 kJ/kg of work	2.2
Eschbach et al., 2002	11 (11/0)	54.9	6.0	23.1	CE	Simulated 5-km time trial	0.8
Bell & McLellan, 2002 (CAF users)	13 (NR)	51.2	5.0	25.8	CE	Ride until exhaustion at 80% VO_{2max}	26.1
Bell& McLellan, 2002 (CAF nonusers)	8 (NR)	50.7	5.0	25.8	CE	Ride until exhaustion at 80% VO_{2max}	15.0
Hunter et al., 2002	8 (8/0)	64.6	6.0	42.5	CE	Simulated 100-km time trial	1.3
Bell & McLellan, 2003	9 (9/0)	52	5.0	25.8	CE	Ride until exhaustion at 80% VO_{2max}	22.8
MacLeod, 2004	8 (0/8)	56.1	5.0	NR	CE	Ride until exhaustion at 80% VO_{2max}	12.9
van Nieuwenhoven et al., 2005	98 (90/8)	NR	1.3	65.5	OR	18-km competitive run	0.4
King, O'Hara, & Carlton, 2006	10 (10/0)	58.1	NR	37.9	CE	Ride until exhaustion at 90% VO_{2max}	1.8
Smith, Stover, Lovett, & Zachwieja, 2006	10 (10/0)	53.8	1.3	31.4	CE	Simulated 40-km time trial	0.7
Cureton et al., 2007	16 (16/0)	71.2	5.3	66.2 or 56.4[a]	CE	Total work completed in 15 min	15.1
Ganio et al., 2007	14 (14/0)	60.4	5.9	66.2 or 56.4[a]	CE	Total work completed in 15 min	3.6
Slivka, Hailes, Cuddy, & Ruby, 2008	11 (11/0)	59.5	10.8	48.0	CE	Simulated 20-km time trial	–0.3
Hogervorst et al., 2008	24 (24/0)	56.6	4.1	45.0	CE	Ride until exhaustion at 75% VO_{2max}	27.4
Hulston & Jeukendrup, 2008	10 (10/0)	65.7	5.3	30.1	CE	Time to complete a set amount of work (T[J] = 0.75 × W_{max} × 2,700)	4.6

Note. CHO = carbohydrate; CAF = caffeine; VO_{2max} = maximal oxygen uptake; EM = exercise mode; TR = treadmill running; CE = cycle ergometer; NR = not reported; T(J) = total work in Joules; W_{max} = maximum Watts; OR = outdoor running.

[a]CHO content was different in CHO and CHO+CAF conditions.

*ES*s for CHO+CAF Versus CHO Analysis

The *ES*s for the 21 studies used in our primary meta-analysis ranged from –0.08 (trivial effect favoring CHO) to 1.01 (large effect favoring CHO+CAF) and are listed in ascending order in Figure 1. Eighteen of the 21 studies yielded a positive *ES* (i.e., favoring CHO+CAF). The overall *ES* of the meta-analysis was small in magnitude (*ES* = 0.26, 95% *CI* 0.15–0.38) but statistically different from zero ($p < .001$; Figure 1). This indicates that CHO+CAF increases endurance-exercise performance over CHO. Although the total number of available studies that met our inclusion and exclusion criteria was limited, no single study unduly influenced the results. For example, when we eliminated the study with the greatest *ES,* of 1.01 (a subgroup of subjects identified as CAF naïve), by Bell and McLellan (2002), the overall *ES,* although reduced slightly (i.e., from 0.26 to 0.24), remained statistically significant ($p < .001$, 95% *CI* 0.13–0.34). In addition, when we eliminated the two studies that had other ingredients in the CHO+CAF trials (Cureton et al., 2007; Ganio et al., 2007), the *ES* of 0.24 remained significant ($p < .001$, 95% *CI* 0.13–0.36).

Moderator Variables for CHO+CAF Versus CHO Analysis

Additional analyses assessing the effects of moderator variables were conducted to investigate potential underlying explanations for the *ES* variability observed among the studies. These results are summarized in Table 2. None of the variables probed had a significant impact on study *ES* variation (i.e., CAF dose, subjects' fitness level [VO_{2max}], timing of CAF ingestion, mode of exercise, subject gender, or completion of a sustained endurance-exercise bout before the performance task). Because performance was the primary dependent measure of interest, and the test protocol used to assess performance has been identified as producing differential outcomes, two test protocol models were compared: a time-to-exhaustion/fatigue test (i.e., endurance capacity) in 7 studies and a fixed-endpoint task (i.e., time trial and/or performing as much work as possible in set time) in 14 studies. Table 2 indicates there was no significant difference ($p = .09$) in the *ES*s of studies that used an open-endpoint (time-to-fatigue) protocol versus fixed endpoint (time trial), and both test methods elicited less than a moderate *ES* (<0.50).

