

1 **Title: Enteric-coated sodium bicarbonate supplementation improves high-intensity cycling**
2 **performance in trained cyclists**

3

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23 Abstract

24 *Purpose:* Enteric-coated sodium bicarbonate (NaHCO₃) can attenuate gastrointestinal (GI) symptoms
25 following acute bicarbonate loading, although the subsequent effects on exercise performance have not
26 been investigated. The purpose of this study was to examine the effects of enteric-coated NaHCO₃
27 supplementation on high-intensity exercise performance and GI symptoms. *Methods:* Eleven trained
28 male cyclists completed three 4 km time trials after consuming; a placebo or 0.3 g·kg⁻¹ body mass
29 NaHCO₃ in enteric-coated or gelatin capsules. Exercise trials were timed with individual peak blood
30 bicarbonate ion concentration ([HCO₃⁻]). Blood acid-base balance was measured pre-ingestion, pre-
31 exercise and post-exercise, whereas GI symptoms were recorded pre-ingestion and immediately pre-
32 exercise. *Results:* Pre-exercise blood [HCO₃⁻] and potential hydrogen (pH) were greater for both
33 NaHCO₃ conditions ($P < 0.0005$) when compared to placebo. Performance time was faster with enteric-
34 coated (-8.5 ± 9.6 s, $P = 0.044$) and gelatin (-9.6 ± 7.2 s, $P = 0.004$) NaHCO₃ compared to placebo,
35 with no significant difference between conditions (mean difference = 1.1 ± 5.3 s, $P = 1.000$).
36 Physiological responses were similar between conditions, although blood lactate ion concentration was
37 higher with gelatin NaHCO₃ (2.4 ± 1.7 mmol·L⁻¹, $P = 0.003$) compared with placebo. Furthermore,
38 fewer participants experienced GI symptoms with enteric-coated ($n = 3$) compared to gelatin ($n = 7$)
39 NaHCO₃. *Discussion:* Acute enteric-coated NaHCO₃ consumption mitigates GI symptoms at the onset
40 of exercise and improves subsequent 4 km cycling TT performance. Athletes who experience GI side-
41 effects after acute bicarbonate loading may therefore benefit from enteric-coated NaHCO₃
42 supplementation prior to exercise performance.

43

44 **Keywords:** Alkalosis · Extracellular buffering · Gastrointestinal symptoms · High-intensity exercise

45 Abbreviations

46	[Cl ⁻]	Chloride ion concentration
47	[H ⁺]	Hydrogen ion concentration
48	[HCO ₃ ⁻]	Bicarbonate ion concentration
49	[K ⁺]	Potassium ion concentration
50	[La ⁻]	Lactate ion concentration
51	[Na ⁺]	Sodium ion concentration
52	AU	Arbitrary units
53	CI	Confidence intervals
54	<i>g</i>	Hedge's <i>g</i>
55	GI	Gastrointestinal
56	H ⁺	Hydrogen ion
57	NaHCO ₃	Sodium bicarbonate
58	pH	Potential hydrogen
59	ROF	Rating of perceived fatigue
60	RPE	Rating of perceived exertion
61	RPE-L	Localised rating of perceived exertion
62	SD	Standard deviation
63	TT	Time trial
64	$\dot{V}O_{2peak}$	Peak oxygen uptake
65	η^2	Eta-squared

66 **Introduction**

67 High-intensity exercise bouts are impaired by peripheral fatigue (Thomas et al. 2015), typically as a
68 result of disturbances to intramuscular homeostasis (Jones et al. 2008). Significant decreases in muscle
69 and blood potential hydrogen (pH) have been reported (Hollidge-Horvat et al. 2000) as a result of the
70 glycolytic contribution during high-intensity exercise (Baker et al. 2010; Gustin, 2001). While the
71 mechanisms responsible for the decline in muscular force across the neuromuscular junction are
72 equivocal (Fitts, 2016; Westerblad, 2016), reductions in muscle pH are associated with simultaneous
73 declines in muscle excitability (Cairns & Lindinger, 2008), contractility (Spriet et al. 1985), glycolytic
74 enzyme activity (MacLaren, 1989) and exercise performance (Raymer et al. 2004). Exercise training
75 and nutritional strategies that offset these perturbations to acid-base balance have therefore received
76 considerable attention.

77 Inducing metabolic alkalosis prior to exercise, which can be achieved by oral ingestion of
78 sodium bicarbonate (NaHCO_3), has been shown to improve various performance measures (e.g. power,
79 speed, performance time) during single-bouts of high-intensity exercise (Matson & Tran, 1993; Peart
80 et al. 2012; Lancha Junior et al. 2015). Through increases in extracellular bicarbonate ion concentration
81 ($[\text{HCO}_3^-]$), NaHCO_3 supplementation can augment buffering capacity (Siegler et al. 2010) and strong
82 ion handling (Raymer et al. 2004), both of which favour high-intensity exercise performance. Although
83 0.2 to 0.4 $\text{g}\cdot\text{kg}^{-1}$ body mass NaHCO_3 is generally regarded as ergogenic during high-intensity exercise
84 (McNaughton et al. 2016), gastrointestinal (GI) symptoms can be a problematic side-effect, with some
85 individuals reporting severe symptoms (e.g. vomiting and diarrhoea) at the onset of exercise (Burke &
86 Pyne, 2007; Kahle et al. 2013). While some studies have shown that NaHCO_3 can improve exercise
87 performance despite GI distress (Price & Simons, 2010), there is evidence to suggest that symptoms
88 may compromise the performance-enhancing effects of supplementation (Cameron et al. 2010;
89 Saunders et al. 2014; Deb et al. 2018). Furthermore, there is evidence to suggest that athletes may be
90 deterred from supplementing with NaHCO_3 due to the risk of GI symptoms during training and/or
91 competition (Heibel et al. 2018).

