


ORIGINAL ARTICLE

Carbohydrate mouth rinse improves morning high-intensity exercise performance

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Abstract

Oral carbohydrate (CHO) rinsing has been demonstrated to provide beneficial effects on exercise performance of durations of up to one hour. The aim of the present study was to investigate the effects of CHO mouth rinsing on morning high-intensity exercise performance. Following institutional ethical approval and familiarisation, 12 healthy males (mean \pm SD age: 23 ± 3 years, height: 175.5 ± 7.4 cm, body mass: 75.4 ± 7.5 kg) participated in this study. Countermovement jump (CMJ) height, isometric mid-thigh pull peak force, 10 m sprint time and bench press and back squat repetitions to failure were assessed following CHO and placebo (PLA) rinsing or a control condition (CON). All testing took place at 07:30 following an 11 hour overnight fast. Performance of CMJ height (CHO: 39 ± 7 cm; PLA: 38 ± 7 cm; CON: 36 ± 6 cm; $P = .003$, $\eta_p^2 = 0.40$), 10 m sprint time (CHO: 1.78 ± 0.07 s; PLA: 1.81 ± 0.07 s; CON: 1.85 ± 0.05 s; $P = .001$, $\eta_p^2 = 0.47$), the number of bench press (CHO: 25 ± 3 ; PLA: 24 ± 4 ; CON: 22 ± 4 ; $P < .001$, $\eta_p^2 = 0.55$) and squat (CHO: 31 ± 4 ; PLA: 29 ± 5 ; CON: 26 ± 6 ; $P < .001$, $\eta_p^2 = 0.70$) repetitions and mean felt arousal (CHO: 5 ± 1 ; PLA: 4 ± 0 ; CON: 4 ± 0 ; $P = .009$, $\eta_p^2 = 0.25$) improved following CHO rinsing. However, isometric mid-thigh pull peak force was unchanged (CHO: 2262 ± 288 N; PLA: 2236 ± 354 N; CON: 2212 ± 321 N; $P = .368$, $\eta_p^2 = 0.08$). These results suggest that oral CHO rinsing solution significantly improved the morning performance of CMJ height, 10 m sprint times, bench press and squat repetitions to failure and felt arousal, although peak force during an isometric mid-thigh pull, rating of perceived exertion and heart rate were unaffected.

Keywords: Maltodextrin, oral receptors, arousal

Highlights

- Oral carbohydrate rinsing significantly improved the morning performance of CMJ height, 10 m sprint time, bench press and squat repetitions to failure, and felt arousal.
- Peak force during an isometric mid-thigh pull, RPE and heart rate were unaffected by morning carbohydrate mouth rinsing.

Introduction

Oral rinsing of a carbohydrate (CHO) solution prior to, and during, exercise can improve performance without altering metabolic responses (e.g. Carter, Jeukendrup, & Jones, 2004; Kasper et al., 2016; Rollo, Homewood, Williams, Carter, & Goosey-Tolfrey, 2015; Rollo, Williams, Gant, & Nute, 2008). The underlying mechanism is believed to relate to the presence of CHO in the mouth inducing increased brain activity within the orbitofrontal cortex (De Pauw et al., 2015). In addition, Gant, Stinear, and Byblow (2010) demonstrated that

CHO ingestion can immediately affect performance by increasing corticomotor excitability through non-sweet receptors in the oral cavity area and counteract the decreasing motor activity. Similar findings were reported by Chambers, Bridge, and Jones (2009), in that, independent of sweetness, CHO can activate brain regions related to reward and motor control, possibly through non-sweet taste receptors found in the mouth.