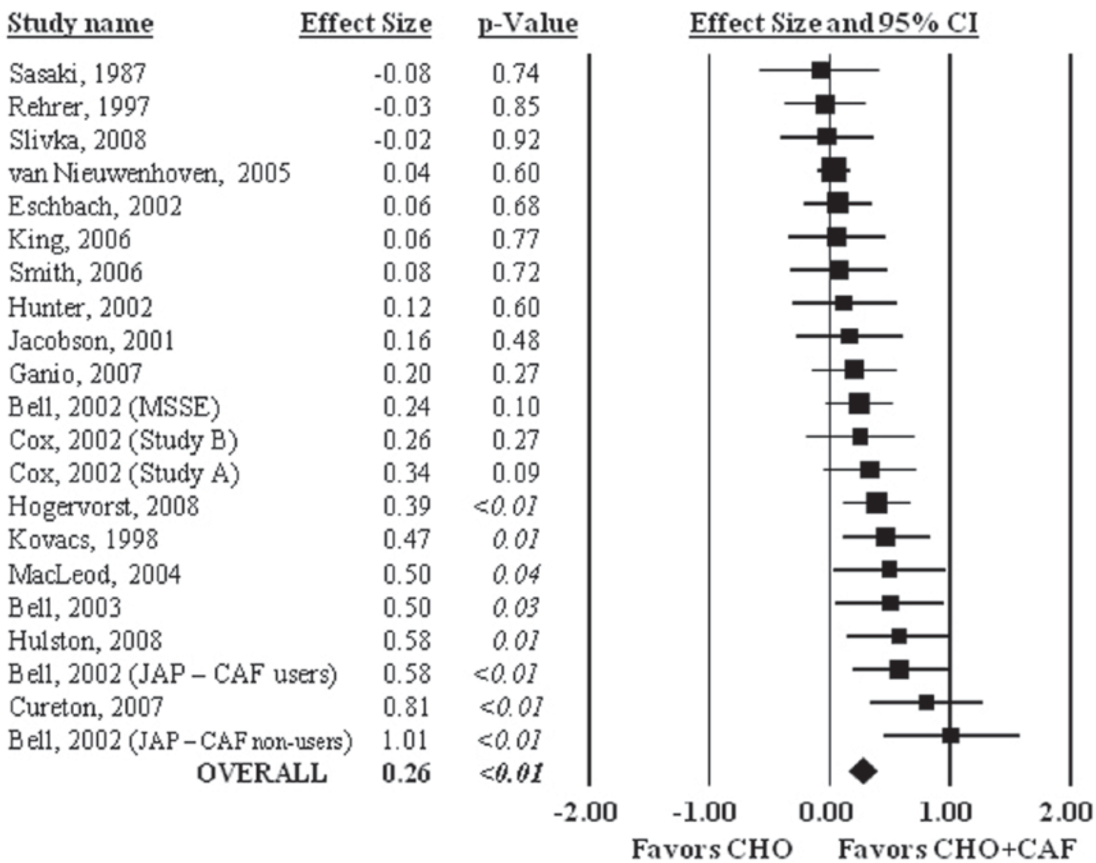

Figure 1 — Forest plot with effect size (*ES*) for individual studies (square) and overall summary *ES* (diamond; Hedges's *g*) on performance when carbohydrate (CHO) ingestion is compared with CHO+caffeine (CHO+CAF). Line indicates 95% confidence interval, and the size of the square indicates the relative weight assigned to the individual study. Studies are listed in ascending order of *ES*.

Table 2 Summary of Moderator-Variable Analysis for CHO Versus CHO+CAF Meta-Analysis by Subgroup and Metaregression

Moderator variable	p^a	Comparison
Timing of CAF administration	.69	Preexercise + During:
		immediately before or during exercise (*n* = 9, *ES* = 0.26, 95% *CI* 0.09–0.42)
		≥60 min before and during exercise (*n* = 4, *ES* = 0.16, 95% *CI* –0.11 to 0.42)
		Preexercise only:
		30–90 min prior (*n* = 9, *ES* = 0.34, 95% *CI* 0.16–0.52)
		>90 min prior (*n* = 1, *ES* = 0.38, 95% *CI* –0.18 to 0.95)
Exercise mode	.10	Cycling (*n* = 18, *ES* = 0.30, 95% *CI* 0.18–0.42)
		Running (*n* = 3, *ES* = 0.08, 95% *CI* –0.15 to 0.32)
Performance test	.09	Open endpoint: time to fatigue (*n* = 7, *ES* = 0.40, 95% *CI* 0.21–.060)
		Fixed endpoint: time trial (*n* = 14, *ES* = 0.20, 95% *CI* 0.08–0.33)
Sustained submaximal exercise bout before performance task	.68	No (*n* = 10, *ES* = 0.29, 95% *CI* 0.13–0.46)
		Yes (*n* = 11, *ES* = 0.24, 95% *CI* 0.08–0.40)
Gender	.59	Men (*n* = 16, *ES* = 0.23, 95% *CI* 0.10–0.37)
		Men and women (*n* = 4, *ES* = 0.33, 95% *CI* 0.09–0.58)
		Women (*n* = 1, *ES* = 0.50, 95% *CI* –0.11 to 0.11)
Publication status	.12	Unpublished studies (*n* = 6, *ES* = 0.13, 95% *CI* –0.08 to 0.33)
		Published studies (*n* = 15, *ES* = 0.32, 95% *CI* 0.19–0.46)
CAF dose	.99	Metaregression of CAF dose vs. *ES* (slope = .0004, 95% *CI* –0.04 to 0.05)
Maximal oxygen uptake (VO_{2max})	.20	Metaregression of VO_{2max} vs. *ES* (slope = –.0095, 95% *CI* –0.02 to 0.01)
Duration of performance task	.09	Metaregression of duration vs. *ES* (slope = –.003, 95% *CI* –0.006 to 0.0004)

Note. CHO = carbohydrate; CAF = caffeine; *n* = number of studies; *ES* = effect size; *CI* = confidence interval

[a]Test for statistical difference between the moderator-variable subgroups (e.g., for performance test, open versus fixed endpoint tended to differ, *p* = .09) and metaregression (e.g., duration of performance tended to be related to study *ES*, *p* = .09, such that longer tests elicited lower *ES*s).

Because unpublished studies tend to report smaller *ES*s (and, often, nonsignificant findings), a subgroup meta-analysis was run on unpublished studies (*n* = 6) compared with published studies (*n* = 15). The *ES* for CHO+CAF versus CHO in the unpublished studies resulted in an *ES* of 0.13 compared with the published studies' overall *ES* (0.32), which tended to be different from each other (*p* = .09) as illustrated in Table 2. Therefore, inclusion of the unpublished studies reduced the overall *ES* from 0.32 to 0.26 but did not affect the summary conclusions regarding the performance enhancement of CHO+CAF compared with CHO. Publication bias was also assessed by examining a funnel plot of the standard error versus *ES*. In the absence of publication bias, the studies are distributed symmetrically about the mean *ES* because the sampling error is random. The funnel plot illustrated a disproportionate number of studies to the right of the overall *ES* (favoring CHO+CAF). Using Duval and Tweedie's (2000) trim-and-fill correction, six "studies" would need to be imputed into the analysis to produce symmetry about the mean *ES* (with studies favoring CHO). The results of the trim-and-fill correction to produce symmetry reduced the overall *ES* of CHO+CAF to 0.14 (95% *CI* 0.02–0.27), which approaches a trivial *ES* but is still statistically significant.

Study Characteristics for CAF Versus Placebo Analysis

In all, 152 articles were identified for potential inclusion in the analysis. Thirty-three peer-reviewed research articles met the inclusion criteria (Alves et al., 1995; Bell, Jacobs, & Zamecnik, 1998; Bell & McLellan, 2002; Berglund & Hemmingsson, 1982; Bridge & Jones, 2006; Butts & Crowell, 1985; Cadarette, Levine, Berube, Posner, & Evans, 1983; Cha et al., 2001; Cohen et al., 1996; Collomp et al., 2002; Conway, Orr, & Stannard, 2003; Costill et al., 1978; Denadai & Denadai, 1998; French et al., 1991; Fulco et al., 1994; Graham, Hibbert, & Sathasivam, 1998; Graham & Spriet, 1991; Greer, Hudson, Ross, & Graham, 2001; Ivy et al., 1979; Jenkins, Trilk, Singhal, O'Conner, & Cureton, 2008; Lindinger, Graham, & Spriet, 1993; MacIntosh & Wright, 1995; McLellan & Bell, 2004; McLellan, Bell, & Kamimori, 2004; McNaughton et al., 2008; Norager, Jensen, Madsen, & Laurberg, 2005; Pasman et al., 1995; Powers, Byrd, Tulley, & Callendar, 1983; Sasaki et al., 1987; Slivka et al., 2008; Spriet et al., 1992; Trice & Haymes, 1995; Van Soeren & Graham, 1998; Table 3). Three research articles (Bell & McLellan, 2002; Berglund & Hemmingsson, 1982; Butts & Crowell, 1985) reported