92 Novel ingestion strategies are being investigated to alleviate GI symptoms, such as the
93 administration of NaHCO_3 in gastro-resistant capsules (Hilton et al. 2019a). Through the application of

94 an enteric coating, which resists dissolution at a low pH (e.g. stomach), acid-sensitive ingredients such
95 as NaHCO₃ can bypass the stomach (Barbosa et al. 2017). Consequently, this reduces the neutralisation
96 of gastric acid and minimises adverse side-effects (e.g. GI symptoms associated with elevated carbon
97 dioxide tension in the GI tract. Indeed, delayed-release NaHCO₃ has been shown to reduce the incidence
98 and severity of GI symptoms compared with an aqueous solution, whilst increasing blood [HCO₃⁻] and
99 pH to comparable levels. In a recent study, enteric-coated NaHCO₃ was shown to attenuate GI
100 symptoms beyond encapsulation in gelatin and delayed-release capsules, which may be more
101 favourable for those who experience GI symptoms post-ingestion (Hilton et al. 2019b). Nevertheless,
102 changes in blood [HCO₃⁻] and pH were lower with enteric-coated NaHCO₃, potentially due to the
103 absorption of bicarbonate across the intestinal mucosa (Turnberg et al. 1970) and less time available for
104 absorption. Given that the degree of alkalosis can modulate the effects of NaHCO₃ ingestion on exercise
105 performance (Carr et al. 2011a), enteric-coated formulations may not favour performance
106 improvements compared with alternative ingestion strategies. While enteric-coated NaHCO₃ can reduce
107 GI symptoms post-ingestion, no study to date has investigated the effects of supplementation on
108 exercise performance. Therefore, it is unknown whether ingesting NaHCO₃ in enteric-coated capsules
109 alters the overall ergogenicity of supplementation. Furthermore, knowledge of the performance-
110 enhancing potential of enteric-coated NaHCO₃ would help to elucidate the impact of GI symptoms and
111 acid-base balance on exercise performance, as well as improve the practical recommendations for
112 athletes. The aim of the present study, therefore, was to determine whether enteric-coated NaHCO₃
113 improves high-intensity exercise performance using an acute loading protocol.

114

115 **Methods**

116 **Participants**

117 Eleven trained male cyclists (according to DePauw et al. 2013) were recruited for the study (mean ±
118 SD: age, 32 ± 12 years; body mass, 81.5 ± 12.5 kg; height 1.8 ± 0.1 m; peak oxygen uptake [$\dot{V}O_{2peak}$],
119 63.2 ± 4.9 mL·kg⁻¹·min⁻¹) based upon sample size estimation. Sample size was determined *a priori* and
120 revealed that eleven participants were required to detect changes (~ 3 s; 1.3%) in performance time
121 between conditions with high statistical power ($\alpha = 0.05$; $\beta = 0.20$). The benchmark for change in

122 performance was chosen as it reflects the difference in performance time between podium and non-
123 podium positions for similar cycling events (Christensen et al. 2017). All participants undertook regular
124 cycling (≥ 3 d·week⁻¹) for at least 5 h·week⁻¹ and were free of GI-related disorders. Exclusion criteria
125 included those with hypertension, renal impairment or following a salt-restricted diet, and no
126 participants were ingesting any nutritional supplements or medications at the time of the study. Ethical
127 approval was obtained by the institutional research ethics committee and all participants gave written
128 informed consent to take part in the study.

129

130 **Experimental design**

131 In a randomised, double-blind, and crossover design, participants attended the laboratory on six
132 occasions, separated by at least 48 h and at the same time of day (0900 h). During the initial visit,
133 participants completed a preliminary test to determine $\dot{V}O_{2\max}$ before familiarisation with the 4 km
134 cycling time trial (TT). During the further two visits, individual responses to NaHCO₃ ingestion (gelatin
135 and enteric-coated) were established to determine subsequent ingestion timings. Throughout the next
136 three visits, participants performed a maximal 4 km cycling TT under three different experimental
137 conditions that were administered in a counterbalanced order. Experimental trials involved the
138 consumption of 0.3 g·kg⁻¹ body mass of NaHCO₃ in either enteric-coated or gelatin capsules, or a
139 placebo containing cornflour prior to the 4 km TT. Participants were instructed to abstain from alcohol
140 and caffeine consumption for 12 h, and strenuous exercise 24 h before each laboratory visit. Water
141 intake was encouraged in the 24 h preceding experimental testing and participants were asked to arrive
142 at the laboratory well-hydrated and after an overnight fast to minimise the confounding effects of food
143 intake on gastric emptying rates (Davis et al., 1986). On arrival to the laboratory, pre-test instructions
144 were confirmed verbally to limit confounding nutritional effects on exercise performance. Physiological
145 (heart rate and blood lactate) and perceptual responses were recorded throughout the 4 km TT, whereas
146 acid-base balance and GI symptoms were recorded immediately pre- and post-exercise.

147

148 **Preliminary testing**

149 Participants undertook an incremental exercise test to volitional exhaustion on an electromagnetically-
150 braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands) which confirmed that
151 $\dot{V}O_{2\text{peak}}$ was $> 55 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The protocol involved a 5 min warm-up at 70 W and a self-selected
152 cadence (70–120 $\text{rev}\cdot\text{min}^{-1}$), after which the workload increased by 1 W every 2 s (30 $\text{W}\cdot\text{min}^{-1}$) until
153 volitional exhaustion. Breath-by-breath gases were measured continuously throughout using a gas
154 analyser (Oxycon ProTM, Jaeger, Germany) whereas heart rate (Polar[®], Kempele, Finland) and whole-
155 body ratings of perceived exertion (RPE) were recorded each minute (Borg, 1973). The following
156 criteria were used to confirm that $\dot{V}O_{2\text{peak}}$ had been reached: (i) heart rate within 10 $\text{beats}\cdot\text{min}^{-1}$ of age-
157 predicted maximum; (ii) respiratory exchange ratio > 1.10 arbitrary units (AU); (iii) RPE $> 18/20$ AU
158 (Midgley et al. 2007). After a period of recovery (30 min), participants performed a 4 km cycling TT
159 to familiarise themselves with the exercise protocol.

160 Individual responses to the ingestion of enteric-coated and gelatin NaHCO_3 were established to
161 allow exercise to be scheduled with peak bicarbonate buffering capacity. This method accounts for the
162 inter-individual variability in acid-base kinetics following NaHCO_3 ingestion (Jones et al. 2016) and
163 differences between ingestion forms (Hilton et al. 2019b). Semi-nude body mass was recorded (Bod
164 Pod[®], Cosmed, Rome, Italy) after bladder evacuation to determine the dose of NaHCO_3 . Participants
165 then consumed $0.3 \text{ g}\cdot\text{kg}^{-1}$ body mass of NaHCO_3 which was administered in either size 0 opaque
166 enteric-coated (BicarbiTM, Nephcentric[®], Arizona, USA), or gelatin capsules (Bulk PowdersTM,
167 Colchester, UK). Enteric-coated capsules were pre-filled by the manufacturer, whereas gelatin capsules
168 were manually filled by the researcher using a capsule filling device (Capsule Connection LLC,
169 Arizona, USA). Given that each capsule contained 0.65 g of NaHCO_3 , supplements were administered
170 to the nearest whole capsule. All supplements were checked for accuracy (Ohaus[®], Fisher ScientificTM,
171 Pennsylvania, USA) prior to administration and were ingested with an equal volume ($6 \text{ mL}\cdot\text{kg}^{-1}$ body
172 mass) of water (Evian[®], Danone, Paris, France) within 5 min of commencing ingestion. Fingertip
173 capillary blood samples (95 μL) were drawn pre-ingestion and then every 20 min for 180 min post-
174 ingestion, with 10 min sampling from 80 to 140 min. Fingertip capillary blood samples were collected
175 in heparin-coated glass capillary tubes (Radiometer Medical Ltd, Copenhagen, Denmark) using an

176 aseptic technique and analysed immediately (Radiometer ABL800 BASIC, Copenhagen, Denmark) for
177 blood $[\text{HCO}_3^-]$ and pH.

