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

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ABSTRACT

Carbohydrate (CHO) and caffeine (CAF) both improve endurance performance. Whether CAF ingested with CHO (CHO+CAF) improves endurance performance more than CHO alone was examined by systematic literature review coupled with meta-analysis. Databases were searched using key words: caffeine, endurance, exercise, carbohydrate, and performance. Criterion for inclusion were studies utilizing human subjects performing an endurance exercise performance task and both a CHO and CHO+CAF condition. Effect sizes (ES) were calculated as the standardized mean difference. Twenty-one studies met the criteria for the analysis. ES 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, $p < 0.001$), indicating CHO+CAF provides a small but significant performance benefit over CHO. ES was not significantly ($p > 0.05$) related to CAF dosage, exercise duration, or performance assessment method. To determine whether ES of CHO+CAF versus CHO was different than CAF compared to water (placebo), a subgroup meta-analysis compared 36 "CAF vs. placebo" studies against the 21 "CHO+CAF vs. CHO" studies. Overall ES for the former group of studies (ES = 0.51, 95% CI 0.40 – 0.61) was nearly two-fold greater than "CHO+CAF vs. CHO" studies ($p = 0.006$). CHO+CAF ingestion provides a significant but small effect to improve endurance performance compared to CHO alone. However, the magnitude of the performance benefit that CAF provides is less when added to CHO than when added to placebo.

KEY WORDS: meta-analysis, performance, nutrition, supplement, fatigue

INTRODUCTION

Nutritional ergogenic aids are commonly used by recreational and elite athletes as a method for 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 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 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 caffeine (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 due to 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 caffeine's benefit (Cox, et al., 2002; Graham, Helge, Maclean, Kiens, & Richter, 2000; Graham & Spriet, 1991; Jackman, et al., 1996; Kovacs, Stegen, & Brouns, 1998). Alternate mechanisms have been proposed for the ergogenicity of CAF including those related to CNS and/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). Since CHO ingestion aids performance by supporting vital CHO metabolism and CAF potentially acts via alternate pathways (e.g., facilitating neuromuscular force production), it is tempting to speculate that CHO combined with CAF (CHO+CAF) may prove additive in augmenting endurance exercise performance compared to CHO alone.

To date, exercise performance studies investigating CHO+CAF compared to 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) while others demonstrate no additional benefit (Hunter, St. Clair Gibson, Collins, Lambert, & Noakes, 2002; Sasaki, Maeda, Usui, & Ishiko, 1987; van Nieuwenhoven, Brouns, & Kovacs, 2005) beyond CHO ingestion alone. The reason for equivocal results is unclear but may be due to a variety of experimental factors across the studies such as subject characteristics, caffeine dosage, 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 dosage and other aspects of the test protocol to assess performance) that could account for the variability in standardized mean differences or effect size (ES) among studies were also examined. Furthermore, in order 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 to placebo control) for endurance is similar to that when CAF is combined with CHO via systematic review/meta-analysis. If the ES of CAF is the same no matter what it is combined with, then it would suggest CAF's mechanism of action is independent of that for CHO (e.g., CHO facilitates metabolism while 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(s) 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 utilized studies on human subjects with a cross-over (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 minutes duration. However, the studies (Cureton, et al., 2007; Eschbach, et al., 2002; Ganio, 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 either pre-exercise ingestion of CHO and CHO+CAF within 90 minutes prior, ingestion during exercise, or both (pre-exercise ingestion and at some point(s) during exercise). Investigations that were published in peer-reviewed journals, as well as those available as scientific conference proceedings or theses/dissertations (in the case of one study by MacLeod, 2004) were included in order to avoid publication bias. Publication bias, as documented previously (Borenstein, Hedges, Higgins, & Rothstein, 2009) can occur because studies that report higher effect sizes are more likely to be published than those studies with low effect sizes; thus, this bias would then be introduced into the meta-analysis if only published studies are included.