Table 3 Summary of the Studies Included in the Placebo Versus CAF Meta-Analysis Listed in Chronological Order

Study	*N* (M/F)	VO_{2max} (ml · kg^{-1} · min^{-1})	CAF dose (mg/kg)	EM	Performance task	Average % change in performance
Costill et al., 1978	9 (7/2)	M: 60.2, F: 60.0	4.7	CE	Run until exhaustion at 80% VO_{2max}	19.5
Ivy et al., 1979	9 (7/2)	M: 58.5, F: 47.3	7.2	CE	Total work completed in 2 hr (kpm)	7.4
Berglund & Hemmingsson, 1982 (low altitude)	14 (10/4)	NR	6.0	XX	Time to complete a set distance (20 or 23 km)	1.8
Berglund & Hemmingsson, 1982 (high altitude)	13 (8/5)	NR	6.0	XX	Time to complete a set distance (20 or 23 km)	3.5
Powers et al., 1983	7 (7/0)	56	5.0	CE	Ride until exhaustion: graded test starting at 30 W, increased 30 W every 3 min	1.8
Cadarette et al., 1983	8 (4/4)	M: ≥50, F: ≥45	2.2, 4.4, 8.8	TR	Run until exhaustion at 80% VO_{2max}	24.3
Butts & Crowell, 1985 (men)	13 (13/0)	49.4	4.0	CE	Ride until exhaustion at 70–75% VO_{2max}	3.0
Butts & Crowell, 1985 (women)	15 (0/15)	47.9	5.1	CE	Ride until exhaustion at 70–75% VO_{2max}	12.6
Sasaki et al., 1987	5 (5/0)	62.7	7.3	TR	Run until exhaustion at 80% VO_{2max}	33.4
French et al., 1991	6 (6/0)	57.9	10.0	TR	Run until exhaustion at 75% VO_{2max}	1.9
Graham & Spriet, 1991	7 (6/1)	72.6	9.0	TR, CE	Ride or run until exhaustion at 85% VO_{2max}	47.4
Spriet et al., 1992	8 (7/1)	54.7	9.0	CE	Ride until exhaustion at 80% VO_{2max}	26.9
Lindinger et al., 1993	8 (8/0)	74.6	3, 6, 9	TR	Run until exhaustion at 85% VO_{2max}	19.2
Fulco et al., 1994	8 (8/0)	50.4	4.0	CE	Ride until exhaustion at 80% VO_{2max} at various altitudes (SL, acute and chronic at 4,300 m)	27.1
MacIntosh & Wright, 1995	11 (7/4)	NR	6.0	PS	Time to complete a set distance (1,500 m)	1.8
Trice & Haymes, 1995	8 (8/0)	54.5	5.0	CE	Ride until exhaustion at 85–90% VO_{2max}	26.5
Pasman et al., 1995	9 (NR)	65.1	5, 9, 13	CE	Ride until exhaustion at 80% W_{max}	25.1
Alves et al., 1995	8 (8/0)	36.9	10.0	CE	Ride until exhaustion at 80% W_{max}	15.9
Cohen et al., 1996	7 (5/2)	NR	5, 9	OR	21-km competitive outdoor run	0.3

(continued)

Table 3 *(continued)*

Study	*N* (M/F)	VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$)	CAF dose (mg/kg)	EM	Performance task	Average % change in performance
Graham et al., 1998	9 (8/1)	M: 69.1, F: 52.5	4.5	TR	Run until exhaustion at 85% VO_{2max}	14.3
Bell et al., 1998	8 (8/0)	47	5.0	CE	Ride until exhaustion at 85% VO_{2peak}	14.3
Van Soeren & Graham, 1998	6 (6/0)	54.5	6.0	CE	Ride until exhaustion at 80–85% VO_{2max}	30.4
Denadai & Denadai, 1998	8 (8/0)	NR	5.0	CE	Ride until exhaustion at 10% below and 10% above AT	26.0
Greer et al., 2001	8 (8/0)	57.5	6.0	CE	Ride until exhaustion at 80% VO_{2max}	26.3
Cha et al., 2001	5 (5/0)	53.2	5.0	CE	Ride until exhaustion at 80% VO_{2max}	42.3
Bell & McLellan, 2002 (CAF users)	13 (NR)	51.2	5.0	CE	Ride until exhaustion at 80% VO_{2max}	20.7
Bell & McLellan, 2002 (CAF nonusers)	8 (NR)	50.7	5.0	CE	Ride until exhaustion at 80% VO_{2max}	11.5
Collomp et al., 2002	8 (8/0)	54.4	3.6	CE	Mean power during 10 min at 90% VO_{2max}	2.2
Conway et al., 2003	9 (NR)	72.0	6.0	CE	Time to complete target work equivalent to 30 min at 80% VO_{2max}	20.3
McLellan, Bell, & Kamimori, 2004	16 (NR)	47.8	7.2	TR, SB	Run until exhaustion at 80% VO_{2max}, time to complete 6 sandbag walls	5.9
McLellan & Bell, 2004	13 (9/4)	52.0	4.1, 5.0, 6.1, 8.1	CE	Ride until exhaustion at 80% VO_{2max}	26.6
Norager et al., 2005	30 (15/15)	NR	6.0	CE	Ride until exhaustion at 65% expected HR_{max}	16.5
Bridge & Jones, 2006	8 (8/0)	NR	3.0	TK	Competitive 8-km track run	1.2
Jenkins et al., 2008	13 (13/0)	55.2	1, 2, 3	CE	Total work performed in 15 min	2.1
McNaughton et al., 2008	8 (8/0)	63.6	6.0	CE	Distance completed in 60 min at 2% grade	4.1
Slivka et al., 2008	9 (9/0)	59.5	10.8	CE	Time to complete 20 km	4.7

Note. CAF = caffeine; VO_{2max} = maximal oxygen uptake; EM = exercise mode; CE = cycle ergometer; NR = data not reported; XX = cross-country skiing; TR = treadmill running; SL = sea level; PS = pool swimming; W_{max} = maximum workload; OR = outdoor running; AT = anaerobic threshold; SB = sandbag piling; expected HR_{max} = 220 – age; TK = track running.