178

179 **Experimental trials**

180 Upon arrival to the laboratory, participants sat resting for 20 min before a baseline (pre-ingestion)
181 capillary blood sample was taken. Participants then ingested either $0.3 \text{ g}\cdot\text{kg}^{-1}$ body mass of NaHCO_3
182 administered in gelatin or enteric-coated capsules, or a placebo. Opaque gelatin capsules were also used
183 in the placebo trials and an equal number of capsules (39 ± 13 capsules) were given to mask the
184 experimental conditions. Pre-exercise acid-base balance was determined with a further blood sample,
185 after the pre-determined time-to-reach peak blood $[\text{HCO}_3^-]$ had passed. All blood samples were
186 analysed immediately for $[\text{HCO}_3^-]$ and pH, as well as sodium ($[\text{Na}^+]$), potassium ($[\text{K}^+]$) and chloride
187 ion ($[\text{Cl}^-]$) concentrations.

188

189 **Time trials**

190 Participants selected a preferred handlebar and saddle position which was then replicated for all other
191 experimental trials. After a 5 min self-selected warm-up and 3 min rest, participants performed a
192 maximal 4 km cycling TT on an electromagnetically-braked cycle ergometer (Velotron Pro®,
193 RacerMate™, Seattle, USA) from a static start. Participants were instructed to complete the TT as fast
194 as possible and were free to change gears throughout, although gear ratios were fixed. Visual feedback
195 of cadence, gearing and distance travelled was provided on-screen, although participants were blinded
196 from power output, speed and time elapsed. Strong verbal encouragement was given by the same
197 individual at regular (0.5 km) intervals throughout and no water was provided during the TT. All TTs
198 took place under standardised laboratory conditions (temperature $18\text{-}20 \text{ }^\circ\text{C}$, humidity $45 \pm 5\%$) and a
199 fan was placed 5 m in front of the cycle ergometer to promote evaporative cooling. Participants
200 undertook a 5 min cool-down at a self-selected workload immediately after completion of the TT.

201

202 **Physiological and perceptual measures**

203 During each TT, blood lactate ion concentration ($[La^-]$) was measured pre- and post-exercise, and every
204 1 km throughout using a portable lactate monitor (Lactate Pro 2, Arkray, Japan). At the same time
205 points, lower-limb ratings of perceived exertion (RPE-L) and RPE were recorded using a 6–20 scale
206 (Borg, 1973), whereas perceived ratings of fatigue (ROF) were recorded on a 10-point Likert scale
207 (Micklewright et al. 2017). Heart rate was measured pre- and post-exercise, and every 0.5 km
208 throughout the TT (Polar®, Kempele, Finland). Symptoms of GI distress were recorded immediately
209 pre-exercise using an adapted GI symptom questionnaire (Carr et al. 2011b) including nausea,
210 flatulence, stomach cramping, belching, stomach ache, bowel urgency, diarrhoea, vomiting, and
211 stomach bloating. Symptoms were self-measured on a 10 cm visual analogue scale where “0 = No
212 symptom” and “10 = Severe symptom” (Miller et al. 2016). Symptom terminology was explained to
213 participants before the experimental trials commenced to ensure consistency in the reporting of
214 symptoms.

215

216 **Statistical analyses**

217 Data normality was assessed using the Shapiro–Wilk test and by visual inspection of the normality plots
218 (Grafen & Hails, 2002). One-way analysis of variance (ANOVA) for repeated-measures were used to
219 compare performance time and GI symptom scores. All performance (i.e. power), acid-base balance
220 (i.e. blood $[HCO_3^-]$, pH, $[Na^+]$, $[K^+]$ and $[Cl^-]$), physiological (i.e. blood $[La^-]$ and heart rate) and
221 perceptual (i.e. RPE, RPE-L and ROF) variables were analysed using two-way (condition \times time)
222 ANOVA for repeated-measures. Where a significant main effect was revealed, Bonferroni-adjusted
223 post-hoc paired comparisons were determined (Atkinson, 2002). Effect sizes were reported as eta-
224 squared (η^2) for one- and two-way ANOVA, whereas Hedge’s g and 95% confidence intervals (CI)
225 were calculated for paired comparisons (Lakens, 2013). Effects were discussed in relation to the
226 relevant literature (Thompson, 2007) and described as small ($\eta^2 = 0.01$; $g = 0.2$), medium ($\eta^2 = 0.06$; g
227 $= 0.5$), or large ($\eta^2 = 0.14$; $g = 0.8$) as previously suggested (Cohen, 1988). Statistical significance was
228 set at $P < 0.05$ and values for P of “0.000” given by the statistical package were corrected to “ < 0.0005 ”
229 (Kinnear & Gray, 1995). Descriptive data are presented as mean \pm standard deviation (SD) throughout.

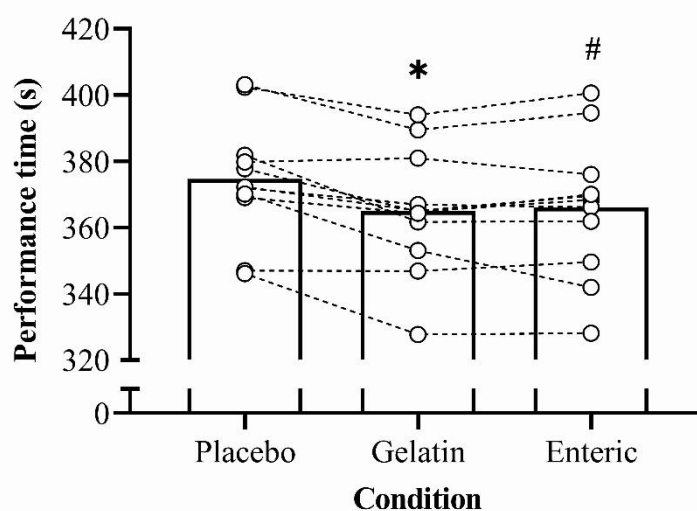
230 Data were analysed using the Statistical Package for the Social Sciences version 25 software (IBM®,
 231 Chicago, USA), whereas sample size was calculated using GPower® version 3.1.9.2 (Faul et al. 2007).