For the primary meta-analysis comparing CHO+CAF versus CHO, the following key words 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 to water (or placebo) the key words caffeine AND (performance OR endurance OR exercise) were utilized. 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 was converted into the same format by calculating the standardized difference in means:$(\text{mean}_{CAF} - \text{mean}_{no\ CAF})/SD_{Pooled}$ where SD_{Pooled}

is the pooled standard deviation (Borenstein, et al., 2009). The SD_{Pooled} was calculated as follows:

$$(SD^2_{no\ CAF} + SD^2_{CAF} - 2 \times r_{no\ CAF,CAF} \times SD_{no\ CAF} \times SD_{CAF})^{0.5}/(2 \times (1 - r_{no\ CAF,CAF}))^{0.5}$$

where $r_{no\ CAF,CAF}$ is the inter-trial correlation between the no CAF and the 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 $r_{no\ CAF,CAF}$ were obtained from the study authors (Cureton, et al., 2007; Rehrer, Cusdin, & Deutsch, 1997). For studies in which we were not able to obtain inter-trial correlations, the mean of the reported/obtained correlations (r = 0.74, SD = 0.09, range 0.62 – 0.86; for CHO+CAF vs CHO, r = 0.86, SD = 0.12, range 0.68 – 0.99 for CAF vs. placebo) was used. The Hedges' correction (Hedges' g) was used to account for potential bias due to the small sample sizes that were 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):

$$1 - (3/(4 \times (\text{Number of Subjects}_{no\ CAF,CAF} - 1) - 1)$$

In studies that reported more than one study outcome, an average of the study's ES and their associated variances were used in the calculation of the meta-analysis' overall ES. 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 since experimental factor levels had wide variation such as caffeine dosage and test protocols to assess endurance performance. 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 while a positive ES would indicate that the condition with CAF yielded better performance outcomes. The reference points developed by Cohen (Cohen, 1988) were used for interpretation, i.e., that ES of 0.2, 0.5, 0.8 were considered to be of small, moderate and large magnitude, respectively.

To assess whether various experimental factors could explain the variation in ES observed among the studies, subgroup meta-analyses or meta-regressions (method-of-moments model) were conducted. These analyses included meta-regressions of continuous data: (1) CAF dosage, (2) duration of the performance task, and (3) subjects' fitness level (VO_{2max}) against study ES. Subgroup meta-analyses were used to examine the effects of categorical data: (1) timing of the CAF administration (e.g., before or during exercise), (2) exercise mode (cycling vs. running), (3) type of performance task (time to fatigue vs. fixed endpoint task such as a time trial or work completed in fixed time), (4) gender of subjects (men, women, or both), and (5) completion of an exercise bout prior to performance event (yes or no), and (6) published versus unpublished studies. Publication bias was also assessed by displaying the relationship between ES of each study and standard error in a funnel plot combined with a trim and fill correction (Duval & Tweedie, 2000). These techniques were utilized previously in a meta-analysis from our group (Warren, Park, Maresca, McKibans, & Millard-Stafford, 2010).

All calculations were made with Comprehensive Meta Analysis, Version 2.2 (Biostat, Englewood, NJ) software package. An α-level of 0.05 was used for all analyses to indicate statistical significance.

