



Caffeine and physiological responses to submaximal exercise: a meta-analysis

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Brief Review

1 **Caffeine and physiological responses to submaximal exercise: a meta-analysis**

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28 **Abstract**

29 The aim of this study was to carry out a systematic review and meta-analysis of the effects of
30 caffeine supplementation on physiological responses to submaximal exercise. 26 studies met
31 the inclusion criteria of adopting double-blind, randomised, crossover designs that included a
32 sustained (5 – 30 minutes) fixed-intensity bout of submaximal exercise (constrained to 60 –
33 85% $\dot{V}O_{2\max}$) using a standard caffeine dose of 3 – 6 $\text{mg}\cdot\text{kg}^{-1}$ administered 30 – 90 minutes
34 prior to exercise. Meta-analyses were completed using a random-effects model, and data are
35 presented as raw mean difference (D) with associated 95% confidence limits (CL_{95}). Relative
36 to placebo, caffeine led to significant increases in submaximal measures of minute ventilation
37 ($D = +3.36 \text{ L}\cdot\text{min}^{-1}$; $CL_{95}[+1.63, +5.08]$; $p = 0.0001$; $n = 73$), blood lactate ($D = +0.69$
38 $\text{mmol}\cdot\text{L}^{-1}$; $CL_{95}[+0.46, +0.93]$; $p < 0.00001$; $n = 208$), and blood glucose ($D = +0.42 \text{ mmol}\cdot\text{L}^{-1}$;
39 $CL_{95}[+0.29, +0.55]$; $p < 0.00001$; $n = 129$). In contrast, caffeine had a suppressive effect on
40 ratings of perceived exertion ($D = -0.8$; $CL_{95}[-1.1, -0.6]$; $p < 0.00001$; $n = 147$). Caffeine had
41 no effect on measures of heart rate ($p = 0.99$; $n = 207$), respiratory exchange ratio ($p = 0.18$; n
42 $= 181$), or $\dot{V}O_2$ ($p = 0.92$; $n = 203$). The positive effects of caffeine supplementation on
43 sustained high-intensity exercise performance are widely accepted; though the mechanisms to
44 explain that response are currently unresolved. This meta-analysis has revealed clear effects
45 of caffeine on various physiological responses during submaximal exercise, which may help
46 to explain its ergogenic action.

47

48 **Key words:** Ergogenic aids, methylxanthine, endurance exercise, adenosine receptor.

49

50 Introduction

51 Caffeine, a trimethylxanthine, is a ubiquitous socially acceptable drug with no apparent long-
52 term health effects.¹ While there is some evidence that caffeine may improve single² and
53 repeated sprint activities,³ effects are most consistently observed in sustained bouts of high-
54 intensity aerobic exercise.¹ Typical ergogenic doses of 3 – 6 mg·kg⁻¹ ingested 30 – 90
55 minutes prior to exercise have been shown to result in performance increases of up to 6% in
56 events lasting from a few minutes to several hours.¹ The key mechanism by which caffeine is
57 believed to exert its effect is via the antagonism of adenosine receptors, leading to increases
58 in neurotransmitter release, motor unit firing rates, and pain suppression.⁴ However, the
59 ubiquitous nature of adenosine receptors, coupled with their ability to produce differential
60 responses depending on the site of action and the receptor subtype involved, has made it
61 difficult to identify the precise mechanisms by which caffeine exerts its ergogenic effect.

62

63 One of the problems with trying to evaluate the mechanisms by which caffeine improves
64 high-intensity endurance performance is that the associated physiological responses are likely
65 to be influenced by the increase in exercise intensity responsible for the increase in
66 performance. Although some studies have attempted to address this problem by including a
67 fixed-intensity submaximal bout of exercise (generally at around 60 – 85% $\dot{V}O_{2max}$) prior to a
68 performance-based test, often as part of a warm-up or when attempting to simulate the steady
69 state conditions that typically occur in the early stages of endurance events, the results
70 contain some discrepancies. For example, whilst some studies have found no effect of
71 caffeine on minute ventilation (\dot{V}_E),⁵⁻¹¹ others have reported a significant increase.^{12,13}
72 Similarly, many studies report no effect of caffeine on respiratory exchange ratio
73 (RER),^{6,8,9,11,13-23} though some have reported a significant decrease,^{10,12,24-26} and one, a
74 significant increase.⁵ These discrepancies could easily be attributed to statistical error
75 resulting from the relatively small sample sizes that are typical of these investigations, and
76 have often been criticised.^{27,28} The aim of this systematic review and meta-analysis was
77 therefore to investigate the effects of caffeine supplementation on physiological responses to
78 submaximal exercise.

