

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

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Running Head: Ergogenicity of Caffeine Added to Carbohydrate

1 **ABSTRACT**

2 Carbohydrate (CHO) and caffeine (CAF) both improve endurance performance. Whether CAF  
3 ingested with CHO (CHO+CAF) improves endurance performance more than CHO alone was  
4 examined by systematic literature review coupled with meta-analysis. Databases were searched  
5 using key words: caffeine, endurance, exercise, carbohydrate, and performance. Criterion for  
6 inclusion were studies utilizing human subjects performing an endurance exercise performance  
7 task and both a CHO and CHO+CAF condition. Effect sizes (ES) were calculated as the  
8 standardized mean difference. Twenty-one studies met the criteria for the analysis. ES for  
9 individual studies ranged from -0.08 (trivial effect favoring CHO) to 1.01 (large effect favoring  
10 CHO+CAF). The overall ES equaled 0.26 (95% CI 0.15 – 0.38,  $p < 0.001$ ), indicating  
11 CHO+CAF provides a small but significant performance benefit over CHO. ES was not  
12 significantly ( $p > 0.05$ ) related to CAF dosage, exercise duration, or performance assessment  
13 method. To determine whether ES of CHO+CAF versus CHO was different than CAF compared  
14 to water (placebo), a subgroup meta-analysis compared 36 “CAF vs. placebo” studies against the  
15 21 “CHO+CAF vs. CHO” studies. Overall ES for the former group of studies (ES = 0.51, 95%  
16 CI 0.40 – 0.61) was nearly two-fold greater than “CHO+CAF vs. CHO” studies ( $p = 0.006$ ).  
17 CHO+CAF ingestion provides a significant but small effect to improve endurance performance  
18 compared to CHO alone. However, the magnitude of the performance benefit that CAF provides  
19 is less when added to CHO than when added to placebo.

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

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## 24 INTRODUCTION

25 Nutritional ergogenic aids are commonly used by recreational and elite athletes as a  
26 method for improving performance during endurance competitions. Two ergogenic aids that  
27 have routinely been used by athletes and investigated over several decades are carbohydrate  
28 (CHO) and caffeine (CAF). It is well established that CHO ingestion during prolonged ( $\geq 1$  hr),  
29 endurance exercise delays the onset of fatigue and improves exercise performance (Angus,  
30 Hargreaves, Dancy, & Febbraio, 2000; Below, Mora-Rodriguez, Gonzalez-Alonso, & Coyle,  
31 1995; Coggan & Coyle, 1987; Coyle, et al., 1983; Millard-Stafford, Sparling, Roskopf, &  
32 DiCarlo, 1992; Sherman, et al., 1989). The improvement observed in endurance exercise  
33 performance has generally been attributed to the provision of exogenous fuel source, increased  
34 rates of CHO oxidation, and maintenance of blood glucose to optimally supply the energy  
35 requirements for sustained high-intensity exercise (Coggan & Coyle, 1991; Coyle, 1992).  
36 Recent work has also suggested CHO may improve endurance performance via central nervous  
37 system (CNS) activation (Carter, Jeukendrup, & Jones, 2004; Del Coso, Estevez, & Mora-  
38 Rodriguez, 2008).

39 The ergogenic effect of caffeine (CAF) during endurance exercise has also been  
40 examined extensively (Costill, Dalsky, & Fink, 1978; Graham & Spriet, 1991, 1995; Ivy, Costill,  
41 Fink, & Lower, 1979; Jackman, Wendling, Friars, & Graham, 1996). However, several possible  
42 mechanisms, not all directly linked to energy metabolism, could explain improved endurance  
43 with CAF. It was originally postulated that performance improvements were due to a metabolic  
44 effect; specifically, CAF increased fat oxidation (Costill, et al., 1978; Ivy, et al., 1979), thereby  
45 reducing the reliance on muscle glycogen during exercise. Recent investigations have not  
46 validated this as the primary explanation for caffeine's benefit (Cox, et al., 2002; Graham, Helge,