Several 30-minute to 1-hour time trial studies exist where the effect of CHO mouth rinsing has been investigated during cycling (Chambers et al., 2009;

Lane, Bird, Burke, & Hawley, 2013; Pottier, Bouckaert, Gilis, Roels, & Derave, 2010) and running (Clarke, Thomas, Kagka, Ramsbottom, & Delextrat, 2016; Rollo et al., 2008; Rollo, Williams, & Nevill, 2011). However, most of the literature focuses on endurance-based exercise, so evidence of possible ergogenic benefits on high-intensity and resistance exercise is lacking. Furthermore, those studies investigating the effect of CHO rinsing on high-intensity exercise have produced inconsistent results (Beaven, Maulder, Pooley, Kilduff, & Cook, 2013; Bortolotti, Pereira, Oliveira, Cyrino, & Altimari, 2013; Chong, Guelfi, & Fournier, 2011; Dorling & Earnest, 2013; Kasper et al., 2016; Phillips, Findlay, Kavaliauskas, & Grant, 2014; Přibyslavská et al., 2016). CHO rinsing has been shown to induce no significant improvements in performance whilst completing one repetition maximum or muscular endurance (Clarke, Kornilios, & Richardson, 2016; Dunkin & Phillips, 2017; Painelli et al., 2011), but beneficial in attenuating torque reduction during a series of maximal voluntary contractions (Jensen, Stellingwerff, & Klimstra, 2015). Similarly, Rollo et al. (2015) and Dorling and Earnest (2013) demonstrated that sprint performance during the Loughborough Intermittent Shuttle Running Test was not significantly improved following CHO rinsing, whereas Beaven et al. (2013) reported that mean and peak power output were increased during the first of five six-second sprints. However, information relating to other high-intensity activities is limited, although Rollo et al. (2015) speculated that in the presence of a perceived impending increase in fuel supply during CHO rinsing, the balance of excitation and inhibition of the brain's motor cortex may be altered in favour of excitation, allowing athletes to improve their performance. Furthermore, although the effect size of this improvement on performance may be trivial to small, it is likely to be practically significant (Peart, 2016).

One possible explanation for inconsistent findings is the nutritional status of the participants, with participants arriving at the laboratory after an overnight fast (Jensen et al., 2015) or their usual pre-exercise meal (Clarke, Kornilios, et al., 2016). Although the effects of CHO rinsing appear more profound after an overnight fast, there is still evidence to support beneficial effects after the ingestion of a meal (Fares & Kayser, 2011; Jeukendrup, 2013). Furthermore, athletes training in the early morning frequently choose to begin activity without eating, with some athletes preferring to consume water over CHO during the session. Such choices may be explained by the reported gastrointestinal problems and distress reported by participants regarding CHO consumption before and during exercise (de Oliveira, Burini, & Jeukendrup, 2014), which are likely due to stress of the abdominal

organs caused by the CHO and movements during exercise (Van Nieuwenhoven, Brouns, & Kovacs, 2005). Therefore, the aim of the present study was to investigate the effects of CHO mouth rinsing on morning high-intensity exercise performance.

Methods

Following institutional ethical approval and familiarisation, 12 healthy males (mean \pm SD age: 23 ± 3 years, height: 175.5 ± 7.4 cm, body mass: 75.4 ± 7.5 kg) who trained three to four times a week for between 8 and 12 months, and therefore met the intermediate resistance training experience classification as per the National Strength and Conditioning Association (Sheppard & Triplett, 2015) participated in this study. Participants were instructed to avoid caffeine ingestion for a minimum of 12 hours prior to the trials and refrain from strenuous exercise for 24 hours. In addition, a 24-hour dietary record was completed by each participant during the familiarisation session; it was then photocopied and handed back to the participants so that the same diet could be repeated for subsequent trials. All procedures were undertaken in accordance with the Declaration of Helsinki.

A randomised, Latin-square, crossover, placebo (PLA)-controlled design was employed during this study. **Each participant attended the laboratory on four occasions.** The first session was to establish one repetition maximum (1-RM) for the squat and bench press, and to allow familiarisation with the exercises. Following a standardised warm-up, squat and bench press 1-RM testing was then conducted following the National Strength and Conditioning Association guidelines (McGuigan, 2015). The 1RM testing began with a warm-up at 50% of their predicted 1RM. The load was then increased to the predicted 1RM for the first attempt. If that attempt was successful, five minutes of rest were given after which another 1RM was attempted; this sequence was repeated until the 1RM attempt was unsuccessful or the subject refused to continue; the highest load successfully lifted was recorded as the 1RM value. The subsequent three sessions were to complete the exercise battery under each condition and were separated by seven days to allow recovery.