232

233 Results

234 Exercise performance

235 There was a significant improvement in performance time (Fig. 1) in the NaHCO₃ trials compared with
 236 the placebo ($F_{2.0, 20.0} = 10.6$, $P = 0.001$, $\eta^2 = 0.52$). Performance time was significantly faster with
 237 enteric-coated (mean difference = 8.5 s [-2.3%], $P = 0.044$, 95% CI [0.2, 16.9 s], $g = 0.4$) and gelatin
 238 (mean difference = 9.6 s [-2.6%], $P = 0.004$, 95% CI [3.4, 15.9 s], $g = 0.5$) NaHCO₃ compared with
 239 the placebo, but there was no difference between enteric-coated and gelatin NaHCO₃ (mean difference
 240 = -1.1 s, $P = 1.00$, 95% CI [-5.7, 3.5 s], $g = 0.1$).



241

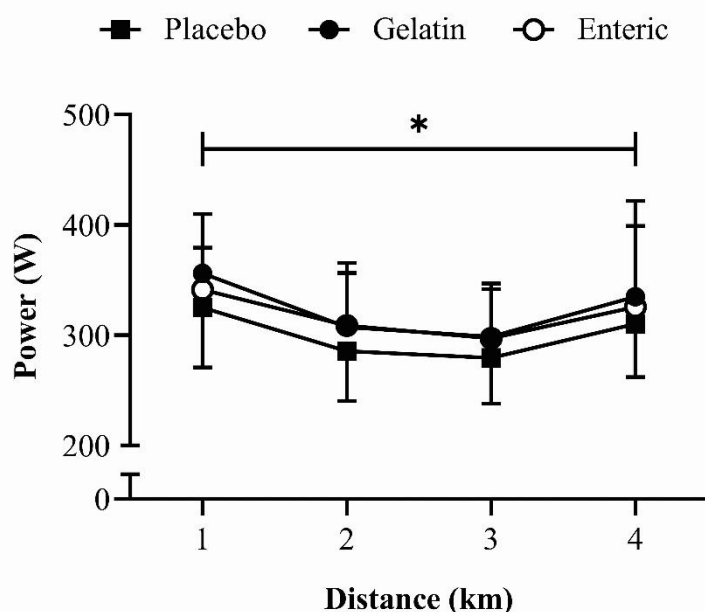
242 **Fig. 1** Mean \pm SD 4 km TT performance time following the ingestion of 0.3 g·kg⁻¹ body mass NaHCO₃
 243 in gelatin or enteric-coated capsules, or a placebo. Dotted lines denote individual performance times.

244 *Significant difference between gelatin NaHCO₃ and placebo ($P < 0.05$). #Significant difference
 245 between enteric-coated NaHCO₃ and placebo ($P < 0.05$)

246

247 Acute bicarbonate loading had a significant effect on power output ($F_{2.0, 20.0} = 8.8$, $P = 0.002$,
 248 $\eta^2 = 0.10$; Fig. 2), with higher values during the gelatin trial when compared with the placebo (mean
 249 difference = 24 W [+7.7%], $P = 0.023$, 95% CI [3, 45 W], $g = 0.5$). No further differences in power

250 output were shown between trials ($P > 0.05$). There was significant variation in power output across the
 251 TT ($F_{1.4, 14.1} = 12.8$, $P = 0.002$, $\eta^2 = 0.34$) with power output declining between 1 and 2 km ($P = 0.001$)
 252 before reaching a plateau ($P = 0.123$) at 3 km, followed by an increase towards 4 km ($P = 0.026$). Pacing
 253 strategies were similar between conditions (Fig. 2), with no significant condition \times time interaction ($F_{2.6,$
 254 $26.1 = 0.4$, $P = 0.746$, $\eta^2 = 0.01$). No order effect on TT performance was shown given that neither
 255 performance time nor power output differed between the first to last trial (all $P > 0.05$).



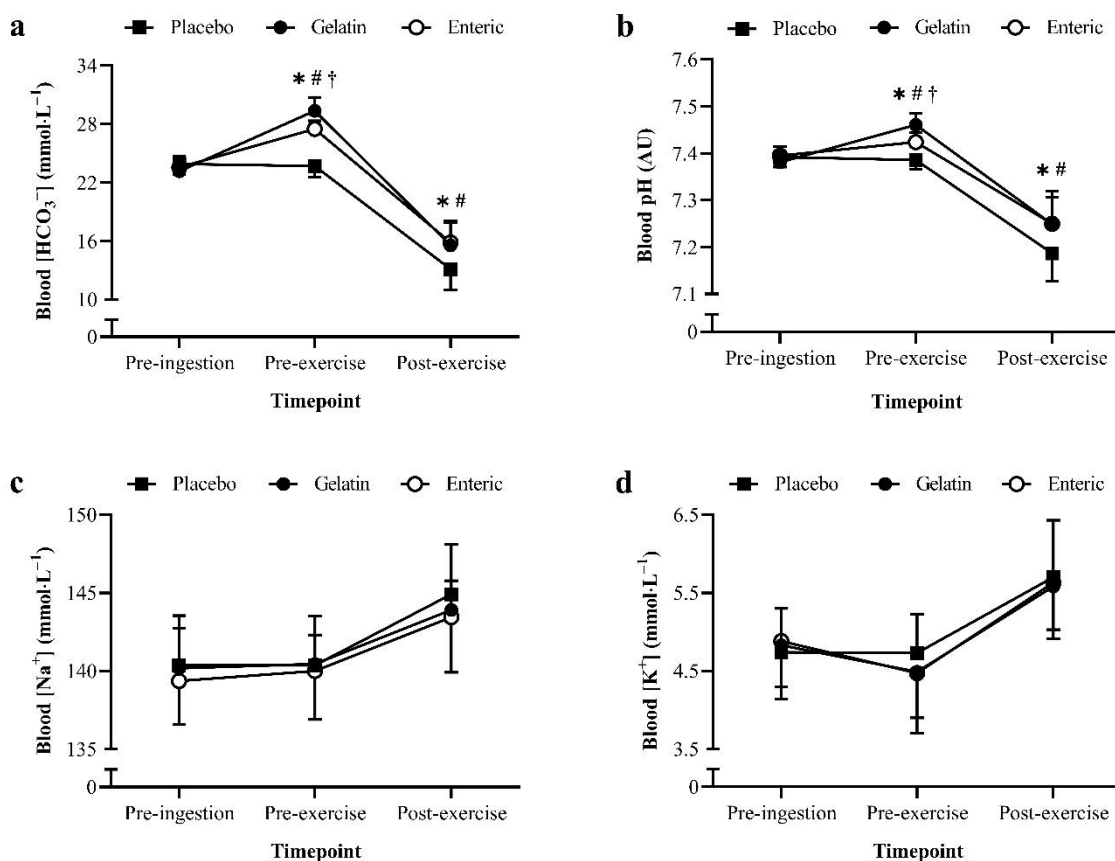
256
 257 **Fig. 2** Mean \pm SD power output following the ingestion of $0.3 \text{ g} \cdot \text{kg}^{-1}$ body mass NaHCO_3 in gelatin or
 258 enteric-coated capsules, or a placebo. *Significant difference between gelatin NaHCO_3 and placebo (P
 259 < 0.05)