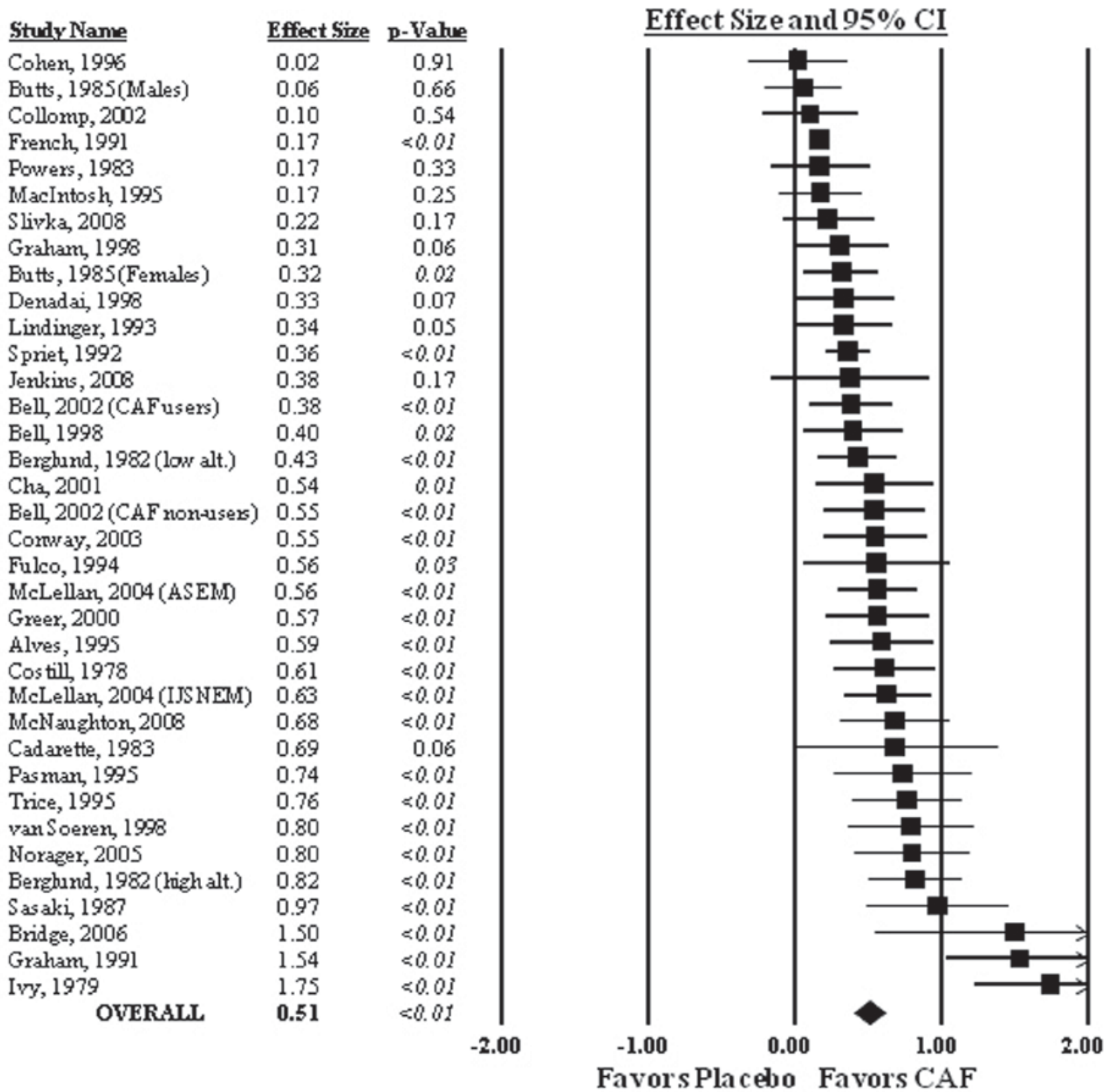

Figure 2 — Forest plot with individual studies and overall summary effect size (*ES;* diamond, Hedges's *g*) on performance when placebo is compared with caffeine (CAF). Studies are listed in ascending order of *ES*.

results using subgroups with different subjects. Thus, in all, 36 studies were used in the analysis. There was a total of 352 subjects in the 33 studies, with 79% of the subjects being men. Subjects' average VO_{2max} ranged among the studies from 37 to 75 ml · kg^{-1} · min^{-1}. The CAF dose administered ranged from 1 to 13 mg/kg (median dose 5.0 mg/kg). In addition, none of these studies reported a CHO meal within 2 hr of the test.

*ES*s for CAF Versus Placebo Analysis

All 36 study *ES*s were positive, ranging from 0.02 to 1.75. The overall *ES* for the meta-analysis (*ES* = 0.51, 95% *CI* 0.41–0.62) was moderate in magnitude and statistically different from zero ($p < .001$; Figure 2). As in the previous analysis, no single study unduly influenced the results. For example, when we eliminated the study with the greatest *ES* (1.75), the overall *ES* (0.49) remained statistically significant ($p < .001$).

Comparison of the CHO+CAF Versus CHO and CAF Versus Placebo Analyses

The subgroup meta-analysis that compared all 57 studies indicated that the *ES* for CHO+CAF versus CHO (*ES* = 0.27, 95% *CI* 0.14–0.41) compared with CAF versus placebo (*ES* = 0.51, 95% *CI* 0.41–0.61) was significantly different ($p = .006$); consequently, CAF had less of an ergogenic benefit when added to CHO than when it was added to placebo. It is important to note that this comparison was not for caffeine alone versus CAF+CHO. Only three studies would have been available to perform that analysis and, as such, were insufficient to help assess the effect of CAF alone compared with CAF+CHO.

Discussion

The unique focus of this analysis was to determine whether CAF (a well-known endurance ergogenic aid) ingested with CHO would augment the already well-documented ergogenic effect of CHO alone. Our systematic review and meta-analysis indicate that CHO+CAF ingestion can significantly improve endurance-exercise performance compared with CHO alone, with a small overall *ES* (0.26). This appears to also be practically relevant for endurance-sport competition because performance differences of <1% are deemed meaningful, particularly at the elite level (Hopkins, Hawley, & Burke, 1999; Hopkins, Schabort, & Hawley, 2001). It has previously been documented in a systematic review (Ganio et al., 2009) and a meta-analysis (Doherty & Smith, 2004) that CAF's influence on endurance-exercise performance has a moderate *ES* (0.63) that is similar in magnitude to that observed in the current analysis (*ES* = 0.51). However, we extended this finding by reporting that CAF coingested with CHO added less of a performance benefit than when CAF was added to placebo. This suggests that the benefits derived from the combination of these two ergogenic aids are not truly "additive"; otherwise the *ES*s should have been similar no matter what CAF was coingested with.

It is therefore unlikely that the mechanisms of CAF's and CHO's actions are independent from each other when coingested, in contrast to the conclusions from at least one study used in the current analysis (Cox et al., 2002). Those authors (Cox et al., 2002) reported that a cola beverage aided endurance-cycling performance, and when they tested CAF and CHO separately each component appeared to have independent benefits. However, if the mechanisms of action were truly independent, one would predict that the overall *ES* of CAF would be the same regardless of what CAF was ingested or combined with (i.e., placebo or CHO). Instead, the additional benefit of CAF when combined with CHO was small compared with moderate (vs. placebo).