47 Maclean, Kiens, & Richter, 2000; Graham & Spriet, 1991; Jackman, et al., 1996; Kovacs,  
48 Stegen, & Brouns, 1998). Alternate mechanisms have been proposed for the ergogenicity of CAF  
49 including those related to CNS and/or peripheral actions on skeletal muscle. For example,  
50 adenosine receptor antagonism (Davis, et al., 2003) in the CNS may explain the decreased  
51 perception of effort often observed with CAF during exercise (Cole, et al., 1996; Cox, et al.,  
52 2002; Doherty & Smith, 2005; Jacobson, Febbraio, Arkinstall, & Hawley, 2001). Moreover,  
53 peripheral mechanisms such as improved skeletal muscle force production may also underlie  
54 purported benefits (Lopes, Aubier, Jardim, Aranda, & Macklem, 1983; Meyers & Cafarelli,  
55 2005). Since CHO ingestion aids performance by supporting vital CHO metabolism and CAF  
56 potentially acts via alternate pathways (e.g., facilitating neuromuscular force production), it is  
57 tempting to speculate that CHO combined with CAF (CHO+CAF) may prove additive in  
58 augmenting endurance exercise performance compared to CHO alone.

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

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

## 83 **METHODS**

84           *Identification of studies for inclusion.* The databases of PubMed, SportDiscus, and  
85 ProQuest and conference proceedings from the American College of Sports Medicine Annual  
86 meeting (from the past 19 years) were searched through April 2009. Our review utilized studies  
87 on human subjects with a cross-over (within subject) research design. The studies were required  
88 to contain an endurance exercise bout that included a performance task (i.e., exercise time to  
89 fatigue, time to complete a set amount of work, or work completed in a set amount of time), and  
90 both a CHO and CHO+CAF condition. Our operational definition of endurance performance  
91 was that the exercise performance test per se be at least 10 minutes duration. However, the

92 studies (Cureton, et al., 2007; Eschbach, et al., 2002; Ganio, 2007) with test duration of 10-15  
93 min were preceded by a prolonged bout of submaximal exercise so that the total exercise  
94 duration of the test protocol was on average for all studies 94.0 min and ranged from 19.6 to  
95 250.4 min. For inclusion in the analysis, all study protocols had either pre-exercise ingestion of  
96 CHO and CHO+CAF within 90 minutes prior, ingestion during exercise, or both (pre-exercise  
97 ingestion and at some point(s) during exercise). Investigations that were published in peer-  
98 reviewed journals, as well as those available as scientific conference proceedings or  
99 theses/dissertations (in the case of one study by MacLeod, 2004) were included in order to avoid  
100 publication bias. Publication bias, as documented previously (Borenstein, Hedges, Higgins, &  
101 Rothstein, 2009) can occur because studies that report higher effect sizes are more likely to be  
102 published than those studies with low effect sizes; thus, this bias would then be introduced into  
103 the meta-analysis if only published studies are included.

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

113 ***Statistical analysis.*** Data from each study was converted into the same format by  
114 calculating the standardized difference in means:  $(\text{mean}_{\text{CAF}} - \text{mean}_{\text{no CAF}}) / \text{SD}_{\text{Pooled}}$  where  $\text{SD}_{\text{Pooled}}$

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

$$117 \quad (SD_{no\ CAF}^2 + SD_{CAF}^2 - 2 \times r_{no\ CAF,CAF} \times SD_{no\ CAF} \times SD_{CAF})^{0.5} / (2 \times (1 - r_{no\ CAF,CAF}))^{0.5}$$

118 where  $r_{no\ CAF,CAF}$  is the inter-trial correlation between the no CAF and the CAF conditions. In  
 119 seven studies, we were able to calculate  $r_{no\ CAF,CAF}$  from the reported data (Bell, McLellan, &  
 120 Sabiston, 2002; Eschbach, et al., 2002; French, McNaughton, Davies, & Tristram, 1991; Graham  
 121 & Spriet, 1991; MacLeod, 2004; Pasman, van Baak, Jeukendrup, & De Haan, 1995; Spriet, et al.,  
 122 1992) and in two instances  $r_{no\ CAF,CAF}$  were obtained from the study authors (Cureton, et al.,  
 123 2007; Rehrer, Cusdin, & Deutsch, 1997). For studies in which we were not able to obtain inter-  
 124 trial correlations, the mean of the reported/obtained correlations ( $r = 0.74$ ,  $SD = 0.09$ , range  $0.62$   
 125  $- 0.86$ ; for CHO+CAF vs CHO,  $r = 0.86$ ,  $SD = 0.12$ , range  $0.68 - 0.99$  for CAF vs. placebo) was  
 126 used. The Hedges' correction (Hedges'  $g$ ) was used to account for potential bias due to the small  
 127 sample sizes that were used in the reviewed studies. To do this, the standardized mean  
 128 difference and standard error were multiplied by the following correction factor (Borenstein, et  
 129 al., 2009):

$$130 \quad 1 - (3 / (4 \times (\text{Number of Subjects}_{no\ CAF,CAF} - 1) - 1))$$