260

261 Acid–base balance

262 The time-to-reach individual peak blood $[\text{HCO}_3^-]$ was 110 ± 20 min (range 80-140 min) and 90 ± 20
 263 min (range 60-130 min) in the enteric-coated and gelatin conditions, respectively. Blood $[\text{HCO}_3^-]$ was
 264 significantly higher in the NaHCO_3 conditions compared with the placebo ($F_{2.0, 20.0} = 23.5$, $P < 0.0005$,
 265 $\eta^2 = 0.04$, Fig. 3a), with no difference between enteric-coated and gelatin capsules ($P = 1.0$). Blood
 266 $[\text{HCO}_3^-]$ increased pre-exercise ($P < 0.0005$) followed by a decrease post-exercise ($P < 0.0005$), with a
 267 condition \times time interaction ($F_{4.0, 40.0} = 48.2$, $P < 0.0005$, $\eta^2 = 0.87$). Pre-exercise blood $[\text{HCO}_3^-]$ was

268 significantly higher in the enteric-coated ($3.8 \pm 1.0 \text{ mmol}\cdot\text{L}^{-1}$, $P < 0.0005$, 95% CI [3.0, 4.7 $\text{mmol}\cdot\text{L}^{-1}$],
 269 $g = 3.8$) and gelatin ($5.6 \pm 1.5 \text{ mmol}\cdot\text{L}^{-1}$, $P < 0.0005$, 95% CI [4.3, 6.3 $\text{mmol}\cdot\text{L}^{-1}$], $g = 4.3$) conditions
 270 compared with the placebo. Furthermore, blood $[\text{HCO}_3^-]$ was significantly lower with enteric-coated
 271 compared with gelatin capsules pre-exercise (mean difference = $1.8 \text{ mmol}\cdot\text{L}^{-1}$, $P = 0.012$, 95% CI [0.4,
 272 $3.3 \text{ mmol}\cdot\text{L}^{-1}$], $g = 1.5$).



273
 274 **Fig. 3** Mean \pm SD blood (a) $[\text{HCO}_3^-]$ (b) pH (c) $[\text{Na}^+]$ and (d) $[\text{K}^+]$ pre-ingestion, pre-exercise (post-
 275 ingestion) and post-exercise. *Significant difference between gelatin NaHCO_3 and placebo ($P < 0.05$).
 276 #Significant difference between enteric-coated NaHCO_3 and placebo ($P < 0.05$). †Significant difference
 277 between gelatin and enteric-coated NaHCO_3 ($P < 0.05$)

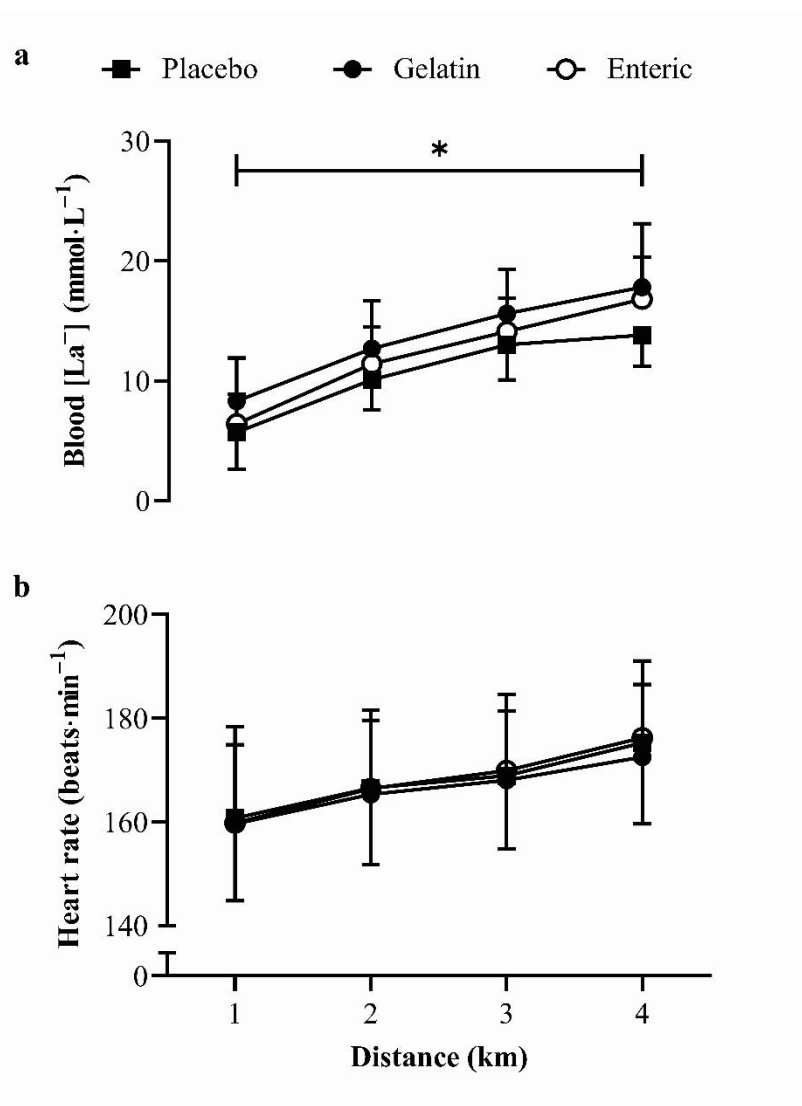
278
 279 Blood pH was significantly higher in the NaHCO_3 conditions compared with the placebo ($F_{2,0}$,
 280 $_{20.0} = 14.6$, $P < 0.0005$, $\eta^2 = 0.04$, Fig. 3b), with no difference between enteric-coated and gelatin capsules
 281 ($P = 1.0$). Blood pH increased pre-exercise ($P < 0.0005$) followed by a decrease post-exercise ($P <$

282 0.0005), with a condition \times time interaction ($F_{2.0, 19.7} = 48.2$, $P = 0.001$, $\eta^2 = 0.03$). Pre-exercise blood
283 pH was significantly higher in the enteric-coated (0.038 ± 0.016 AU, $P < 0.0005$, 95% CI [0.024, 0.052
284 AU]) and gelatin (0.074 ± 0.019 AU, $P < 0.0005$, 95% CI [0.058, 0.091 AU]) conditions compared with
285 the placebo. Blood pH was also significantly lower with enteric-coated compared with gelatin capsules
286 pre-exercise (mean difference = 0.037 AU, $P = 0.001$, 95% CI [0.018, 0.055 AU], $g = 1.6$).