RESULTS

Study characteristics for CHO+CAF vs. CHO analysis. A total of 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, Hailes, Cuddy, & Ruby, 2008; van Nieuwenhoven, et al., 2005), five published abstracts from conference proceedings (Eschbach, et al., 2002; Ganio, et al., 2007; King, O'Hara, & Carlton, 2006; Rehrer, et al., 1997; Smith, Stover, Lovett, & Zachwieja, 2006), and one unpublished master's thesis (MacLeod, 2004). We included these well-designed scientific abstracts and thesis despite the tendency to influence the results towards a null finding. One research article (Cox, et al., 2002) reported results from two independent studies, and another (Bell & McLellan, 2002) used two sub-groups with different subjects (caffeine users and non-users). Thus, a total of 21 studies were used in the analysis. The dosages of both caffeine and carbohydrate were quite variable among these studies (as indicated in Table 1) and not reported in two studies (Bell, et al., 2002; MacLeod, 2004). CAF dosage in the CHO+CAF vs. CHO meta-analysis ranged from 1.3 to 10.8 mg per kg of body weight (median = 5 mg/kg). CHO dosage ingested across the duration of exercise ranged from 23.1 to 113.6 g per hr of exercise (median = 56.4 g/hr). Four studies did not consume the CHO and CAF at the same time points: CAF was consumed either three hr before beginning exercise (Eschbach, et al., 2002), one hr before beginning exercise (Rehrer, et al., 1997), or one hour before and during exercise (Cox Study 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 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 dosages were within a range previously determined to be ergogenic (Coyle, 1992; Coyle, et al., 1983). The CHO+CAF in these two studies also included small amounts of other ingredients (e.g. taurine, carnitine) which are not presently 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 % performance difference reported in the studies (last column in Table 1) suggests CHO+CAF might result in a 6% performance improvement versus CHO.

Effect sizes for CHO+CAF vs CHO analysis. The effect sizes 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 ($p < 0.001$)

(Figure 1). This indicates that CHO+CAF increases endurance exercise performance over CHO. Although the total number of available studies that met our inclusion/exclusion criteria was limited, no single study unduly influenced the results. For example, when eliminating the study with the greatest ES of 1.01 (a sub-group of subjects identified as CAF naïve; (Bell & McLellan, 2002), the overall ES, while reduced slightly (i.e., ES from 0.26 to 0.24), remained statistically significant ($p < 0.001$, 95% CI 0.13 – 0.34). In addition, when eliminating the two studies which had other ingredients in the CHO+CAF trials (Cureton, et al., 2007; Ganio, et al., 2007), the ES of 0.24 remained significant (p < 0.001, 95% CI 0.13 – 0.36).

Moderator variables for CHO+CAF vs. 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 dosage, fitness level (VO_{2max}) of the subjects, timing of CAF ingestion, mode of exercise, subject gender or completion of a sustained endurance exercise bout prior to the performance task). Since 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: 1) a time to exhaustion/fatigue test (i.e., endurance capacity), n=7 studies or, 2) a fixed endpoint task (i.e. time trial and/or performing as much work as possible in set time), n=14 studies. Table 2 indicates there was no significant difference ($p = 0.09$) in the ES of studies that utilized an open end point (time to fatigue) protocol versus fixed end point (time trial) and both test methods elicited less than a "moderate" ES (< 0.50).

Since unpublished studies tend to report smaller ES (and, frequently, non-significant findings), a sub-group meta-analysis was run on unpublished studies (n=6) compared to published studies (n=15). The ES for CHO+CAF versus CHO in the unpublished studies resulted in an ES of 0.13 compared to the published studies overall ES (0.32) which tended to be different from each other (p=0.09) as illustrated in Table 2. Therefore, inclusion of the unpublished studies reduced the overall ES from 0.32 to 0.26 but did not impact the summary conclusions regarding the performance enhancement of CHO+CAF compared to 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 since 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 trim and fill correction (Duval & Tweedie, 2000), 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 vs. placebo analysis. A total of 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 results using sub-groups with different subjects. Thus, a total of 36 studies were used in the analysis. There were 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 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$. The CAF dosage administered ranged from 1 to 13 mg/kg (median dosage = 5.0 mg/kg). In addition, none of these studies reported a CHO meal within 2 hrs of the test.

Effect sizes for CAF vs. Placebo analysis. All 36 study effect sizes 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 ($p < 0.001$) (Figure 2). As in the previous analysis, no single study unduly influenced the results. For example, when eliminating the study with the greatest ES (1.75), the overall ES (ES = 0.49) remained statistically significant ($p < 0.001$).

Comparison of the CHO+CAF vs. CHO and CAF vs. Placebo analyses. The sub-group 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 to CAF versus placebo (ES = 0.51, 95% CI 0.41 – 0.61) was significantly different ($p = 0.006$); consequently, CAF added less of an ergogenic benefit when added to CHO than when CAF was added to placebo. It is important to note that this comparison was not for caffeine alone vs. CAF+CHO. Only three studies would have been available to perform that analysis and, as such, insufficient to help assess the effect of CAF alone compared to CAF+CHO.