All testing took place at 07:30 after the ingestion 500 mL of water 60 minutes prior to arrival and following an 11 hour overnight fast. On arrival, participants completed a warm-up which involved 5 minutes of sub-maximal cycling on a cycle ergometer at 150 W and then performed no more than 2 sets of 12 repetitions at a self-selected, light intensity for the squat and bench press. The warm-up weights

selected during the initial trial were recorded and repeated prior to subsequent trials. The participants then orally rinsed either 25 mL of CHO or taste-matched-PLA solution for 10 seconds before each exercise or no fluid. The participants performed a series of exercise tests and were monitored on the performances of countermovement jump (CMJ) height, isometric mid-thigh pull peak force, 10 m sprint times and bench press and back squat repetitions to failure at 60% 1-RM. Each exercise, excluding the bench press and squat performance, was performed three times and the best result recorded. Furthermore, there was a five-minute rest period between each exercise.

The participants performed three vertical CMJ with the arms held akimbo on a force platform (AMTI AccuPower, Watertown, MA, USA) sampling at 400 Hz. All participants were instructed to jump as high as possible and jump height was calculated using the velocity at take-off (Hatze, 1998) (Technical error of measurement (TEM) = 0.68). The participants then performed a maximal isometric mid-thigh pull on a portable standing force plate (AMTI AccuPower, Watertown, MA, USA) sampling at 400 Hz. For this test a custom designed rig was used that allowed a fixed bar to be adjusted to meet the required height for each participant with the stationary bar positioned in the middle of their thigh. The participants used lifting straps to improve the grip and were instructed to get in a comfortable and stable position with self-selected knee and hip angles (Comfort, Jones, McMahon, & Newton, 2015). Once in this position participants performed a maximal isometric pull for five seconds. All participants were instructed to pull as hard and fast as possible and there was a 90-second break recovery period between each repetition. Peak force was identified as the highest instantaneous value observed during the trial (TEM = 6.36).

The participants then completed a maximal 10 m sprint from a standing position. The time was measured using an infrared timing system (Smart Speed, Fusion Sports, Australia) and all participants were instructed to run as fast as possible. Each participant performed this task three times with 90 s between each trial and the fastest time recorded (TEM = 0.14). After five minutes, the participants began the 60% to failure bench press protocol (TEM = 0.79). A five-minute rest period was allowed before participants began the squat protocol (TEM = 1.06). For both exercises, a metronome was used to provide a cadence of two seconds for both the eccentric and concentric phases of movement.

The felt arousal scale (Svebak & Murgatroyd, 1985), used to monitor arousal throughout the trials, and rating of perceived exertion (RPE) (Borg, 1973) was recorded immediately after each of the

exercises. Heart rate (HR) (Polar Electro Oy, Kempele, Finland) was recorded immediately before and after administration of the treatment, after the warm-up, and following each exercise.

Rinsing protocol

Prior to each exercise either 25 mL of a 6% CHO solution (maltodextrin: My Protein, Manchester, UK) (CHO) or water (PLA) were rinsed around the buccal cavity for 10 s. Participants then expectorated the solution back into the plastic cup before starting the exercise protocol. All solutions were flavoured with orange (No added sugar orange squash, Sainsbury's, London, UK). During the remaining session, no solution was rinsed (CON).

Statistical analysis

Data are reported as the mean \pm the standard deviation (SD). The Shapiro–Wilk test was used to confirm normal distribution. Furthermore, due to variation between participants and the suggestion that CHO mouth rinsing may be worth investigating on an individual basis (Peart, 2016), individual performance responses are also presented. A one-way analysis of variance (ANOVA) with repeated measures was used to compare all data except for RPE, felt arousal and HR, which were analysed with two-way ANOVA with repeated measures. Sphericity was analysed by Mauchly's test of sphericity followed by the Greenhouse–Geisser adjustment where required. Where any differences were identified, 95% confidence intervals and pairwise comparisons with Bonferroni correction were used to show where they lay. All statistical procedures were conducted using IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp.). Sample size was calculated using G*Power software (version 3.1.9.2, Franz Faul, Universitat Kiel, Dusseldorf, Germany) for repeated measures ANOVA for detecting a small effect size (0.3) with α as 0.05 and a 1 – β error probability of 0.8 revealed that a sample size of 12 participants was required. Furthermore, effect sizes using partial eta squared (η_p^2) and Cohen's d were calculated, which were defined as trivial (0–0.19), small (0.20–0.49), moderate (0.50–0.79) or large (≥ 0.80) (Cohen, 1992).