79

80 Methods

81 *Systematic review*

82 The databases of Pubmed, SportDiscus, Science Direct, and Web of Science were searched
83 for peer-reviewed publications (prior to September 2015) containing 'caffeine' in the title and
84 any of the following words in the title or the abstract: 'endurance', 'submaximal', 'aerobic',
85 'steady state', 'exhaustion', or 'fixed intensity'. Reference lists of those studies that passed
86 the initial screening for potential inclusion in the analysis along with those from relevant
87 review articles^{4,27-35} and textbooks¹ were also examined for publications which may have
88 eluded the search of online databases.

89

90 *Inclusion and exclusion criteria*

91 Studies considered for inclusion in this investigation were limited to those conducted on adult
92 (age: ≥ 18 years) humans, which had adopted double-blind, randomised, crossover designs
93 using a standard effective caffeine dose of 3 – 6 mg·kg⁻¹ administered 30 – 90 minutes prior
94 to exercise. Studies examining combinations of supplements were included in the analysis if
95 the experimental design incorporated a caffeine versus placebo comparison.^{5,25} In cases

96 where studies had investigated the effects of different caffeine doses,^{10,13,18,36} the dose closest
97 to the upper limit of the inclusion range was used in the analysis. Exercise intensities were
98 constrained to those required to elicit 60 – 85% $\dot{V}O_{2\max}$, since those intensities span the range
99 typically experienced in prolonged endurance events,³⁷ and as such, were the most commonly
100 used to evaluate the effects of caffeine on submaximal physiological responses. On those
101 occasions where studies had investigated the effects of caffeine supplementation on several
102 exercise intensities,^{19,22,26,36,38} the intensity closest to the middle of the inclusion range was
103 chosen for the analysis. Exercise duration was limited to a minimum of 5 minutes, to provide
104 sufficient time for physiological responses to achieve a steady state; and to a maximum of 30
105 minutes to reduce any effect that fatigue may have on the results. Studies using bouts of
106 submaximal exercise longer than 30 minutes were included in the analysis if physiological
107 measurements were made within the 5 – 30 minutes inclusion window. In instances where
108 authors had made multiple measurements within the 5 – 30 minutes inclusion window, values
109 closest to the upper limit of 30 minutes were used in the meta-analysis. No inclusion
110 restrictions were placed on potential moderator variables of gender, training status, caffeine
111 habituation, or supplementation method, since previous research has failed to establish
112 whether any of those variables influence the effects of caffeine on endurance performance.¹
113 However, subgroup meta-analyses were used to investigate potential influences of
114 supplementation method and exercise intensity on the physiological responses to caffeine
115 (see below).

116

117 ***Data extraction***

118 For the meta-analysis, data were extracted from relevant publications as means, standard
119 deviations (SD), and sample sizes. In instances where data were presented in a graphical
120 format, images were enlarged to improve the precision of the data estimates. Physiological
121 responses were limited to those which were most commonly evaluated during submaximal
122 exercise, which were: heart rate, oxygen uptake ($\dot{V}O_2$), RER, \dot{V}_E , rating of perceived exertion
123 (RPE), blood lactate concentration [BLa], and blood glucose concentration [BGl]. Measures
124 of RPE were constrained to those evaluated using the 15-point scale.³⁹