DISCUSSION

The unique focus of this analysis was to determine if 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 to CHO alone with a small overall ES (0.26). This appears to also be practically relevant for endurance sport competition since 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 meta-analysis (Doherty & Smith, 2004) that CAF's influence on endurance exercise performance has a moderate ES (0.63) which is similar in magnitude to that observed in the present analysis (ES=0.51). However, we extended this finding by reporting that CAF co-ingested with CHO added less of a performance benefit compared to when CAF is added to placebo. This suggests that the benefits derived from the combination of these two ergogenic aids are not truly "additive" or otherwise the ES should have been similar no matter what CAF was co-ingested with.

It is, therefore, unlikely that the mechanisms of CAF's and CHO's actions are independent from each other when co-ingested, in contrast to the conclusions from at least one study used in the present analysis (Cox, et al., 2002). These authors (Cox, et al., 2002) reported that a cola beverage aided endurance cycling performance and when testing 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 to “moderate” (versus placebo).

If the benefit of CHO+CAF is not truly independent, what is then the explanation for CHO+CAF to further improve endurance performance over CHO alone? Those studies that have observed endurance exercise performance improvements 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) compared to CHO alone. Furthermore, the rate of CHO oxidation observed (Yeo, Jentjens, Wallis, & Jeukendrup, 2005) was significantly higher by 26% with CHO+CAF ingestion than measured in the comparable exercise condition with CHO alone and speculated to be due to 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 either centrally and/or peripherally (Davis, et al., 2003; Lopes, et al., 1983; Meyers & Cafarelli, 2005). As an example, CAF is a known adenosine antagonist which 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 by increasing motor unit recruitment and activity, reducing sensations of force, pain or other direct skeletal muscle factors that result in attenuated intrinsic muscular 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 muscular 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 since cycling was the exercise mode utilized in nearly all of the studies in the CHO+CAF vs. 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 and impractical due to the few studies available (n=3) that had CAF versus CHO+CAF comparisons. Since CAF acts potentially via multiple mechanisms, some of which might mimic those of CHO (e.g. metabolic) in addition to alternate effects (e.g., CNS, neuromuscular), this cannot be ruled out. However, this is unlikely due to the fact that CHO benefits are also not limited to metabolic benefits either (Hargreaves, 2008).

Although the present analysis cannot provide mechanistic explanations as to why the combination of CHO+CAF is more efficacious compared to CHO alone, it does provide insight into factors that have been thought to influence variable results among investigations. Whether CAF dosage is related to the ES of studies comparing CHO+CAF to CHO had not been previously analyzed systematically. In the few dose-response studies in our meta-analysis comparing CHO+CAF to 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 endurance was further enhanced at CAF dosages > 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 meta-regression indicate that CAF dosage was not related to the ES of performance benefits for CHO+CAF vs. CHO; however, it must be acknowledged that the dosage utilized in the 20 studies clustered between 4 to 6 mg/kg.

To further understand the variability among studies regarding efficacy of ergogenic aids, the test protocol utilized 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 end point" protocol is limited in external validity since it fails to represent a task that is utilized 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 into 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 vs. CHO comparison (Table 1) indicate that although the largest *mean* performance improvement occurred with open end-point (e.g. 15% improvement) compared to fixed endpoint protocols (3%

improvement), the ES for open (0.40) versus fixed (0.20) were statistically indifferent with overlapping confidence intervals (Table 2), although time to fatigue tests tended to elicit greater ES. A previous meta-analysis examining the effects of CAF on exercise testing also found a twofold difference between open versus fixed protocols (Doherty & Smith, 2004). The main point from the present 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 utilized does not fully explain the variability observed in the literature.