Results

A small increase in CMJ height during both rinsing conditions was observed ($F_{(2, 22)} = 7.395$; $P = .003$, $\eta_p^2 = 0.40$; Figure 1a). Jump height was significantly

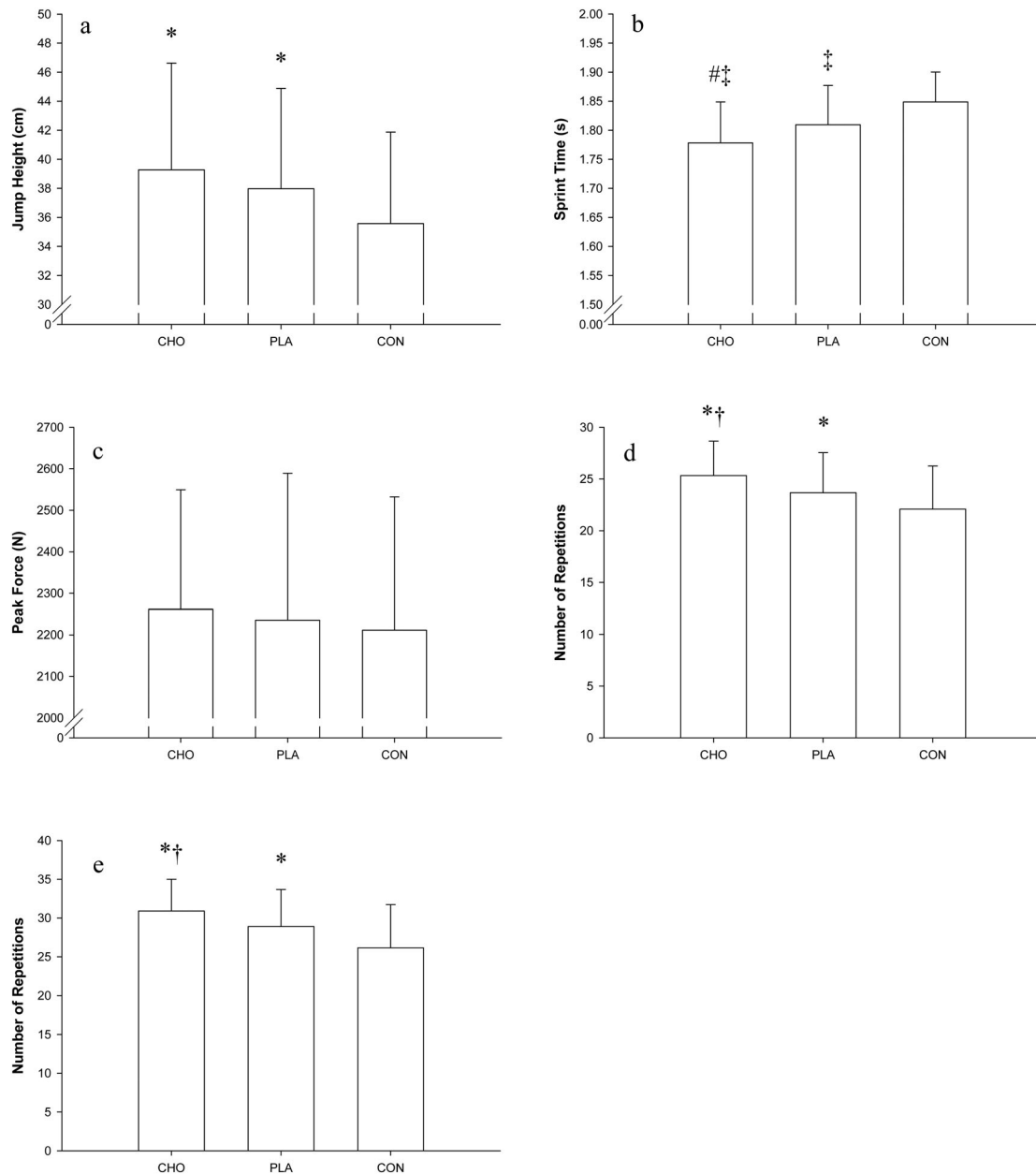


Figure 1. Mean \pm SD ($n = 12$) CMJ height (a), 10 m sprint time (b), mid-thigh pull peak force (c), number of bench press repetitions (d) and number of squat repetitions (e). *Significantly greater than CON. †Significantly greater than PLA. #Significantly faster than PLA. ‡Significantly faster than CON.