If the benefit of CHO+CAF is not truly independent, what is the explanation for CHO+CAF to further improve endurance performance over CHO alone? Studies that have observed improvements in endurance-exercise performance when combining CAF with CHO have suggested potential metabolic advantages. CHO+CAF ingestion facilitated higher rates of CHO oxidation that coincided with greater exercise intensity sustained during a performance ride (Cureton et al., 2007) than with CHO alone. Furthermore, the rate of CHO oxidation observed (Yeo, Jentjens, Wallis, & Jeukendrup, 2005) was significantly higher by 26% with CHO+CAF ingestion than in the comparable exercise condition with CHO alone; this was speculated to be because of facilitated CHO absorption across the gut wall (van Nieuwenhoven, Brummer, & Brouns, 2000; Yeo et al., 2005). However, higher CHO oxidation rates with CHO+CAF are not always reported (Sasaki et al., 1987), and intestinal absorption data are not currently available. Moreover, glucose metabolism during exercise appears similar for CAF when not ingested with CHO (placebo conditions; Battram, Shearer, Robinson, & Graham, 2004; Graham et al., 2000; Titlow, Ishee, & Riggs, 1991; Weir, Noakes, Myburgh, & Adams, 1987). Therefore, whether CHO+CAF provides some synergistic metabolic advantage (enhanced peak rate of CHO oxidation beyond that of ingesting CHO alone) remains to be verified as a potential mechanism underlying improved exercise performance.

Other potential mechanistic explanations by which CAF added to CHO might further improve performance are not well established. Performance improvements with CHO+CAF might be explained by CAF's additional mechanisms acting centrally or peripherally (Davis et al., 2003; Lopes et al., 1983; Meyers & Cafarelli, 2005). As an example, CAF is a known adenosine antagonist that can block the perception of fatigue (Davis et al., 2003), thereby explaining the lower perceived exertion observed with CAF in another meta-analysis (Doherty & Smith, 2005). Increased force production resulting from increasing motor-unit recruitment and activity, reducing sensations of force, pain or other direct skeletal-muscle factors that result in attenuated intrinsic muscle-strength loss have previously been suggested (Cureton et al., 2007) to explain the ergogenicity of CHO+CAF. It was recently reported (Warren et al., 2010) that CAF improves maximum voluntary strength in the knee-extensor muscle group (*ES* = 0.37) and muscle endurance (*ES* = 0.28) when the test is an open-endpoint test (e.g., time to fatigue for maintenance of a submaximal isometric force). Therefore, these strength improvements in a muscle group recruited heavily during cycling could also translate into endurance performance benefits, particularly because cycling was the exercise mode used in nearly all the studies in the CHO+CAF versus CHO meta-analysis.

Another possibility is that CAF could simply be a more robust ergogenic aid than CHO alone. Whether CAF alone is equal to or superior to CHO+CAF was not addressed in our analysis; this would have been impractical because of the few studies available (n = 3) that had CAF versus CHO+CAF comparisons. Because CAF acts potentially via multiple mechanisms, some of which might mimic those of CHO (e.g., metabolic) in addition to alternative effects (e.g., CNS, neuromuscular), this cannot be ruled out. However, this is unlikely because CHO benefits are not limited to metabolic benefits (Hargreaves, 2008).

Although the current analysis cannot provide mechanistic explanations as to why the combination of CHO+CAF is more efficacious than CHO alone, it does provide insight into factors that have been thought to influence variable results among investigations. Whether CAF dose is related to the *ES* of studies comparing CHO+CAF with CHO had not been previously analyzed systematically. In the few dose-response studies in our meta-analysis comparing CHO+CAF and CHO, one (Kovacs et al., 1998) found that CHO+CAF improved cycling performance at 2.1, 3.2, or 4.5 mg/kg versus CHO alone but that endurance was further enhanced at CAF doses >3 mg/kg. In contrast, another (Cox et al., 2002) reported that 1.5 and 3 mg/kg of CAF produced equally positive effects on endurance-cycling performance. Our results using metaregression indicate that CAF dose was not related to the *ES* of performance benefits for CHO+CAF versus CHO; however, it must be acknowledged that the dose used in the 20 studies clustered between 4 and 6 mg/kg.

To further understand the variability among studies regarding efficacy of ergogenic aids, the test protocol used to assess performance has often been cited as a potential intervening factor. Performance-test protocol has been debated over the years regarding reliability (Doyle & Martinez, 1998; Jeukendrup, Saris, Brouns, & Kester, 1996) and sensitivity (Hopkins et al., 2001). A time-to-exhaustion or open-endpoint protocol is limited in external validity because it fails to represent a task used in the competitive sport setting and produces greater variability (coefficient of variation of 27%; Jeukendrup et al., 1996). However, when time-to-exhaustion changes are converted to equivalent changes in power output, this test produces a very reliable measure of performance (Hopkins et al., 2001). On the other hand, although a fixed-task (time-trial) test intuitively has greater ecological validity, it can be negatively influenced by subjects' errors in pacing strategy. Recently, fixed- versus open-endpoint tests were observed to have similar sensitivity in detecting changes in endurance performance (Amann, Hopkins, & Marcora, 2008). Moreover, the studies in the CHO+CAF versus CHO comparison (Table 1) indicate that although the largest *mean* performance improvement occurred with open-endpoint (e.g., 15% improvement) compared with fixed-endpoint protocols (3% improvement), the *ES*s for open (0.40) versus fixed (0.20) were not statistically different with overlapping confidence intervals (Table 2), although time-to-fatigue tests tended to elicit greater *ES*s. A previous meta-analysis examining the effects of CAF on exercise testing also found a twofold difference between open and fixed protocols (Doherty & Smith, 2004). The main point from the current study, however, is that both test protocols are capable of detecting the benefits of CHO+CAF as an ergogenic aid versus CHO, and, thus, the performance test used does not fully explain the variability observed in the literature.

Because there was substantial heterogeneity in study *ES*s for the combined effect of CHO+CAF and none of the aforementioned factors appeared to adequately explain this *ES* dispersion, we also examined the impact of including unpublished studies in the meta-analysis. As we would have predicted, the overall *ES* of unpublished studies tended to be lower than in the published studies. This suggests that if additional studies were identified or performed that resulted in an *ES* favoring CHO, the overall *ES* could eventually shift toward a trivial benefit for CHO+CAF versus CHO. A funnel plot of standard error versus *ES* revealed asymmetry, and when the trim-and-fill correction was calculated (to artificially "adjust" the funnel plot to make the data symmetrical), including another six studies on the side favoring CHO would shift the overall *ES* of adding CAF to CHO to 0.14 (intermediate between a trivial and small benefit). This suggests potential publication bias and, thus, indicates a potential limitation of our systematic review (i.e., other unpublished, unidentified studies may exist) and an overall limitation in meta-analysis as a whole. Moreover, both authors and journal reviewers may not fully understand the importance of publishing studies with "null" effects to enhance accurate interpretation of the literature. So it should be recognized that as additional studies are performed (and published) over time, the current conclusions derived from this meta-analysis may be altered.