125

126 ***Meta-analysis***

127 From an initial search result of 483 studies, 26 met the inclusion criteria for the meta-analysis
128 (Table 1). Meta-analyses were conducted using specialist software (Review Manager Version
129 5.3. The Nordic Cochrane Centre, Copenhagen: The Cochrane Collaboration, 2014). Meta-
130 analyses were completed using a random-effects model and data are presented as raw mean
131 difference (D) with associated 95% confidence limits (CL_{95}). The choice to use D rather than
132 a standardized mean difference was based on the fact that each physiological response was
133 measured on the same scale.⁴⁰ Moreover, the advantage of using D is that it provides an
134 outcome to the analysis which is intuitively meaningful to the reader.⁴⁰ Heterogeneity
135 between studies was examined using the I^2 statistic, which describes the percentage of
136 variability in mean difference estimates due to heterogeneity rather than chance. When I^2 was
137 $> 25\%$ (25 – 50% represents moderate heterogeneity⁴¹), a subgroup meta-analysis was
138 completed to investigate the source of heterogeneity. In line with recommendations regarding
139 tests for heterogeneity,⁴² CL_{95} for I^2 were calculated using the method outlined by Higgins &
140 Thompson.⁴³ Subgroup meta-analyses were performed, when appropriate, to investigate the
141 influence of the following potential moderator variables: 1) exercise intensity (constrained to
142 comparisons between the upper [‘high intensity’] and lower [‘low intensity’] half of the

143 inclusion range); and 2) supplementation method (capsule versus drink formats). Of the
144 remaining potential moderator variables, no comparisons were made to investigate the effects
145 of: 1) exercise mode: since most had used either cycling ($n = 17$) or running ($n = 5$) and there
146 was no rationale to expect any differential effects of caffeine; 2) gender: since only one study
147 (2) had used solely female participants; 3) training status: since between-study inconsistencies
148 in the way that this variable was reported/measured did not allow quantification with
149 adequate precision; 4) caffeine dose: since most studies ($n = 21$) had used doses of 5 – 6
150 $\text{mg}\cdot\text{kg}^{-1}$; and 5) administration time: since most studies had administered the supplement 60
151 minutes prior to exercise ($n = 21$). Heterogeneity between subgroups was also evaluated
152 using the I^2 statistic. Statistical significance was accepted at $p < 0.05$ for all analyses.

153

154 **Results**

155 ***Heart rate***

156 Relative to placebo, there was no significant effect of caffeine on heart rate (Figure 1) ($D = -$
157 $0.01 \text{ b}\cdot\text{min}^{-1}$; $\text{CL}_{95}[-1.43, +1.42]$; $p = 0.99$; $n = 207$). There was a moderate degree of
158 heterogeneity in heart rate responses between the 21 studies included in the analysis ($I^2 =$
159 27% ; $\text{CL}_{95}[0, 57]$). Subgroup analyses revealed that there was no evidence of heterogeneity
160 between studies performed in the upper half of the exercise intensity inclusion range or
161 between those studies that administered caffeine in a drink format (Table 2). Nevertheless,
162 there were still no effects of caffeine on heart rate, regardless of subgroup, and there was no
163 evidence of heterogeneity between subgroups (Table 2).

164

165 ***Oxygen uptake***

166 The effects of caffeine on $\dot{V}\text{O}_2$ during submaximal exercise are presented in Figure 2.
167 Relative to placebo, caffeine had no significant effect on $\dot{V}\text{O}_2$ ($D = -0.00 \text{ L}\cdot\text{min}^{-1}$; $\text{CL}_{95}[-0.04,$
168 $+0.03]$; $p = 0.92$; $n = 203$) and the level of heterogeneity across the 20 studies that were
169 analysed was low ($I^2 = 24\%$; $\text{CL}_{95}[0, 56]$).

170

171 ***Respiratory exchange ratio***

172 In comparison with placebo, there was no significant effect of caffeine on RER during
173 submaximal exercise ($D = -0.01$; $\text{CL}_{95}[-0.01, 0.00]$; $p = 0.18$; $n = 181$) (Figure 2). There was,
174 however, evidence of high heterogeneity between the 18 studies that were analysed ($I^2 =$
175 69% ; $\text{CL}_{95}[50, 81]$). Evidence of high between-study heterogeneity remained in each of the
176 subgroups analysed (Table 2), but there was no evidence of heterogeneity between subgroups
177 (Table 2).