higher following CHO (95%CI; 1.2, 6.2; $P = .008$; $d = 0.54$) and PLA (95%CI; 0.5, 5; $P = .047$; $d = 0.36$) compared with CON. Furthermore, only a trivial difference in jump height between CHO and PLA (95%CI; -0.1 , 2.7; $P = .070$; $d = 0.18$) was observed. Individual CMJ results (Figure 2a) show that 67% of the participants had a greater CMJ height in the CHO trial. A small decrease in the time to complete the 10 m sprint following CHO and PLA was observed ($F_{(2, 22)} = 9.683$; $P = .001$, $\eta_p^2 = 0.47$; Figure 1b).

Sprint time was significantly faster following CHO compared with CON (95%CI; -0.1 , -0.3 ; $P = .003$; $d = 1.14$) and PLA (95%CI; -0.6 , -0.01 ; $P = .024$; $d = 0.45$) trials. Furthermore, sprint time was significantly faster following PLA than CON (95%CI; -0.8 , -0.003 ; $P = .036$; $d = 0.65$). Individual times (Figure 2b) show that 58% of the participants were faster following CHO rinsing.

Only trivial differences in the peak force produced during the isometric mid-thigh pull were observed

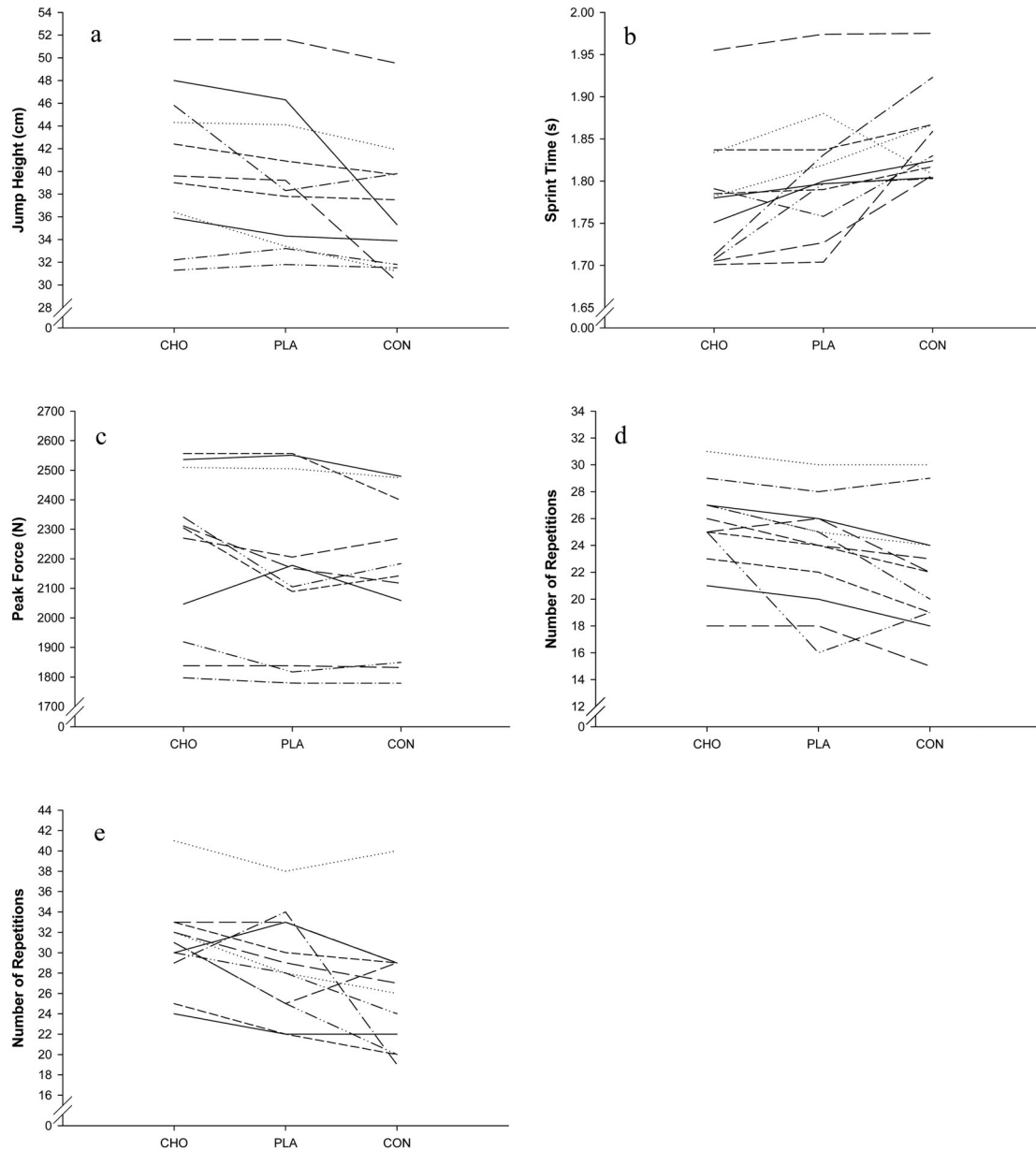


Figure 2. Individual CMJ height (a), 10 m sprint time (b), mid-thigh pull peak force (c), number of bench press repetitions (d) and number of squat repetitions (e).

($F_{(2, 22)} = 1.048$; $P = .368$, $\eta_p^2 = 0.08$; Figure 1c). There were no significant differences between CHO and CON (95%CI; $-26, 125$; $P = .174$; $d = 0.16$), CHO and PLA (95%CI; $-70, 122$; $P = .564$; $d = 0.10$) and PLA and CON (95%CI; $-24, 71.4$; $P = .294$; $d = 0.08$). A moderate increase in the number of bench press repetitions performed during the rinsing trials compared with CON was observed ($F_{(2, 22)} = 13.253$; $P < .001$, $\eta_p^2 = 0.55$; Figure 1d). The number of bench press repetitions following CHO was significantly greater than PLA (95%CI; $0.1, 3.2$; $P = .039$; $d = 0.46$) and CON