131 In studies that reported more than one study outcome, an average of the study's ES and their  
 132 associated variances were used in the calculation of the meta-analysis' overall ES. The overall  
 133 ES was calculated using a random-effects model that accounts for true variation in effects  
 134 occurring from study to study as well as random error within a single study. The random-effects  
 135 model was chosen over a fixed-effect model since experimental factor levels had wide variation  
 136 such as caffeine dosage and test protocols to assess endurance performance. An ES of zero  
 137 would indicate that there is no difference between the two treatments. A negative ES would

138 indicate that the condition without CAF yielded better performance while a positive ES would  
139 indicate that the condition with CAF yielded better performance outcomes. The reference points  
140 developed by Cohen (Cohen, 1988) were used for interpretation, i.e., that ES of 0.2, 0.5, 0.8 were  
141 considered to be of small, moderate and large magnitude, respectively.

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

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

## 158 **RESULTS**

159 *Study characteristics for CHO+CAF vs. CHO analysis.* A total of 140 articles were  
160 identified for potential inclusion in the analysis. After reviewing the articles, 121 were



161 eliminated as not meeting the inclusion criteria (e.g., an endurance performance task of at least 10  
162 min, and comparing both CHO and CHO+CAF conditions). Nineteen studies met the inclusion  
163 criteria (Table 1): thirteen peer-reviewed research articles (Bell & McLellan, 2002, 2003; Bell, et  
164 al., 2002; Cox, et al., 2002; Cureton, et al., 2007; Hogervorst, et al., 2008; Hulston &  
165 Jeukendrup, 2008; Hunter, et al., 2002; Jacobson, et al., 2001; Kovacs, et al., 1998; Sasaki, et al.,  
166 1987; Slivka, Hailes, Cuddy, & Ruby, 2008; van Nieuwenhoven, et al., 2005), five published  
167 abstracts from conference proceedings (Eschbach, et al., 2002; Ganio, et al., 2007; King,  
168 O'Hara, & Carlton, 2006; Rehrer, et al., 1997; Smith, Stover, Lovett, & Zachwieja, 2006), and  
169 one unpublished master's thesis (MacLeod, 2004). We included these well-designed scientific  
170 abstracts and thesis despite the tendency to influence the results towards a null finding. One  
171 research article (Cox, et al., 2002) reported results from two independent studies, and another  
172 (Bell & McLellan, 2002) used two sub-groups with different subjects (caffeine users and non-  
173 users). Thus, a total of 21 studies were used in the analysis. The dosages of both caffeine and  
174 carbohydrate were quite variable among these studies (as indicated in Table 1) and not reported  
175 in two studies (Bell, et al., 2002; MacLeod, 2004). CAF dosage in the CHO+CAF vs. CHO  
176 meta-analysis ranged from 1.3 to 10.8 mg per kg of body weight (median = 5 mg/kg). CHO  
177 dosage ingested across the duration of exercise ranged from 23.1 to 113.6 g per hr of exercise  
178 (median = 56.4 g/hr). Four studies did not consume the CHO and CAF at the same time points:  
179 CAF was consumed either three hr before beginning exercise (Eschbach, et al., 2002), one hr  
180 before beginning exercise (Rehrer, et al., 1997), or one hour before and during exercise (Cox  
181 Study A and B) (Cox, et al., 2002). The CAF was ingested in the form of a capsule (Bell &  
182 McLellan, 2002, 2003; Bell, et al., 2002; Cox, et al., 2002; Eschbach, et al., 2002; Hunter, et al.,  
183 2002; Jacobson, et al., 2001; Rehrer, et al., 1997; Slivka, et al., 2008), dissolved in a drink