Since there was substantial heterogeneity in study ES 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 unpublished studies being included in the meta-analysis. As we would have predicted, the overall ES of unpublished studies tended to be lower compared to 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 towards 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), the inclusion of 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 present 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 prior to and/or during endurance exercise results in significantly improved performance compared to 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 dosage or test protocol for endurance performance (time trial versus 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.

ACKNOWLEDGEMENTS

The authors would like to thank Angus Hunter, Marta Oliveira, Nancy Rehrer, Dustin Slivka, and John Eric Smith for providing additional details from their studies needed for this meta-analysis. In previous studies, Dr. Warren and Dr. Millard-Stafford have received industry research funding from The Coca Cola Company for work with carbohydrate and caffeine-containing products but only one of these studies is included (Cureton, et al., 2007) in this meta-analysis.

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LIST OF FIGURES

Table 1. Summary of the studies included in the CHO vs. CHO+CAF meta-analysis listed in chronological order.

Author, Year	***n (M/F)***	***VO_{2max} (ml/kg/min)***	***Total CAF Dosage (mg/kg)***	***Total CHO Dosage (g/hr)***	***Exercise Mode***	***Performance Task***	***% change in performance vs CHO***
Sasaki, 1987	5 (5/0)	62.7	6.2	52.9	Treadmill running	Run until exhaustion @ 80% VO_{2max}	-2.6
Rehrer, 1997	15 (15/0)	63	4.2	60.0	Cycle ergometer	Total work completed in 30 min	-0.4
Kovacs, 1998	15 (15/0)	NR	2.1, 3.2, or 4.5	74.8	Cycle ergometer	Time to complete a set amount of work (T(J) = 0.75 × W_{max} × 3600)	3.5
Jacobson, 2001	8 (8/0)	65.2	6.0	67.9	Cycle ergometer	Time trial to complete 7 kJ/kg of work	4.3
Bell, 2002 (MSSE)	12 (10/2)	57.5	4.0	NR	Treadmill running	10km treadmill run	1.7
Cox, 2002 (Study A)	12 (12/0)	66.4	1.3 or 6.0	74.8 or 60.4	Cycle ergometer	Time trial to complete 7 kJ/kg of work	3.3
Cox, 2002 (Study B)	8 (8/0)	71.2	1.9	113.6 or 84.0	Cycle ergometer	Time trial to complete 7 kJ/kg of work	2.2
Eschbach, 2002	11 (11/0)	54.9	6.0	23.1	Cycle ergometer	Simulated 5km time trial	0.8
Bell, 2002 (JAP – CAF users)	13 (NR)	51.2	5.0	25.8	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	26.1
Bell, 2002 (JAP – CAF nonusers)	8 (NR)	50.7	5.0	25.8	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	15.0
Hunter, 2002	8 (8/0)	64.6	6.0	42.5	Cycle ergometer	Simulated 100km time trial	1.3
Bell, 2003	9 (9/0)	52	5.0	25.8	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	22.8
MacLeod, 2004	8 (0/8)	56.1	5.0	NR	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	12.9
van Nieuwenhoven, 2005	98 (90/8)	NR	1.3	65.5	Outdoor running	18km competitive run	0.4
King, 2006	10 (10/0)	58.1	NR	37.9	Cycle ergometer	Ride until exhaustion @ 90% VO_{2max}	1.8
Smith, 2006	10 (10/0)	53.8	1.3	31.4	Cycle ergometer	Simulated 40km time trial	0.7
Cureton, 2007	16 (16/0)	71.2	5.3	66.2 or 56.4[a]	Cycle ergometer	Total work completed in 15 min	15.1
Ganio, 2007	14 (14/0)	60.4	5.9	66.2 or 56.4[a]	Cycle ergometer	Total work completed in 15 min	3.6
Slivka, 2008	11 (11/0)	59.5	10.8	48.0	Cycle ergometer	Simulated 20km time trial	-0.3
Hogervorst, 2008	24 (24/0)	56.6	4.1	45.0	Cycle ergometer	Ride until exhaustion @ 75% VO_{2max}	27.4
Hulston, 2008	10 (10/0)	65.7	5.3	30.1	Cycle ergometer	Time to complete a set amount of work (T(J) = 0.75 × W_{max} × 2700)	4.6

[a] CHO content was different in CHO and CHO+CAF conditions,
NR = data not reported
VO_{2max} = maximal oxygen uptake
W_{max} = maximum Watts
T(J) = total work in Joules

Table 2. Summary of moderator variable analysis for CHO vs CHO+CAF meta-analysis by sub-group and meta-regression.