In conclusion, a systematic review and meta-analysis of the literature through early 2009 indicate that CHO+CAF ingestion before and/or during endurance exercise results in significantly improved performance compared with CHO alone. Based on the literature available, this ergogenic benefit does not appear to be directly related to factors often believed to influence results, such as the CAF dose or test protocol for endurance performance (time trial vs. time to fatigue). However, the magnitude of the performance benefit of adding CAF to CHO is less than when CAF is added to water (placebo). Future experimental investigations examining the impact of two potentially ergogenic substances ingested alone or in combination could address this issue mechanistically to advance our understanding of the limits of fatigue on endurance performance.

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References

Alves, M.N.M., Ferrari-Auarek, W.M., Pinto, K.M.C., Sá, K.R., Viveiros, J.P., Pereira, H.A.A., . . . Rodrigues, L.O.C. (1995). Effects of caffeine and tryptophan on rectal temperature, metabolism, total exercise time, rate of perceived exertion and heart rate. *Brazilian Journal of Medical and Biological Research, 28*(6), 705–709.

Amann, M., Hopkins, W.G., & Marcora, S.M. (2008). Similar sensitivity of time to exhaustion and time-trial to changes in endurance. *Medicine and Science in Sports and Exercise, 40*(3), 574–578.

Angus, D.J., Hargreaves, M., Dancey, J., & Febbraio, M.A. (2000). Effect of carbohydrate or carbohydrate plus medium-chain triglyceride ingestion on cycling time trial performance. *Journal of Applied Physiology, 88,* 113–119.

Battram, D.S., Shearer, J., Robinson, D., & Graham, T.E. (2004). Caffeine ingestion does not impede the resynthesis of proglycogen and macroglycogen after prolonged exercise and carbohydrate supplementation in humans. *Journal of Applied Physiology, 96,* 943–950.

Bell, D.G., Jacobs, I., & Zamecnik, J. (1998). Effects of caffeine, ephedrine and their combination on time to exhaustion during high-intensity exercise. *European Journal of Applied Physiology and Occupational Physiology, 77,* 427–433.

Bell, D.G., & McLellan, T.M. (2002). Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers. *Journal of Applied Physiology, 93,* 1227–1234.

Bell, D.G., & McLellan, T.M. (2003). Effect of repeated caffeine ingestion on repeated exhaustive exercise endurance. *Medicine and Science in Sports and Exercise, 35*(8), 1348–1354.

Bell, D.G., McLellan, T.M., & Sabiston, C.M. (2002). Effect of ingesting caffeine and ephedrine on 10-km run performance. *Medicine and Science in Sports and Exercise, 34*(2), 344–349.

Below, P.R., Mora-Rodriguez, R., Gonzalez-Alonso, J., & Coyle, E.F. (1995). Fluid and carbohydrate independently improve performance during 1 hr of intense exercise. *Medicine and Science in Sports and Exercise, 27,* 2000–2010.

Berglund, B., & Hemmingsson, P. (1982). Effects of caffeine ingestion on exercise performance at low and high altitudes in cross-country skiers. *International Journal of Sports Medicine, 3*(4), 234–236.

Borenstein, M., Hedges, L.V., Higgins, J.P.T., & Rothstein, H.R. (2009). *Introduction to meta-analysis*. West Sussex, UK: Wiley.

Bridge, C.A., & Jones, M.A. (2006). The effect of caffeine ingestion on 8km run performance in a field setting. *Journal of Sports Sciences, 24*(4), 433–439.

Burke, L.M. (2008). Caffeine and sports performance. *Applied Physiology, Nutrition, and Metabolism, 33*(6), 1319–1334.

Butts, N.K., & Crowell, D. (1985). Effect of caffeine ingestion on cardiorespiratory endurance in men and women. *Research Quarterly for Exercise and Sport, 56*(4), 301–305.

Cadarette, B.S., Levine, L., Berube, C.L., Posner, B.M., & Evans, W.J. (1983). Effects of varied dosages of caffeine on endurance exercise to fatigue. In N. G. Knuttgen, J. A. Vogel & J. Poortmans (Eds.), *International series on sports sciences* (Vol. 13, pp. 871–876). Champaign, IL: Human Kinetics.

Carter, J.M., Jeukendrup, A.E., & Jones, D.A. (2004). The effect of carbohydrate mouth rinse on 1-h cycle time trial performance. *Medicine and Science in Sports and Exercise, 36*(12), 2107–2111.

Cha, Y-S., Choi, S-K., Suh, H., Lee, S-N., Cho, D., & Lim, K. (2001). Effects of carnitine coingested caffeine on carnitine metabolism and endurance capacity in athletes. *Journal of Nutritional Science and Vitaminology, 47*(6), 378–384.

Coggan, A.R., & Coyle, E.F. (1987). Reversal of fatigue during prolonged exercise by carbohydrate infusion or ingestion. *Journal of Applied Physiology, 63,* 2388–2395.

Coggan, A.R., & Coyle, E.F. (1991). Carbohydrate ingestion during prolonged exercise: Effects on metabolism and performance. In J.O. Holloszy (Ed.), *Exercise and sport sciences reviews* (Vol. 19, pp. 1–40). Baltimore, MD: Williams & Wilkins.

Cohen, B.S., Nelson, A.G., Prevost, M.C., Thompson, G.D., Marx, B.D., & Morris, G.S. (1996). Effects of caffeine ingestion on endurance racing in heat and humidity. *European Journal of Applied Physiology and Occupational Physiology, 73*(3-4), 358–363.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ: Lawrence Erlbaum.

Cole, K.J., Costill, D.L., Starling, R.D., Goodpastor, B.H., Trappe, S.W., & Fink, W.J. (1996). Effect of caffeine ingestion on perception of effort and subsequent work production. *International Journal of Sport Nutrition, 6,* 14–23.

Collomp, K., Candau, R., Millet, G., Mucci, P., Borrani, F., Préfaut, C., & De Ceaurriz, J. (2002). Effects of salbutamol and caffeine ingestion on exercise metabolism and performance. *International Journal of Sports Medicine, 23,* 549–554.

Conway, K.J., Orr, R., & Stannard, S.R. (2003). Effect of a divided caffeine dose on endurance cycling performance, postexercise urinary caffeine concentration, and plasma paraxanthine. *Journal of Applied Physiology, 94,* 1557–1562.

Costill, D.L., Dalsky, G.P., & Fink, W.J. (1978). Effects of caffeine ingestion on metabolism and exercise performance. *Medicine and Science in Sports, 10*(3), 155–158.

Cox, G.R., Densbrow, B., Montgomery, P.G., Anderson, M.E., Bruce, C.R., Macrides, T.A., . . . Burke, L.M. (2002). Effect of different protocols of caffeine intake on metabolism and endurance performance. *Journal of Applied Physiology, 93,* 990–999.

Coyle, E.F. (1992). Carbohydrate supplementation during exercise. *The Journal of Nutrition, 122,* 788–795.