184 (Cureton, et al., 2007; Ganio, et al., 2007; Hulston & Jeukendrup, 2008; King, et al., 2006;  
185 Kovacs, et al., 1998; MacLeod, 2004; Sasaki, et al., 1987; van Nieuwenhoven, et al., 2005), or in  
186 a performance bar (Hogervorst, et al., 2008). Only three studies used a CHO condition that  
187 contained only CHO (plus flavoring) (MacLeod, 2004; Rehrer, et al., 1997; Sasaki, et al., 1987).  
188 In most of the other studies, the CHO condition was a sports drink with electrolytes (Bell &  
189 McLellan, 2002, 2003; Cox, et al., 2002; Cureton, et al., 2007; Eschbach, et al., 2002; Ganio, et  
190 al., 2007; Hunter, et al., 2002; King, et al., 2006; Kovacs, et al., 1998; Smith, et al., 2006; van  
191 Nieuwenhoven, et al., 2005). Two studies included in the analysis (Cureton, et al., 2007; Ganio,  
192 et al., 2007) used slightly different CHO drink concentrations (~1%) between the CHO and  
193 CHO+CAF study conditions; however, both were commercially-available sports drinks and  
194 CHO dosages were within a range previously determined to be ergogenic (Coyle, 1992; Coyle, et  
195 al., 1983). The CHO+CAF in these two studies also included small amounts of other ingredients  
196 (e.g. taurine, carnitine) which are not presently known to be ergogenic at the levels consumed.  
197 The 21 studies yielded a total of 333 subjects with 93% being men. The median number of  
198 subjects in a study was 11. Subjects were well trained with mean  $VO_{2max}$  ranging among the  
199 studies from 51 to 71  $ml \cdot kg^{-1} \cdot min^{-1}$ . The average % performance difference reported in the  
200 studies (last column in Table 1) suggests CHO+CAF might result in a 6% performance  
201 improvement versus CHO.

202 *Effect sizes for CHO+CAF vs CHO analysis.* The effect sizes for the 21 studies used in  
203 our primary meta-analysis ranged from -0.08 (trivial effect favoring CHO) to 1.01 (large effect  
204 favoring CHO+CAF) and are listed in ascending order in Figure 1. Eighteen of the 21 studies  
205 yielded a positive ES (i.e., favoring CHO+CAF). The overall ES of the meta-analysis was small  
206 in magnitude (ES = 0.26, 95% CI 0.15 – 0.38) but statistically different from zero ( $p < 0.001$ )

207 (Figure 1). This indicates that CHO+CAF increases endurance exercise performance over CHO.  
208 Although the total number of available studies that met our inclusion/exclusion criteria was  
209 limited, no single study unduly influenced the results. For example, when eliminating the study  
210 with the greatest ES of 1.01 (a sub-group of subjects identified as CAF naïve; (Bell & McLellan,  
211 2002), the overall ES, while reduced slightly (i.e., ES from 0.26 to 0.24), remained statistically  
212 significant ( $p < 0.001$ , 95% CI 0.13 – 0.34). In addition, when eliminating the two studies which  
213 had other ingredients in the CHO+CAF trials (Cureton, et al., 2007; Ganio, et al., 2007), the ES  
214 of 0.24 remained significant ( $p < 0.001$ , 95% CI 0.13 – 0.36).

215 ***Moderator variables for CHO+CAF vs. CHO analysis.*** Additional analyses assessing  
216 the effects of moderator variables were conducted to investigate potential underlying  
217 explanations for the ES variability observed among the studies. These results are summarized in  
218 Table 2. None of the variables probed had a significant impact on study ES variation (i.e., CAF  
219 dosage, fitness level ( $VO_{2max}$ ) of the subjects, timing of CAF ingestion, mode of exercise, subject  
220 gender or completion of a sustained endurance exercise bout prior to the performance task).  
221 Since performance was the primary dependent measure of interest and the test protocol used to  
222 assess performance has been identified as producing differential outcomes, two test protocol  
223 models were compared: 1) a time to exhaustion/fatigue test (i.e., endurance capacity),  $n=7$   
224 studies or, 2) a fixed endpoint task (i.e. time trial and/or performing as much work as possible in  
225 set time),  $n=14$  studies. Table 2 indicates there was no significant difference ( $p = 0.09$ ) in the ES  
226 of studies that utilized an open end point (time to fatigue) protocol versus fixed end point (time  
227 trial) and both test methods elicited less than a “moderate” ES ( $< 0.50$ ).