(95%CI; $2.1, 4.4$; $P < .001$; $d = 0.86$). Furthermore, a significant greater number of bench press repetitions following PLA compared with CON was observed (95%CI; $0.2, 3$; $P = .029$; $d = 0.39$). Individual bench press repetitions to failure (Figure 2d) show that 75% of the participants performed a greater number of repetitions following CHO. Moderately more squat repetitions were performed following CHO and PLA compared with CON ($F_{(2, 22)} = 25.729$; $P < .001$, $\eta_p^2 = 0.70$; Figure 1e). A significantly higher number of squat repetitions were observed following CHO compared with PLA

(95%CI; 3.9, 10.6; $P = .001$; $d = 0.45$) and CON (95%CI; 5.4, 12.2; $P < .001$; $d = 0.97$). In addition, significantly more squats repetitions were performed following PLA compared with CON (95%CI; 0.2, 3; $P = .029$; $d = 0.53$). Individual squat repetitions to failure (Figure 2e) show that 75% of the participants performed a greater number of repetitions following CHO.

A small interaction between condition and time was observed for felt arousal ($F_{(12, 132)} = 1.046$; $P < .001$, $\eta_p^2 = 0.25$; Table I). A moderate increase in felt arousal occurred throughout the protocol ($F_{(6, 66)} = 6.713$; $P < .001$, $\eta_p^2 = 0.38$) and a moderate difference between conditions was observed ($F_{(2, 22)} = 18.295$; $P < .001$, $\eta_p^2 = 0.63$). Felt arousal was greater following CHO (95%CI; 0.5, 1.3; $P < .001$; $d = 2.04$) and PLA (95%CI; 0.2, 1.2; $P = .009$; $d = 1.30$) compared with CON, although no significant difference between CHO and PLA (95%CI; -0.2, 0.6; $P = .629$; $d = 0.46$) was observed. A large increase in RPE (Table I) was observed during the exercise protocol ($F_{(4, 4)} = 282.563$; $P < .001$, $\eta_p^2 = 0.96$), although only trivial differences were observed between conditions ($F_{(2, 22)} = 0.840$; $P = .445$, $\eta_p^2 = 0.07$). Similarly, a large increase in HR (Table I) occurred during the protocol ($F_{(11, 121)} = 204.961$; $P < .001$, $\eta_p^2 = 0.95$). However, there were no significant differences between conditions ($F_{(2, 22)} = 1.100$; $P = .351$, $\eta_p^2 = 0.01$).