287

288 **Electrolyte responses**

289 Acute bicarbonate loading did not alter blood $[\text{Na}^+]$ ($F_{2.0, 20.0} = 1.0$, $P = 0.394$, $\eta^2 = 0.02$, Fig. 3c),
290 although there were significant increases shown post-exercise ($F_{2.0, 20.0} = 20.5$, $P < 0.0005$, $\eta^2 = 0.42$).
291 No condition \times time interaction was shown for blood $[\text{Na}^+]$ ($F_{4.0, 40.0} = 0.3$, $P = 0.850$, $\eta^2 = 0.01$).
292 Similarly, NaHCO_3 ingestion did not alter blood $[\text{K}^+]$ ($F_{2.0, 20.0} = 0.2$, $P = 0.848$, $\eta^2 = 0.01$, Fig. 3d)
293 despite significant increases post-exercise ($F_{2.0, 20.0} = 41.1$, $P < 0.0005$, $\eta^2 = 0.48$), with no condition \times
294 time interaction ($F_{4.0, 40.0} = 0.6$, $P = 0.660$, $\eta^2 = 0.01$).



295

296 **Fig. 4** Mean \pm SD (a) blood [La⁻] and (b) heart rate response during the 4 km TT following the ingestion
 297 of 0.3 g·kg⁻¹ body mass NaHCO₃ in gelatin or enteric-coated capsules, or a placebo. *Significant
 298 difference between gelatin NaHCO₃ and placebo ($P < 0.05$)

299

300 Physiological and perceptual responses

301 Blood [La⁻] was significantly greater ($F_{2,0, 20} = 7.7$, $P = 0.003$, $\eta^2 = 0.03$; Fig. 4a) in the gelatin trial
 302 compared with the placebo (mean difference = 2.4 mmol·L⁻¹, $P = 0.003$, 95% CI [0.9, 3.8 s], $g = 0.9$).
 303 No further differences in lactate responses were shown between conditions ($P > 0.05$), although blood
 304 [La⁻] progressively increased during all TTs ($F_{1.4, 13.9} = 127.3$, $P < 0.0005$, $\eta^2 = 0.82$), without a condition
 305 \times time interaction ($F_{2.5, 25.2} = 2.0$, $P = 0.152$, $\eta^2 = 0.01$). Heart rate progressively increased throughout
 306 the 4 km TT ($F_{1.1, 10.9} = 43.8$, $P < 0.0005$, $\eta^2 = 0.60$; Fig. 4b), although no significant differences were

307 shown between conditions ($F_{2.0, 20} = 0.7$, $P = 0.491$, $\eta^2 = 0.01$), nor was there a significant condition \times
 308 time interaction ($F_{2.3, 22.5} = 1.0$, $P = 0.385$, $\eta^2 = 0.01$). Despite improvements in TT performance in both
 309 NaHCO₃ conditions, there were no differences in neither RPE ($F_{2.0, 20.0} = 2.2$, $P = 0.137$, $\eta^2 = 0.04$),
 310 RPE-L ($F_{2.0, 20.0} = 0.2$, $P = 0.841$, $\eta^2 = 0.01$) nor ROF ($F_{2.0, 20.0} = 3.5$, $P = 0.05$, $\eta^2 = 0.03$) between
 311 conditions, although there were significant increases in RPE ($F_{3.0, 30.0} = 63.2$, $P < 0.0005$, $\eta^2 = 0.56$),
 312 RPE-L ($F_{1.4, 14.4} = 45.2$, $P < 0.0005$, $\eta^2 = 0.53$) and ROF ($F_{1.2, 12.4} = 2.2$, $P < 0.0005$, $\eta^2 = 0.67$) during
 313 the TT (Table 1). No significant condition \times time interactions were revealed for neither RPE ($F_{6.0, 60.0} =$
 314 0.9 , $P = 0.524$, $\eta^2 = 0.01$), RPE-L ($F_{6.0, 60.0} = 0.4$, $P = 0.893$, $\eta^2 = 0.01$) nor ROF ($F_{6.0, 60.0} = 0.8$, $P =$
 315 0.583 , $\eta^2 = 0.01$).

316

317 **Table 1.** Mean \pm SD perceptual responses during the 4 km TT.

	Placebo	Condition Gelatin	Enteric
RPE (AU)			
1-km	11.6 \pm 1.9	11.5 \pm 2.8	12.5 \pm 2.0
2-km	13.3 \pm 2.2	12.4 \pm 2.5	14.0 \pm 1.7*
3-km	14.8 \pm 2.2*	13.8 \pm 1.8	15.2 \pm 2.1*
4 km	16.6 \pm 2.3*	16.0 \pm 2.8*	16.6 \pm 2.2*
RPE-L (AU)			
1-km	13.5 \pm 2.7	13.6 \pm 2.2	13.7 \pm 2.1
2-km	14.7 \pm 2.5	14.6 \pm 2.2*	15.0 \pm 1.7
3-km	16.1 \pm 1.9*	15.9 \pm 2.0*	16.2 \pm 1.6*
4 km	17.3 \pm 2.4	17.8 \pm 1.7*	18.0 \pm 2.1*
ROF (AU)			
1-km	3.9 \pm 1.8	3.2 \pm 1.3	3.5 \pm 1.1
2-km	5.0 \pm 1.4*	4.7 \pm 0.9*	5.2 \pm 1.0*
3-km	5.8 \pm 1.1*	5.4 \pm 1.2	6.2 \pm 1.3
4 km	7.5 \pm 1.3*	6.6 \pm 1.2*	7.5 \pm 1.4*

*Denotes a significant difference from the previous timepoint ($P < 0.05$).