228 Since unpublished studies tend to report smaller ES (and, frequently, non-significant  
229 findings), a sub-group meta-analysis was run on unpublished studies ( $n=6$ ) compared to

230 published studies (n=15). The ES for CHO+CAF versus CHO in the unpublished studies  
231 resulted in an ES of 0.13 compared to the published studies overall ES (0.32) which tended to be  
232 different from each other ( $p=0.09$ ) as illustrated in Table 2. Therefore, inclusion of the  
233 unpublished studies reduced the overall ES from 0.32 to 0.26 but did not impact the summary  
234 conclusions regarding the performance enhancement of CHO+CAF compared to CHO.  
235 Publication bias was also assessed by examining a funnel plot of the standard error versus ES. In  
236 the absence of publication bias, the studies are distributed symmetrically about the mean ES  
237 since the sampling error is random. The funnel plot illustrated a disproportionate number of  
238 studies to the right of the overall ES (favoring CHO+CAF). Using Duval and Tweedie's trim  
239 and fill correction (Duval & Tweedie, 2000), six "studies" would need to be imputed into the  
240 analysis to produce symmetry about the mean ES (with studies favoring CHO). The results of  
241 the trim and fill correction to produce symmetry reduced the overall ES of CHO+CAF to 0.14  
242 (95% CI 0.02 – 0.27), which approaches a trivial ES but is still statistically significant.

243 ***Study characteristics for CAF vs. placebo analysis.*** A total of 152 articles were  
244 identified for potential inclusion in the analysis. Thirty-three peer-reviewed research articles met  
245 the inclusion criteria (Alves, et al., 1995; Bell, Jacobs, & Zamecnik, 1998; Bell & McLellan,  
246 2002; Berglund & Hemmingsson, 1982; Bridge & Jones, 2006; Butts & Crowell, 1985;  
247 Cadarette, Levine, Berube, Posner, & Evans, 1983; Cha, et al., 2001; Cohen, et al., 1996;  
248 Collomp, et al., 2002; Conway, Orr, & Stannard, 2003; Costill, et al., 1978; Denadai & Denadai,  
249 1998; French, et al., 1991; Fulco, et al., 1994; Graham, Hibbert, & Sathasivam, 1998; Graham &  
250 Spriet, 1991; Greer, Hudson, Ross, & Graham, 2001; Ivy, et al., 1979; Jenkins, Trilk, Singhal,  
251 O'Conner, & Cureton, 2008; Lindinger, Graham, & Spriet, 1993; MacIntosh & Wright, 1995;  
252 McLellan & Bell, 2004; McLellan, Bell, & Kamimori, 2004; McNaughton, et al., 2008; Norager,

253 Jensen, Madsen, & Laurberg, 2005; Pasman, et al., 1995; Powers, Byrd, Tulley, & Callendar,  
254 1983; Sasaki, et al., 1987; Slivka, et al., 2008; Spriet, et al., 1992; Trice & Haymes, 1995; Van  
255 Soeren & Graham, 1998) (Table 3). Three research articles (Bell & McLellan, 2002; Berglund &  
256 Hemmingsson, 1982; Butts & Crowell, 1985) reported results using sub-groups with different  
257 subjects. Thus, a total of 36 studies were used in the analysis. There were a total of 352 subjects  
258 in the 33 studies, with 79% of the subjects being men. Subjects' average  $\text{VO}_{2\text{max}}$  ranged among  
259 the studies from 37 to 75  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . The CAF dosage administered ranged from 1 to 13  
260 mg/kg (median dosage = 5.0 mg/kg). In addition, none of these studies reported a CHO meal  
261 within 2 hrs of the test.

262 ***Effect sizes for CAF vs. Placebo analysis.*** All 36 study effect sizes were positive,  
263 ranging from 0.02 to 1.75. The overall ES for the meta-analysis (ES = 0.51, 95% CI 0.41 –  
264 0.62) was moderate in magnitude and statistically different from zero ( $p < 0.001$ ) (Figure 2). As  
265 in the previous analysis, no single study unduly influenced the results. For example, when  
266 eliminating the study with the greatest ES (1.75), the overall ES (ES = 0.49) remained  
267 statistically significant ( $p < 0.001$ ).