Discussion

The key finding of the present study was that oral CHO rinsing significantly improved the morning performance of CMJ height, 10 m sprint times, bench press and squat repetitions to failure and felt arousal, without changes in perceived exertions or HR. Furthermore, small to moderate performance

improvements in CMJ, 10 m sprint time, and bench and squat repetitions to failure were observed following rinsing with the PLA when compared with the control condition (CON). The results of this study concur with those of Gant et al. (2010), who indicated similar effects following orally rinsing CHO on isometric elbow flexion, Jensen et al. (2015) who reported decreased torque attenuation following CHO mouth rinsing in a fatigued state, and Peart (2016), who concluded a trivial to small overall positive effect of CHO mouth rinsing on performance. Furthermore, it has been demonstrated that CHO rinsing improves peak and mean power output during sprinting (Beaven et al., 2013; Phillips et al., 2014). The proposed mechanism suggests that CHO mouth rinsing activates regions in the brain related to motor output and pleasure/reward (Chambers et al., 2009) and increasing arousal. Similarly, De Pauw et al. (2015) reported that the presence of CHO within the mouth activates the reward centres of the brain, due to a direct link between the buccal mucosa and the brain (Nicolazzo, Reed, & Finnin, 2003). Furthermore, Gant et al. (2010) indicated orally rinsing CHO immediately increased the excitability of the corticomotor pathway. Therefore, the presence of CHO during the rinsing process, the balance of excitation and inhibition of the brain's motor cortex may be altered in favour of excitation, allowing athletes to improve their performance.

Peak isometric force was evaluated using isometric mid-thigh pull performance, although no differences between trials were observed. Several previous studies involving high-intensity exercises (Chong et al., 2011), multiple sprints (Dorling & Earnest, 2013) and maximum strength (Painelli et al., 2011) concluded that CHO mouth rinsing provided did not improve performance. In contrast, Gant et al. (2010) reported that isometric contraction force during elbow flexion increased following CHO

Table I. Mean \pm SD ($n = 12$) felt arousal, RPE and HR throughout the exercise battery.

	Pre-rinse	Post-rinse	CMJ	MTP	Sprint	Bench	Squat
<i>Arousal</i>							
CHO	3 \pm 1	5 \pm 1*	5 \pm 1*	5 \pm 0*	5 \pm 0*	5 \pm 1*	4 \pm 1
PLA	4 \pm 1	4 \pm 1*	4 \pm 1	5 \pm 1*	5 \pm 1	4 \pm 1	4 \pm 1
CON	3 \pm 1	3 \pm 1	4 \pm 1	4 \pm 1	4 \pm 1	4 \pm 1	3 \pm 1
<i>RPE</i>							
CHO			6 \pm 1	10 \pm 1	10 \pm 1	16 \pm 1	18 \pm 1
PLA			7 \pm 1	10 \pm 0	11 \pm 0	16 \pm 0	19 \pm 1
CON			6 \pm 1	10 \pm 2	11 \pm 3	16 \pm 1	18 \pm 1
<i>Heart rate (beats min⁻¹)</i>							
CHO	77 \pm 7	86 \pm 8	109 \pm 10	124 \pm 16	136 \pm 9	149 \pm 14	176 \pm 8
PLA	80 \pm 11	88 \pm 14	108 \pm 15	120 \pm 16	132 \pm 11	142 \pm 13	173 \pm 8
CON		81 \pm 7	99 \pm 11	117 \pm 13	128 \pm 7	147 \pm 10	171 \pm 11

*Significantly greater than CON.