Coyle, E.F., Hagberg, J.M., Hurley, B.F., Martin, W.H., Ehsani, A.A., & Holloszy, J.O. (1983). Carbohydrate feeding during prolonged strenuous exercise can delay fatigue. *Journal of Applied Physiology, 55,* 230–235.

Cureton, K.J., Warren, G.L., Millard-Stafford, M.L., Wingo, J.E., Trilk, J., & Buyckx, M. (2007). Caffeinated sports drink: Ergogenic effects and possible mechanisms. *International Journal of Sport Nutrition and Exercise Metabolism, 17,* 35–55.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,* R399–R404.

Del Coso, J., Estevez, E., & Mora-Rodriguez, R. (2008). Caffeine effects on short-term performance during prolonged exercise in the heat. *Medicine and Science in Sports and Exercise, 40*(4), 744–751.

Denadai, B.S., & Denadai, M.L.D.R. (1998). Effects of caffeine on time to exhaustion in exercise performed below and above the anaerobic threshold. *Brazilian Journal of Medical and Biological Research, 31,* 581–585.

Doherty, M., & Smith, P.M. (2004). Effects of caffeine ingestion on exercise testing: A meta-analysis. *International Journal of Sport Nutrition and Exercise Metabolism, 14,* 626–646.

Doherty, M., & Smith, P.M. (2005). Effects of caffeine ingestion on rating of perceived exertion during and after exercise: A meta-analysis. *Scandinavian Journal of Medicine & Science in Sports, 15,* 69–78.

Doyle, J.A., & Martinez, A.L. (1998). Reliability for testing performance in runners and cyclists. *Research Quarterly for Exercise and Sport, 69*(3), 304–307.

Duval, S., & Tweedie, R. (2000). A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *Journal of the American Statistical Association, 95,* 89–98.

Eschbach, L.C., Drake, S.M., Boyd, J.C., Whitehead, M.T., Magal, M., & Webster, M.J. (2002). The effect of caffeine ingestion on metabolism and performance during prolonged cycling [abstract]. *Medicine and Science in Sports and Exercise, 34*(5, Suppl.) S87.

French, C., McNaughton, L., Davies, P., & Tristram, S. (1991). Caffeine ingestion during exercise to exhaustion in elite distance runners. *Journal of Sports Medicine and Physical Fitness, 31,* 425–432.

Fulco, C.S., Rock, P.B., Trad, L.A., Rose, M.S., Forte, V.A., Young, P.M., & Cymerman, A. (1994). Effect of caffeine on submaximal exercise performance at altitude. *Aviation, Space, and Environmental Medicine, 65,* 539–545.

Ganio, M.S., Klau, J.F., Casa, D.J., Armstrong, L.E., & Maresh, C.M. (2009). Effect of caffeine on sport-specific endurance performance: A systematic review. *Journal of Strength and Conditioning Research, 23*(1), 315–324.

Ganio, M.S., Klau, J.F., Lee, E.C., Yeargin, S.W., McDermott, B.P., Maresh, C.M., & Armstrong, L.E. (2007). Effect of a caffeinated carbohydrate-electrolyte fluid on cycling performance and leg maximal voluntary contraction [abstract]. *Medicine and Science in Sports and Exercise, 39*(5, Suppl.) S89.

Graham, T.E., Helge, J.W., Maclean, D.A., Kiens, B., & Richter, E.A. (2000). Caffeine ingestion does not alter carbohydrate or fat metabolism in human skeletal muscle during exercise. *The Journal of Physiology, 529*(3), 837–847.

Graham, T.E., Hibbert, E., & Sathasivam, P. (1998). Metabolic and exercise endurance effects of coffee and caffeine ingestion. *Journal of Applied Physiology, 85*(3), 883–889.

Graham, T.E., & Spriet, L.L. (1991). Performance and metabolic responses to a high caffeine dose during prolonged exercise. *Journal of Applied Physiology, 71,* 2292–2298.

Graham, T.E., & Spriet, L.L. (1995). Metabolic, catecholamine, and exercise performance responses to various doses of caffeine. *Journal of Applied Physiology, 78,* 867–874.

Greer, F., Hudson, R., Ross, R., & Graham, T. (2001). Caffeine ingestion decreases glucose disposal during a hyperinsulinemic-euglycemic clamp in sedentary humans. *Diabetes, 50,* 2349–2354.

Hargreaves, M. (2008). Fatigue mechanisms determining exercise performance: Integrative physiology is systems biology. *Journal of Applied Physiology, 104,* 1541–1542.

Hogervorst, E., Bandelow, S., Schmitt, J., Jentjens, R., Oliveira, M., Allgrove, J., & Gleeson, M. (2008). Caffeine improves physical and cognitive performance exhaustive exercise. *Medicine and Science in Sports and Exercise, 40*(10), 1841–1851.

Hopkins, W.G., Hawley, J.A., & Burke, L.M. (1999). Design and analysis of research on sport performance enhancement. *Medicine and Science in Sports and Exercise, 31*(3), 472–485.

Hopkins, W.G., Schabort, E.J., & Hawley, J.A. (2001). Reliability of power in physical performance tests. *Sports Medicine (Auckland, N.Z.), 31*(3), 211–234.

Hulston, C.J., & Jeukendrup, A.E. (2008). Substrate metabolism and exercise performance with caffeine and carbohydrate intake. *Medicine and Science in Sports and Exercise, 40*(12), 2096–2104.

Hunter, A.M., St. Clair Gibson, A., Collins, M., Lambert, M., & Noakes, T.D. (2002). Caffeine ingestion does not alter performance during a 100-km cycling time-trial performance. *International Journal of Sport Nutrition and Exercise Metabolism, 12,* 438–452.

Ivy, J.L., Costill, D.L., Fink, W.J., & Lower, R.W. (1979). Influence of caffeine and carbohydrate feedings on endurance performance. *Medicine and Science in Sports, 11*(1), 6–11.

Jackman, M., Wendling, P., Friars, D., & Graham, T.E. (1996). Metabolic, catecholamine, and endurance responses to caffeine during intense exercise. *Journal of Applied Physiology, 81,* 1658–1663.

Jacobson, T.L., Febbraio, M.A., Arkinstall, M.J., & Hawley, J.A. (2001). Effect of caffeine co-ingested with carbohydrate or fat on metabolism and performance in endurance-trained men. *Experimental Physiology, 86*(1), 137–144.

Jenkins, N.T., Trilk, J.L., Singhal, A., O'Conner, P.J., & Cureton, K.J. (2008). Ergogenic effects of low doses of caffeine on cycling performance. *International Journal of Sport Nutrition and Exercise Metabolism, 18,* 328–342.

Jeukendrup, A., Saris, W.H.M., Brouns, F., & Kester, A.D.M. (1996). A new validated endurance performance test. *Medicine and Science in Sports and Exercise, 28*(2), 266–270.