268 ***Comparison of the CHO+CAF vs. CHO and CAF vs. Placebo analyses.*** The sub-group  
269 meta-analysis that compared all 57 studies indicated that the ES for CHO+CAF versus CHO (ES  
270 = 0.27, 95% CI 0.14 – 0.41) compared to CAF versus placebo (ES = 0.51, 95% CI 0.41 – 0.61)  
271 was significantly different ( $p = 0.006$ ); consequently, CAF added less of an ergogenic benefit  
272 when added to CHO than when CAF was added to placebo. It is important to note that this  
273 comparison was not for caffeine alone vs. CAF+CHO. Only three studies would have been  
274 available to perform that analysis and, as such, insufficient to help assess the effect of CAF alone  
275 compared to CAF+CHO.

276

277 **DISCUSSION**

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

292           It is, therefore, unlikely that the mechanisms of CAF's and CHO's actions are  
293 independent from each other when co-ingested, in contrast to the conclusions from at least one  
294 study used in the present analysis (Cox, et al., 2002). These authors (Cox, et al., 2002) reported  
295 that a cola beverage aided endurance cycling performance and when testing CAF and CHO  
296 separately each component appeared to have independent benefits. However, if the mechanisms  
297 of action were truly independent, one would predict that the overall ES of CAF would be the  
298 same regardless of what CAF was ingested or combined with (i.e. placebo or CHO). Instead, the

299 additional benefit of CAF when combined with CHO was “small” compared to “moderate”  
300 (versus placebo).

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

318         Other potential mechanistic explanations by which CAF added to CHO might further  
319 improve performance are not well-established. Performance improvements with CHO+CAF  
320 might be explained by CAF’s additional mechanisms acting either centrally and/or peripherally  
321 (Davis, et al., 2003; Lopes, et al., 1983; Meyers & Cafarelli, 2005). As an example, CAF is a

322 known adenosine antagonist which can block the perception of fatigue (Davis, et al., 2003)  
323 thereby explaining the lower perceived exertion observed with CAF in another meta-analysis  
324 (Doherty & Smith, 2005). Increased force production by increasing motor unit recruitment and  
325 activity, reducing sensations of force, pain or other direct skeletal muscle factors that result in  
326 attenuated intrinsic muscular strength loss have previously been suggested (Cureton, et al., 2007)  
327 to explain the ergogenicity of CHO+CAF. It was recently reported (Warren, et al., 2010) that  
328 CAF improves maximum voluntary strength in the knee extensor muscle group (ES=0.37) and  
329 muscular endurance (ES=0.28) when the test is an open-endpoint test (e.g., time to fatigue for  
330 maintenance of a submaximal isometric force). Therefore, these strength improvements in a  
331 muscle group recruited heavily during cycling could also translate into endurance performance  
332 benefits, particularly since cycling was the exercise mode utilized in nearly all of the studies in  
333 the CHO+CAF vs. CHO meta-analysis.

334 Another possibility is that CAF could simply be a more robust ergogenic aid than CHO  
335 alone. Whether CAF alone is equal to or superior to CHO+CAF was not addressed in our  
336 analysis and impractical due to the few studies available (n=3) that had CAF versus CHO+CAF  
337 comparisons. Since CAF acts potentially via multiple mechanisms, some of which might mimic  
338 those of CHO (e.g. metabolic) in addition to alternate effects (e.g., CNS, neuromuscular), this  
339 cannot be ruled out. However, this is unlikely due to the fact that CHO benefits are also not  
340 limited to metabolic benefits either (Hargreaves, 2008).

341 Although the present analysis cannot provide mechanistic explanations as to why the  
342 combination of CHO+CAF is more efficacious compared to CHO alone, it does provide insight  
343 into factors that have been thought to influence variable results among investigations. Whether  
344 CAF dosage is related to the ES of studies comparing CHO+CAF to CHO had not been



345 previously analyzed systematically. In the few dose-response studies in our meta-analysis  
346 comparing CHO+CAF to CHO, one (Kovacs, et al., 1998) found that CHO+CAF improved  
347 cycling performance at 2.1, 3.2, or 4.5 mg/kg versus CHO alone but endurance was further  
348 enhanced at CAF dosages > 3 mg/kg. In contrast, another (Cox, et al., 2002) reported that 1.5  
349 and 3 mg/kg of CAF produced equally positive effects on endurance cycling performance. Our  
350 results using meta-regression indicate that CAF dosage was not related to the ES of performance  
351 benefits for CHO+CAF vs. CHO; however, it must be acknowledged that the dosage utilized in  
352 the 20 studies clustered between 4 to 6 mg/kg.