mouth rinsing. One potential explanation for the present study demonstrating no improvement during the isometric mid-thigh pull could be that when exercise intensity elicits near maximal effort, despite increases in felt arousal following CHO rinsing, as seen in the present study, it creates a “ceiling effect” which makes any appreciable differences between conditions extremely difficult to distinguish (Beaven et al., 2013; Clarke, Kornilios, et al., 2016). Furthermore, it is possible that the presence of CHO stimulated the reward and/or motivation centres in the brain, but this stimulus was insufficient to affect maximal strength performance (Painelli et al., 2011), as strength-trained individuals usually present little to no neural activation deficits (Ahtiainen & Hakkinen, 2009).

The present study included a fasting period of 11 hours prior to testing consistent with the protocol used by Haase, Cerf-Ducastel, and Murphy (2009) and Turner, Byblow, Stinear, and Gant (2014). However, Beelen et al. (2009) suggested overnight fasting reduces the validity of the findings because in a practical setting, athletes typically ingest a high CHO meal two hours prior to competition and in many situations, ingest the CHO source. In contrast, Příbyslavská et al. (2016) reported female soccer players commonly refuse to eat before early morning training or competitive matches and often ingested water rather than CHO. Therefore, the findings of the present study may be of interest to those athletes who commonly train in a fasted state in the early morning. This nutritional intervention could be practically used as a performance enhancement without the gastrointestinal discomfort often associated with high-intensity exercise (de Oliveira et al., 2014). Furthermore, Kasper et al. (2016) highlighted the method may also be practical for those athletes that integrate phases of CHO restrictions into their training programmes. Consequently, CHO mouth rinsing has recently been incorporated into the nutritional guidelines for short higher intensity exercise (i.e. <1 hour) where glycogen is not a limiting factor for performance (Jeukendrup, 2013; Stellingwerff & Cox, 2014).

The present study employed a non-rinse control trial that has identified a potential PLA effect. Small to moderate performance improvements in CMJ, 10 m sprint time, and bench and squat repetitions to failure were observed after orally rinsing a non-CHO solution. Gam, Guelfi, and Fournier (2013) suggested that a PLA effect of CHO rinsing cannot be excluded. In support of this proposal, the present study observed that when compared with the CON, mouth rinsing with a PLA solution caused a large increase in felt arousal. This occurrence may at least partially explain the improved

performance observed in the PLA trial as Kerr (1997) reports that relatively high levels of felt arousal are a feature of successful performance. One suggestion for this occurrence in the present study is that both solutions were flavoured with artificial sweeteners. However, Chambers et al. (2009) demonstrated that the artificial sweetener PLA caused no effect to areas of the brain such as the anterior cingulate cortex and ventral striatum. Consequently, the effect of the mouth rinse itself may provide ergogenic benefits (Gam et al., 2013). Therefore, due to the potential PLA effect demonstrated in the present study, it would be recommended that future research incorporates a non-rinse control trial.

This study is not without limitations. Despite an inclusion criteria, large standard deviations are evident for some variables. The reason for this is primarily attributed to the variability of athletic standards amongst the participants, which had implications for all recorded measures. Ideally, a more homogeneous population would have been recruited thus avoiding a large range in characteristics and abilities which can result in a greater increase in “noise” within the data. In addition, it is unknown whether a full familiarisation of the 1RM protocols would have impacted on the estimation of the maximal dynamic strength and subsequent weight lifted by the participants during the main trials. However, Comfort and McMahon (2015) demonstrated the back squat to be highly reliable. Finally, it is acknowledged that variable such as CMJ and sprint performance demonstrates within-subject variation. However, TEM was calculated and excluding the bench press and squat performance, all tests was performed three times with the best result recorded.

In conclusion, these results suggest that following an overnight fast, oral rinsing with a CHO solution significantly improved the morning performance of CMJ height, 10 m sprint times, bench press and squat repetitions to failure and felt arousal. However, peak force during an isometric mid-thigh pull, RPE and HR were unaffected, possibly due to the nature of the exercise causing a “ceiling effect”. Furthermore, a PLA effect of CHO rinsing cannot be excluded.

Disclosure statement

No potential conflict of interest was reported by the authors.

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