318

319 **Gastrointestinal symptoms**

320 No GI symptoms were reported pre-ingestion in all conditions. No participants reported GI symptoms
 321 pre-exercise with the placebo, whereas fewer participants experienced symptoms with enteric-coated
 322 ($n = 7$) compared to gelatin ($n = 3$) NaHCO₃. Pre-exercise GI symptom scores were significantly higher

323 following gelatin NaHCO₃ (3.6 ± 3.9 AU) compared with placebo ($P = 0.043$), with no difference
 324 between enteric-coated NaHCO₃ (1.0 ± 1.7 AU) and placebo ($P = 0.324$). Furthermore, pre-exercise GI
 325 symptoms were less severe with enteric-coated NaHCO₃ compared to gelatin at the individual level
 326 (Table 2), although group symptom scores were similar ($P = 0.211$) between enteric-coated and gelatin
 327 capsules (mean difference = 2.6 AU, $P = 0.211$, 95% CI [1.1, 6.2 AU]).

328

329 **Table 2.** Individual GI symptom scores immediately before exercise. Symptoms are displayed in bold
 330 for clarity and scores are displayed in parentheses.

Participant	Condition		
	Placebo	Gelatin	Enteric
1	No symptom (0.0)	No symptom (0.0)	No symptom (0.0)
2	No symptom (0.0)	Diarrhoea (10.0)	No symptom (0.0)
3	No symptom (0.0)	Stomach ache (1.3)	No symptom (0.0)
4	No symptom (0.0)	Stomach cramp (1.5)	No symptom (0.0)
5	No symptom (0.0)	No symptom (0.0)	Flatulence (5.0)
6	No symptom (0.0)	Diarrhoea (6.0)	No symptom (0.0)
7	No symptom (0.0)	Bloating (5.0)	Bloating (3.0)
8	No symptom (0.0)	No symptom (0.0)	No symptom (0.0)
9	No symptom (0.0)	Bowel urgency (5.0)	No symptom (0.0)
10	No symptom (0.0)	Diarrhoea (10.0)	Bloating (2.0)
11	No symptom (0.0)	No symptom (0.0)	No symptom (0.0)

331

332 Discussion

333 This is the first study to investigate the effect of enteric-coated NaHCO₃ supplementation on exercise
 334 performance, specifically that which would typically benefit from extracellular buffering agents. The
 335 main finding of this study was that ingesting enteric-coated NaHCO₃ prior to exercise improved (~
 336 2.3%) subsequent 4 km cycling TT performance among trained cyclists. Despite inducing a lower
 337 degree of metabolic alkalosis with enteric-coated NaHCO₃ (Fig. 3), there were no differences in exercise
 338 performance compared with a standard ingestion form (i.e. gelatin capsules). Furthermore, enteric-
 339 coated NaHCO₃ reduced GI symptoms experienced immediately before exercise compared with gelatin
 340 capsules (Table 2), although subjective ratings of GI symptoms in this sample were low. When taken
 341 together, these data suggest that enteric-coated NaHCO₃ improves high-intensity cycling performance

342 in those with mild to moderate GI symptoms. However, the effects of enteric-coated NaHCO₃ on
343 exercise performance could be greater in those who experience more severe GI symptoms at the onset
344 of exercise, although this warrants further investigation. Enteric-coated NaHCO₃ supplementation may
345 therefore offer an alternate strategy to improve high-intensity exercise performance and mitigate GI
346 symptoms associated with acute bicarbonate loading.

347 Numerous studies have investigated the effects of NaHCO₃ on simulated high-intensity TT
348 events with equivocal outcomes (Callahan et al. 2017; Gough et al. 2018). Where some studies have
349 reported performance improvements (Gough et al. 2018), others have reported no benefit (Callahan et
350 al. 2017; Correia-Oliveira et al. 2017) following supplementation. This disparity between studies could
351 be explained by the timing of supplementation, given that the current study demonstrated positive
352 outcomes when exercise was timed with peak alkalosis. Studies that have reported no effect of NaHCO₃
353 ingestion during similar exercise protocols have administered the supplement at a standardised time
354 (Callahan et al. 2017; Correia-Oliveira et al. 2017) despite considerable variability in the time taken to
355 reach metabolic alkalosis (Jones et al. 2016). Time between ingestion and the onset of exercise largely
356 determines the degree of metabolic alkalosis in terms of blood [HCO₃⁻] and pH (Heibel et al. 2018),
357 which in turn, may influence the ergogenicity of NaHCO₃ supplementation (Carr et al. 2011a).
358 Interestingly, the effect of NaHCO₃ on exercise performance in the present study was mediated by the
359 ingestion form, with a *small to moderate* effect on performance time (2.3–2.6%) with enteric-coated
360 and gelatin NaHCO₃, respectively. The present study reported a mean 5.6 mmol·L⁻¹ increase in blood
361 [HCO₃⁻] with gelatin compared to placebo, which is lower than the 3.8 mmol·L⁻¹ increase shown with
362 the enteric-coated capsules. This finding is consistent with previous studies that have investigated the
363 acid-base kinetics following NaHCO₃ ingestion (Hilton 2019b), which could account for the difference
364 in effect size reported in the present study. Nevertheless, exercise performance still improved with
365 enteric-coated NaHCO₃ supplementation, which questions the 5-6 mmol·L⁻¹ threshold suggested to
366 improve performance (Carr et al. 2011a; Heibel et al. 2018). Furthermore, the improvements in 4 km
367 cycling TT performance in the present study are similar to previous studies, despite higher pre-exercise
368 blood [HCO₃⁻] reported by others (Gough et al. 2018). Given this disparity between studies, it is

369 unlikely that timing is the only factor modulating the ergogenicity of NaHCO₃ during high-intensity
370 exercise.

371 Whilst an individualised ingestion strategy may increase the likelihood of commencing exercise
372 with greater blood buffering capacity, it is not clear whether this optimises the ergogenicity of NaHCO₃
373 supplementation. Individualising the timing of supplementation may also not be practical at present, for
374 some athletes, given that this requires access to a blood-gas analyser. In the current study however,
375 mean ingestion timings corresponded to those that have been previously suggested with enteric-coated
376 NaHCO₃ (Hilton et al. 2019b). Furthermore, it is important to note that enteric-coated capsules delay
377 the time-to-reach peak blood [HCO₃⁻] following NaHCO₃ ingestion, suggesting that current
378 recommendations (e.g. 60-90 min before exercise) are not appropriate for this ingestion form. Instead,
379 the current study adds to the growing body of evidence suggesting that enteric-coated NaHCO₃ should
380 be ingested ~ 120 min prior to exercise to maximise blood [HCO₃⁻] if a standardised ingestion timing
381 strategy is adopted (Hilton et al. 2019b). Whilst participants ingested the capsules in a fasted state in
382 the present study, co-ingestion with food may delay gastric emptying and alter the release of NaHCO₃
383 (Davis et al. 1986). Further research should look to compare the effects of an individualised and
384 standardised ingestion time on subsequent performance, including the effects of prandial state on acid-
385 base responses and GI symptoms following NaHCO₃ ingestion.