178

179 ***Minute ventilation***

180 Eight studies measured the effect of caffeine on \dot{V}_E during submaximal exercise, the effects
181 of which are presented in Figure 2. Relative to placebo, caffeine resulted in a significant
182 increase in \dot{V}_E ($D = +3.36 \text{ L}\cdot\text{min}^{-1}$ [$+1.63, +5.08$]; $p = 0.0001$; $n = 73$), and there was no
183 evidence of heterogeneity between studies ($I^2 = 0\%$; $\text{CL}_{95}[0, 68]$).

184

185 ***Rating of perceived exertion***

186 In comparison with placebo, caffeine resulted in a significant reduction in RPE ($D = -0.8 [-$
187 $1.1, -0.6]$; $p < 0.00001$; $n = 147$) during submaximal exercise (Figure 1). There was, however,
188 evidence of moderate heterogeneity between studies ($n = 15$) ($I^2 = 35%$; $CL_{95}[0, 65]$).
189 Subgroup analyses revealed that there was no evidence of heterogeneity between studies
190 performed in the lower half of the exercise intensity inclusion range or between studies that
191 administered caffeine in a capsule format (Table 2). Nevertheless, there was no evidence of
192 heterogeneity between subgroups and the effect of caffeine on RPE remained regardless of
193 any subgroup heterogeneity (Table 2),

194

195 ***Blood lactate***

196 The effect of caffeine on [BLa] is presented in Figure 3. Relative to placebo, caffeine resulted
197 in a significant increase in [BLa] ($D = +0.69 \text{ mmol}\cdot\text{L}^{-1} [+0.46, +0.93]$; $p < 0.00001$; $n = 208$).
198 However, there was evidence of high heterogeneity between the 21 studies that met the
199 inclusion criteria ($I^2 = 74%$; $CL_{95}[60, 83]$). Evidence of high heterogeneity remained in all
200 subgroup analyses; though the significant effect of caffeine on [BLa] was lost in the subgroup
201 that administered caffeine in a drink format and there was evidence of high heterogeneity
202 between the supplementation method subgroups (Table 2).

203

204 ***Blood glucose***

205 In comparison with placebo, there was a significant increase in [BGI] ($D = +0.42 \text{ mmol}\cdot\text{L}^{-1}$
206 $[+0.29, +0.55]$; $p < 0.00001$; $n = 129$) following caffeine supplementation (Figure 3). There
207 was, however, evidence of high heterogeneity between the 15 studies analysed ($I^2 = 75%$;
208 $CL_{95}[59, 85]$) and there was evidence of heterogeneity in each of the subgroups (Table 2).
209 Nevertheless, the significant effect of caffeine on [BGI] remained in each subgroup, though
210 there was evidence of moderate heterogeneity between the exercise intensity subgroups
211 (Table 2).

212

213 **Discussion**

214 The aim of this study was to carry out a systematic review and meta-analysis of the effects of
215 caffeine supplementation on physiological responses to submaximal exercise. The key
216 findings were that caffeine supplementation resulted in significant increases in \dot{V}_E , [BLa],
217 and [BGI]. In contrast, caffeine had a significant suppressive effect on RPE, and no effect on
218 heart rate, RER, or $\dot{V}O_2$. Despite similar methodological approaches adopted by the studies
219 included in the meta-analysis, there were several instances of moderate to high heterogeneity;
220 although, in several instances, the confidence limits suggest a large degree of uncertainty in
221 the true magnitude of that heterogeneity. Nevertheless, apart from the [BLa] response in the
222 subgroup that administered caffeine in a drink format, the effects of caffeine on the above
223 physiological responses remained regardless of any heterogeneity and the effects of
224 heterogeneity could not be explained by between-study differences in exercise intensity or
225 supplementation method.