353         To further understand the variability among studies regarding efficacy of ergogenic aids,  
354 the test protocol utilized to assess performance has often been cited as a potential intervening  
355 factor. Performance test protocol has been debated over the years regarding reliability (Doyle &  
356 Martinez, 1998; Jeukendrup, Saris, Brouns, & Kester, 1996) and sensitivity (Hopkins, et al.,  
357 2001). A time to exhaustion or “open end point” protocol is limited in external validity since it  
358 fails to represent a task that is utilized in the competitive sport setting and produces greater  
359 variability (coefficient of variation of 27%) (Jeukendrup, et al., 1996). However, when time to  
360 exhaustion changes are converted into equivalent changes in power output, this test produces a  
361 very reliable measure of performance (Hopkins, et al., 2001). On the other hand, although a  
362 fixed task (time trial) test intuitively has greater ecological validity, it can be negatively  
363 influenced by subjects’ errors in pacing strategy. Recently, fixed versus open endpoint tests  
364 were observed to have similar sensitivity in detecting changes in endurance performance  
365 (Amann, Hopkins, & Marcora, 2008). Moreover, the studies in the CHO+CAF vs. CHO  
366 comparison (Table 1) indicate that although the largest *mean* performance improvement occurred  
367 with open end-point (e.g. 15% improvement) compared to fixed endpoint protocols (3%

368 improvement), the ES for open (0.40) versus fixed (0.20) were statistically indifferent with  
369 overlapping confidence intervals (Table 2), although time to fatigue tests tended to elicit greater  
370 ES. A previous meta-analysis examining the effects of CAF on exercise testing also found a  
371 twofold difference between open versus fixed protocols (Doherty & Smith, 2004). The main  
372 point from the present study, however, is that both test protocols are capable of detecting the  
373 benefits of CHO+CAF as an ergogenic aid versus CHO and thus, the performance test utilized  
374 does not fully explain the variability observed in the literature.

375         Since there was substantial heterogeneity in study ES for the combined effect of  
376 CHO+CAF and none of the aforementioned factors appeared to adequately explain this ES  
377 dispersion, we also examined the impact of unpublished studies being included in the meta-  
378 analysis. As we would have predicted, the overall ES of unpublished studies tended to be lower  
379 compared to the published studies. This suggests that if additional studies were identified or  
380 performed that resulted in an ES favoring CHO, the overall ES could eventually shift towards a  
381 “trivial” benefit for CHO+CAF versus CHO. A funnel plot of standard error versus ES revealed  
382 asymmetry and when the trim and fill correction was calculated (to artificially “adjust” the  
383 funnel plot to make the data symmetrical), the inclusion of another six studies on the side  
384 favoring CHO would shift the overall ES of adding CAF to CHO to 0.14 (intermediate between a  
385 trivial and small benefit). This suggests potential publication bias and, thus, indicates a potential  
386 limitation of our systematic review (i.e., other unpublished, unidentified studies may exist) and  
387 an overall limitation in meta-analysis as a whole. Moreover, both authors and journal reviewers  
388 may not fully understand the importance of publishing studies with “null” effects to enhance  
389 accurate interpretation of the literature. So it should be recognized that as additional studies are

390 performed (and published) over time, the present conclusions derived from this meta-analysis  
391 may be altered.

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

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410 research funding from The Coca Cola Company for work with carbohydrate and caffeine-  
411 containing products but only one of these studies is included (Cureton, et al., 2007) in this meta-  
412 analysis.

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## LIST OF FIGURES

FIGURE 1 - Forest plot with effect size (ES) for individual studies (square) and overall summary ES (diamond) (Hedges'  $g$ ) on performance when CHO ingestion is compared with 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.

FIGURE 2 – Forest plot with individual studies and overall summary (diamond) ES (Hedges'  $g$ ) on performance when placebo ingestion is compared with CAF. Studies are listed in ascending order of ES.