King, R.F.G.J., O'Hara, J.P., & Carlton, C.B. (2006). Effects of pre-exercise ingestion of galactose, glucose and fructose on endurance performance [abstract]. *Medicine and Science in Sports and Exercise, 38*(5, Suppl.) S38.

Kovacs, E.M.R., Stegen, J.H.C.H., & Brouns, F. (1998). Effect of caffeinated drinks on substrate metabolism, caffeine excretion, and performance. *Journal of Applied Physiology, 85*(2), 709–715.

Lindinger, M.I., Graham, T.E., & Spriet, L.L. (1993). Caffeine attenuates the exercise-induced increase in plasma [K^+] in humans. *Journal of Applied Physiology, 74*(3), 1149–1155.

Lopes, J.M., Aubier, M., Jardim, J., Aranda, J.V., & Macklem, P.T. (1983). Effect of caffeine on skeletal-muscle function before and after fatigue. *Journal of Applied Physiology, 54,* 1303–1305.

MacIntosh, B.R., & Wright, B.M. (1995). Caffeine ingestion and performance of a 1500-metre swim. *Canadian Journal of Applied Physiology, 20*(2), 168–177.

MacLeod, J.M.M. (2004). *The effect of caffeine on endurance performance in trained female cyclists*. Victoria, BC: University of Victoria.

McLellan, T.M., & Bell, D.G. (2004). The impact of prior coffee consumption on the subsequent ergogenic effect of anhydrous caffeine. *International Journal of Sport Nutrition and Exercise Metabolism, 14,* 698–708.

McLellan, T.M., Bell, D.G., & Kamimori, G.H. (2004). Caffeine improves physical performance during 24 h of active wakefulness. *Aviation, Space, and Environmental Medicine, 75,* 666–672.

McNaughton, L.R., Lovell, R.J., Siegler, J.C., Midgley, A.W., Sandstrom, M., & Bentley, D.J. (2008). The effects of caffeine ingestion on time trial cycling performance. *Journal of Sports Medicine and Physical Fitness, 48*(3), 320–325.

Meyers, B.M., & Cafarelli, E. (2005). Caffeine increases time to fatigue by maintaining force and not altering firing rates during submaximal isometric contractions. *Journal of Applied Physiology, 99,* 1056–1063.

Millard-Stafford, M.L., Sparling, P.B., Rosskopf, L.B., & DiCarlo, L.J. (1992). Carbohydrate-electrolyte replacement improves distance running performance in the heat. *Medicine and Science in Sports and Exercise, 24*(8), 934–940.

Norager, C.B., Jensen, M.B., Madsen, M.R., & Laurberg, S. (2005). Caffeine improves endurance in 75-yr-old citizens: A randomized, double-blind, placebo-controlled, crossover study. *Journal of Applied Physiology, 99,* 2302–2306.

Pasman, W.J., van Baak, M.A., Jeukendrup, A.E., & De Haan, A. (1995). The effect of different dosages of caffeine on endurance performance time. *International Journal of Sports Medicine, 16*(4), 225–230.

Powers, S.K., Byrd, R.J., Tulley, R., & Callendar, T. (1983). Effects of caffeine ingestion on metabolism and performance during graded exercise. *European Journal of Applied Physiology and Occupational Physiology, 50,* 301–307.

Rehrer, N.J., Cusdin, T., & Deutsch, M. (1997). Effects of caffeine and carbohydrate on time trial cycling [abstract]. *Medicine and Science in Sports and Exercise, 29*(5, Suppl.) S252.

Sasaki, H., Maeda, J., Usui, S., & Ishiko, T. (1987). Effect of sucrose and caffeine ingestion on performance of prolonged strenuous running. *International Journal of Sports Medicine, 8,* 261–265.

Sherman, W.M., Brodowicz, G., Wright, D.A., Allen, W.K., Simonsen, J., & Dernbach, A. (1989). Effects of 4 h preexercise carbohydrate feedings on cycling performance. *Medicine and Science in Sports and Exercise, 21,* 598–604.

Slivka, D., Hailes, W., Cuddy, J., & Ruby, B. (2008). Caffeine and carbohydrate supplementation during exercise when in negative energy balance: Effects on performance, metabolism, and salivary cortisol. *Applied Physiology, Nutrition, and Metabolism, 33*(6), 1079–1085.

Smith, J.W., Stover, E.A., Lovett, S.C., & Zachwieja, J.J. (2006). Efficacy of caffeinated and non-caffeinated carbohydrate beverages on cycling performance [abstract]. *Medicine and Science in Sports and Exercise, 38*(11, Suppl.) S29.

Sökmen, B., Armstrong, L.E., Kraemer, W.J., Casa, D.J., Dias, J.C., Judelson, D.A., & Maresh, C.M. (2008). Caffeine use in sports: Considerations for the athlete. *Journal of Strength and Conditioning Research, 22*(3), 978–986.

Spriet, L.L., MacLean, D.A., Dyck, D.J., Hultman, E., Cederbald, G., & Graham, T.E. (1992). Caffeine ingestion and muscle metabolism during prolonged exercise in humans. *American Journal of Physiology. Endocrinology and Metabolism, 262,* E891–E898.

Titlow, L.W., Ishee, J.H., & Riggs, C.E. (1991). Failure of caffeine to affect metabolism during 60 min submaximal exercise. *Journal of Sports Sciences, 9*(1), 15–22.

Trice, I., & Haymes, E.M. (1995). Effects of caffeine ingestion on exercise-induced changes during high-intensity, intermittent exercise. *International Journal of Sport Nutrition, 5*(1), 37–44.

van Nieuwenhoven, M.A., Brouns, F., & Kovacs, E.M.R. (2005). The effect of two sports drinks and water on GI complaints and performance during an 18-km run. *International Journal of Sports Medicine, 26,* 281–285.

van Nieuwenhoven, M.A., Brummer, R., & Brouns, F. (2000). Gastrointestinal function during exercise: comparison of water, sports drink and sports drink with caffeine. *Journal of Applied Physiology, 89,* 1079–1085.

Van Soeren, M.H., & Graham, T.E. (1998). Effect of caffeine on metabolism, exercise endurance, and catecholamine responses after withdrawal. *Journal of Applied Physiology, 85,* 1493–1501.

Warren, G.L., Park, N.D., Maresca, R.D., McKibans, K.I., & Millard-Stafford, M.L. (2010). Effects of caffeine ingestion on muscular strength and endurance: A meta-analysis. *Medicine and Science in Sports and Exercise, 42*(7), 1375–1387.

Weir, J., Noakes, T.D., Myburgh, K., & Adams, B. (1987). A high carbohydrate diet negates the metabolic effects of caffeine during exercise. *Medicine and Science in Sports and Exercise, 19*(2), 100–105.

Yeo, S.E., Jentjens, R.L.P.G., Wallis, G.A., & Jeukendrup, A.E. (2005). Caffeine increases exogenous carbohydrate oxidation during exercise. *Journal of Applied Physiology, 99,* 844–850.