386 Given that enteric-coated NaHCO₃ improves exercise performance among those with mild to
387 moderate GI symptoms, the effects on exercise performance may be enhanced among those with more
388 severe GI symptoms at the onset of exercise. While GI distress was significantly reduced in some
389 individuals in the current study (Table 2), numerous individuals did not report symptoms at the onset
390 of exercise. Although ergogenic doses (~ 0.3 g·kg⁻¹ body mass) of NaHCO₃ may induce GI symptoms,
391 these may not necessarily be timed with exercise performance. This is consistent with previous studies
392 (Hilton et al. 2019a; Hilton et al. 2019b) demonstrating the reduced incidence of GI symptoms at the
393 time of peak alkalosis, despite severe symptoms at other timepoints. It is therefore difficult to elucidate
394 whether GI symptoms can negate the ergogenic effects of NaHCO₃ supplementation from the current
395 data, since the overall incidence and severity of GI symptoms was low. Nevertheless, GI symptoms
396 may hinder high-intensity exercise performance or dampen the ergogenic effects of NaHCO₃

397 supplementation (Saunders et al. 2014). Further research should therefore examine the effects of
398 enteric-coated NaHCO_3 supplementation in those who typically report moderate to severe GI symptoms
399 at the onset of exercise, as the effects may be greater among these individuals. Given that only few
400 participants reported GI symptoms following enteric-coated NaHCO_3 supplementation, future studies
401 could consider increasing the dose ($> 0.3 \text{ g}\cdot\text{kg}^{-1}$ body mass), which may also increase blood $[\text{HCO}_3^-]$.

402 Whilst psychological indicators of perceived exertion and fatigue increased during exercise, no
403 differences were reported between the placebo and NaHCO_3 conditions (Table 1), suggesting an
404 alternative mechanism other than reductions in afferent feedback to the central nervous system (Siegler
405 & Marshall, 2015). Nevertheless, this finding indicates the enhancements in power output were attained
406 at a relatively similar RPE when supplementing with NaHCO_3 . Similarly, despite distinct changes in
407 blood $[\text{Na}^+]$ and $[\text{K}^+]$ during exercise, no differences were shown between NaHCO_3 and placebo (Fig.
408 3). Changes in these strong ions can impair muscle excitability (Cairns & Lindinger, 2008), therefore
409 suggesting that improvements in performance were not due to ionic shifts in $[\text{Na}^+]$ and $[\text{K}^+]$ associated
410 with enhanced contractility. Nevertheless, enhanced muscle contractile function cannot be dismissed as
411 a potential mechanism, as altered calcium handling can improve mechanical efficiency (Siegler et al.
412 2016), although this cannot be elucidated from the current study. Alternatively, given that pre-exercise
413 blood $[\text{HCO}_3^-]$ and pH were greater in the NaHCO_3 conditions compared to placebo, the performance
414 improvements shown in the current study may be attributed to increases in extracellular buffering
415 capacity. Reinforced extracellular concentrations of bicarbonate are suggested to promote H^+ efflux
416 from intramuscular to extracellular regions through increases in monocarboxylate transporter activity,
417 which maintains muscle pH during exercise (Bishop et al. 2006). Given the delayed onset of
418 intramuscular acidosis, NaHCO_3 promotes glycolytic enzyme activity and flux, as indicated through
419 increases in muscle glycogen utilisation and lactate concentrations (Hollidge-Horvat et al. 2000; Siegler
420 et al. 2016). Although muscle pH and lactate were not measured in the current study, increases in muscle
421 pH and lactate efflux have been shown during exercise following NaHCO_3 supplementation (Costill et
422 al. 1984). Augmenting glycolytic flux may have therefore permitted exercise at higher intensities and
423 could explain the performance improvements reported in the current study. This would account for the
424 greater blood $[\text{La}^-]$ shown with gelatin NaHCO_3 , although the increases reported with enteric-coated

425 capsules did not reach significance (Fig. 4a). Given that monocarboxylate transporters 1- and 4 are
426 stimulated by the intra- to extracellular $[H^+]$ gradient, the greater extracellular pH shown with gelatin
427 capsules may have upregulated the co-transport of H^+ and lactate to a greater extent and could account
428 for differences in the ergogenic effect size (0.3%). This may also explain why power output was greater
429 when $NaHCO_3$ was given in gelatin capsules (Fig. 2), although this did not result in greater overall
430 performance times compared to enteric-coated capsules. Therefore, the current evidence suggests that
431 while pre-exercise blood $[HCO_3^-]$ does not determine the overall ergogenicity of $NaHCO_3$
432 supplementation, the magnitude of such effects may be increased by a greater degree of metabolic
433 alkalosis.

434 In summary, this study is the first to demonstrate that $0.3\text{ g}\cdot\text{kg}^{-1}$ body mass of enteric-coated
435 $NaHCO_3$ improves high-intensity exercise performance when timed with peak alkalosis. This study also
436 provides novel data highlighting that ingestion form (e.g. gelatin or enteric-coated capsules) can mediate
437 the effects on exercise performance, potentially through the degree of induced alkalosis. In order to
438 understand the implications of GI symptoms on exercise performance, further research should compare
439 the effects of enteric-coated $NaHCO_3$ supplementation on exercise performance in those who
440 experience severe symptoms immediately before exercise, particularly as GI distress may be ergolytic
441 among these individuals. Furthermore, given the growing range of ingestion forms commercially
442 available to athletes (e.g. liquid, gelatin capsules, enteric-coated capsules), future studies should
443 compare the effects on exercise performance. Nonetheless, acute enteric-coated $NaHCO_3$ consumption
444 improves 4 km cycling TT performance and therefore, may offer an appropriate ergogenic strategy for
445 those who experience GI side-effects following supplementation.

446

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450

451 **Author contributions**

452 NPH, SAS, LRM conceived and designed research. NPH and NKL conducted experiments. NPH
453 analysed the data. NPH wrote the manuscript with ongoing critical comments/input from all
454 other authors. All authors read and approved the manuscript.

455

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459 **Conflicts of interest**

460 NPH, NKL, MMH, SAS and LRM can confirm that there are no competing interests.

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