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

<i>Author, Year</i>	<i>n (M/F)</i>	<i>VO<sub>2max</sub></i> <i>(ml/kg/min)</i>	<i>Total CAF</i> <i>Dosage</i> <i>(mg/kg)</i>	<i>Total CHO</i> <i>Dosage</i> <i>(g/hr)</i>	<i>Exercise Mode</i>	<i>Performance Task</i>	<i>% change in</i> <i>performance</i> <i>vs CHO</i>
Sasaki, 1987	5 (5/0)	62.7	6.2	52.9	Treadmill running	Run until exhaustion @ 80% VO <sub>2max</sub>	-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 ( $T(J) = 0.75 \times W_{max} \times 3600$ )	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 <sub>2max</sub>	26.1
Bell, 2002 (JAP – CAF nonusers)	8 (NR)	50.7	5.0	25.8	Cycle ergometer	Ride until exhaustion @ 80% VO <sub>2max</sub>	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 <sub>2max</sub>	22.8
MacLeod, 2004	8 (0/8)	56.1	5.0	NR	Cycle ergometer	Ride until exhaustion @ 80% VO <sub>2max</sub>	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 <sub>2max</sub>	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 <sup>a</sup>	Cycle ergometer	Total work completed in 15 min	15.1
Ganio, 2007	14 (14/0)	60.4	5.9	66.2 or 56.4 <sup>a</sup>	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 <sub>2max</sub>	27.4
Hulston, 2008	10 (10/0)	65.7	5.3	30.1	Cycle ergometer	Time to complete a set amount of work ( $T(J) = 0.75 \times W_{max} \times 2700$ )	4.6

<sup>a</sup> CHO content was different in CHO and CHO+CAF conditions,

NR = data not reported

VO<sub>2max</sub> = maximal oxygen uptake

W<sub>max</sub> = 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.

<i>Moderator Variable</i>	<i>Comparison</i>	<i>p-value*</i>
Timing of CAF administration sub-groups	<u>Pre-exercise + During:</u> 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) <u>Pre-exercise only:</u> 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 <sub>2max</sub>	Meta-regression of VO <sub>2max</sub> 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

<i>First Author, Year</i>	<i>n (M/F)</i>	<i>VO<sub>2max</sub> (ml/kg/ min)</i>	<i>CAF Dosage (mg/kg)</i>	<i>Exercise Mode</i>	<i>Performance Task</i>	<i>Average % change in performance</i>
Costill, 1978	9 (7/2)	M: 60.2 F: 60.0	4.7	Cycle ergometer	Run until exhaustion @ 80% VO <sub>2max</sub>	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 <sub>2max</sub>	24.3
Butts, 1985 (Males)	13 (13/0)	49.4	4.0	Cycle ergometer	Ride until exhaustion @ 70-75% VO <sub>2max</sub>	3.0
Butts, 1985 (Females)	15 (0/15)	47.9	5.1	Cycle ergometer	Ride until exhaustion @ 70-75% VO <sub>2max</sub>	12.6
Sasaki, 1987	5 (5/0)	62.7	7.3	Treadmill running	Run until exhaustion @ 80% VO <sub>2max</sub>	33.4
French, 1991	6 (6/0)	57.9	10.0	Treadmill running	Run until exhaustion @ 75% VO <sub>2max</sub>	1.9
Graham, 1991	7 (6/1)	72.6	9.0	Treadmill running, Cycle ergometer	Ride/Run until exhaustion @ 85% VO <sub>2max</sub>	47.4
Spriet, 1992	8 (7/1)	54.7	9.0	Cycle ergometer	Ride until exhaustion @ 80% VO <sub>2max</sub>	26.9
Lindinger, 1993	8 (8/0)	74.6	3, 6, 9	Treadmill running	Run until exhaustion @ 85% VO <sub>2max</sub>	19.2
Fulco, 1994	8 (8/0)	50.4	4.0	Cycle ergometer	Ride until exhaustion @ 80% VO <sub>2max</sub> 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 <sub>2max</sub>	26.5
Pasman, 1995	9 (NR)	65.1	5, 9, 13	Cycle ergometer	Ride until exhaustion @ 80% W <sub>max</sub>	25.1
Alves, 1995	8 (8/0)	36.9	10.0	Cycle ergometer	Ride until exhaustion @ 80% W <sub>max</sub>	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 <sub>2max</sub>	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