Moderator Variable	***Comparison***	***p-value****
Timing of CAF administration sub-groups	Pre-exercise + During: Immediately prior to 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 – 0.42) Pre-exercise 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 – 0.95)	0.69
Exercise mode sub-group	Cycling (n = 18, ES = 0.30, 95% CI 0.18 – 0.42) Running (n = 3, ES = 0.08, 95% CI -0.15 – 0.32)	0.10
Performance test sub-group	Open end-point: Time to fatigue (n = 7, ES = 0.40, 95% CI 0.21 – 0.60) Fixed end-point: Time trial (n = 14, ES = 0.20, 95% CI 0.08 – 0.33)	0.09
Sustained submaximal exercise bout prior to performance task	No (n = 10, ES = 0.29, 95% CI 0.13 – 0.46) Yes (n = 11, ES = 0.24, 95% CI 0.08 – 0.40)	0.68
Gender sub-group	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 – 1.10)	0.59
Publication status sub-group	Unpublished studies (n = 6, ES = 0.13, 95% CI -0.08 – 0.33) Published studies (n = 15, ES = 0.32, 95% CI 0.19 – 0.46)	0.12
CAF dose	Meta-regression of CAF dose vs. ES (slope = 0.0004, 95% CI -0.04 – 0.05)	0.99
VO_{2max}	Meta-regression of VO_{2max} vs. ES (slope = -0.0095, 95% CI -0.02 – 0.01)	0.20
Duration of performance task	Meta-regression of duration vs. ES (slope = -0.003, 95% CI -0.006 – 0.0004)	0.09

n = number of studies; ES = effect size; CI = Confidence Interval

* indicates test for statistical difference between the moderator variable subgroups (e.g. for performance test: open versus fixed end-point tended to differ, p=0.09) and meta-regression (e.g., duration of performance tended to be related to study effect size, p=0.09, such that longer tests elicited lower ES).

Table 3. Summary of the studies included in the placebo vs CAF meta-analysis listed in chronological order

First Author, Year	***n (M/F)***	***VO_{2max} (ml/kg/ min)***	***CAF Dosage (mg/kg)***	***Exercise Mode***	***Performance Task***	***Average % change in performance***
Costill, 1978	9 (7/2)	M: 60.2 F: 60.0	4.7	Cycle ergometer	Run until exhaustion @ 80% VO_{2max}	19.5
Ivy, 1979	9 (7/2)	M: 58.5 F: 47.3	7.2	Cycle ergometer	Total work completed in 2 hrs (kpm)	7.4
Berglund, 1982 (Low altitude)	14 (10/4)	NR	6.0	Cross country skiing	Time to complete a set distance (20 or 23 km)	1.8
Berglund, 1982 (High altitude)	13 (8/5)	NR	6.0	Cross country skiing	Time to complete a set distance (20 or 23 km)	3.5
Powers, 1983	7 (7/0)	56	5.0	Cycle ergometer	Ride until exhaustion: graded test starting at 30W, increased 30W every 3 min	1.8
Cadarette, 1983	8 (4/4)	M: ≥50 F: ≥45	2.2, 4.4, 8.8	Treadmill running	Run until exhaustion @ 80% VO_{2max}	24.3
Butts, 1985 (Males)	13 (13/0)	49.4	4.0	Cycle ergometer	Ride until exhaustion @ 70-75% VO_{2max}	3.0
Butts, 1985 (Females)	15 (0/15)	47.9	5.1	Cycle ergometer	Ride until exhaustion @ 70-75% VO_{2max}	12.6
Sasaki, 1987	5 (5/0)	62.7	7.3	Treadmill running	Run until exhaustion @ 80% VO_{2max}	33.4
French, 1991	6 (6/0)	57.9	10.0	Treadmill running	Run until exhaustion @ 75% VO_{2max}	1.9
Graham, 1991	7 (6/1)	72.6	9.0	Treadmill running, Cycle ergometer	Ride/Run until exhaustion @ 85% VO_{2max}	47.4
Spriet, 1992	8 (7/1)	54.7	9.0	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	26.9
Lindinger, 1993	8 (8/0)	74.6	3, 6, 9	Treadmill running	Run until exhaustion @ 85% VO_{2max}	19.2
Fulco, 1994	8 (8/0)	50.4	4.0	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max} at various altitudes (SL, acute and chronic @ 4300m)	27.1
MacIntosh, 1995	11 (7/4)	NR	6.0	Pool swimming	Time to complete a set distance (1500m)	1.8
Trice, 1995	8 (8/0)	54.5	5.0	Cycle ergometer	Ride until exhaustion @ 85-90% VO_{2max}	26.5
Pasman, 1995	9 (NR)	65.1	5, 9, 13	Cycle ergometer	Ride until exhaustion @ 80% W_{max}	25.1
Alves, 1995	8 (8/0)	36.9	10.0	Cycle ergometer	Ride until exhaustion @ 80% W_{max}	15.9
Cohen, 1996	7 (5/2)	NR	5, 9	Outdoor running	21km competitive outdoor run	0.3
Graham, 1998	9 (8/1)	M: 69.1 F: 52.5	4.5	Treadmill running	Run until exhaustion @ 85% VO_{2max}	14.3

Bell, 1998	8 (8/0)	47	5.0	Cycle ergometer	Ride until exhaustion @ 85% VO_{2peak}	14.3
Van Soeren, 1998	6 (6/0)	54.5	6.0	Cycle ergometer	Ride until exhaustion @ 80-85% VO_{2max}	30.4
Denadai, 1998	8 (8/0)	NR	5.0	Cycle ergometer	Ride until exhaustion @ 10% below and 10% above AT	26.0
Greer, 2000	8 (8/0)	57.5	6.0	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	26.3
Cha, 2001	5 (5/0)	53.2	5.0	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	42.3
Bell, 2002 (CAF users)	13 (NR)	51.2	5.0	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	20.7
Bell, 2002 (CAF nonusers)	8 (NR)	50.7	5.0	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	11.5
Collomp, 2002	8 (8/0)	54.4	3.6	Cycle ergometer	Mean power during 10min @ 90% VO_{2max}	2.2
Conway, 2003	9 (NR)	72.0	6.0	Cycle ergometer	Time to complete target work equivalent to 30 min @ 80% VO_{2max}	20.3
McLellan, 2004 (ASEM)	16 (NR)	47.8	7.2	Treadmill running, Sand bag piling	Run until exhaustion @ 80% VO_{2max}, time to complete 6 sand bag walls	5.9
McLellan, 2004 (IJNEM)	13 (9/4)	52.0	4.1, 5.0, 6.1, 8.1	Cycle ergometer	Ride until exhaustion @ 80% VO_{2max}	26.6
Norager, 2005	30 (15/15)	NR	6.0	Cycle ergometer	Ride until exhaustion @ 65% expected HR_{max}	16.5
Bridge, 2006	8 (8/0)	NR	3.0	Track running	Competitive 8km track run	1.2
Jenkins, 2008	13 (13/0)	55.2	1, 2, 3	Cycle ergometer	Total work performed in 15 min	2.1
McNaughton, 2008	8 (8/0)	63.6	6.0	Cycle ergometer	Distance completed in 60 min @ 2% grade	4.1
Slivka, 2008	9 (9/0)	59.5	10.8	Cycle ergometer	Time to complete 20 km	4.7

NR = data not reported
VO_{2max} = maximal oxygen uptake
W_{max} = maximum Workload
SL = sea level
AT = Anaerobic Threshold
Expected HR_{max} = 220-age