226

227 The key mechanism by which caffeine is believed to interact with human tissue, and thereby
228 influence endurance performance, is via the antagonism of adenosine receptors.^{4,31} If this is
229 the case, it should be possible to resolve all of the responses determined in this meta-analysis
230 by that mechanism. Adenosine is a ubiquitous endogenous extracellular signalling molecule,

231 the concentration of which increases during exercise due to the hydrolysis of adenosine
232 triphosphate.^{44,45} Adenosine exerts its effect via its interaction with G-protein coupled cell
233 membrane receptors, widely expressed throughout the body, and of which there are four
234 subtypes (A_1 , A_{2A} , A_{2B} , and A_3).^{44,45} Although adenosine has the highest affinity for the A_1
235 and A_{2A} receptor subtypes,⁴⁵ the ability of adenosine receptors to activate and inhibit the
236 same signalling cascades^{44,45} has made it difficult to identify the precise mechanism by which
237 adenosine exerts its effects. Nevertheless, there is evidence that adenosine signalling affects
238 glucose homeostasis and lipid metabolism,⁴⁴ central nervous system function,⁴⁶ and
239 cardiovascular and respiratory responses;⁴⁷ all of which could explain the physiological
240 responses observed in this meta-analysis.

241

242 During exercise, [BLa] is determined from the balance between lactate production and
243 clearance; with approximately 70 – 80% of the latter achieved via oxidation, and the
244 remainder by gluconeogenesis.⁴⁸ As such, the caffeine-induced increase in [BLa] determined
245 in this meta-analysis could be due to either an increase in lactate production (via glycolysis)
246 or an impairment of clearance. Although there is some evidence that adenosine signalling can
247 inhibit glycolysis via a corresponding reduction in insulin sensitivity,⁴⁹⁻⁵¹ there is no evidence
248 that caffeine antagonises this response. Indeed, despite an increase in [BLa], Graham et al.¹⁷
249 was unable to detect any effect of caffeine on lactate release from active muscle. Moreover,
250 in a subsequent meta-analysis, Graham et al.²⁸ found no effect of caffeine on post-exercise
251 (10 – 15 mins at 70-85% $\dot{V}O_{2max}$) muscle glycogen concentrations. Similar difficulties exist
252 when trying to explain the increase in [BLa] by a possible impairment of lactate clearance, in
253 that whilst there is evidence that adenosine signalling increases gluconeogenesis, caffeine
254 does not appear to impair this process; at least not when determined from the rate of post-
255 exercise [BLa] clearance.⁵² In short, at present, despite a clear effect of caffeine on [BLa]
256 during submaximal exercise, the mechanisms to explain that response remain unresolved.

257

258 As with [BLa], the effects of caffeine on [BGI] can be explained by a mismatch between
259 production and clearance. In the case of clearance, there is evidence that adenosine facilitates
260 intracellular glucose transport, via insulin-dependent and independent mechanisms.⁵³
261 Moreover, while there are likewise many contradictory reports,⁴⁴ there is also evidence that
262 caffeine antagonises that response.⁵⁴ In contrast, the idea that caffeine may increase [BGI] by
263 facilitating an increase in hepatic glucose release seems much less likely; indeed, there is
264 some evidence that adenosine may even increase hepatic glycogenolysis via A_1 receptor
265 signalling.⁴⁴ In short, a caffeine-facilitated impairment of glucose clearance provides the most
266 likely mechanism to explain the increase in [BGI] determined in this meta-analysis.

267

268 One finding from this meta-analysis that is particularly difficult to explain is the lack of any
269 effect of caffeine on RER. Goedecke et al.⁵⁵ reported a strong positive correlation ($r = 0.63$)
270 between RER and [BLa] during exercise at 70% $\dot{V}O_{2max}$. As such, it is surprising that despite
271 the fact that caffeine supplementation resulted in a significant increase in [BLa], there was no
272 corresponding increase in RER; in fact, the pattern of the response was towards a reduction in
273 RER. Nevertheless, caffeine did result in an increase in $\dot{V}_{E,}$ a response which could be
274 explained by the buffering response associated with the disruption of acid-base balance, as
275 indicated by the caffeine-induced increase in [BLa].⁵⁶ Then again, it is possible to explain the
276 increase in \dot{V}_E by a direct stimulatory effect of caffeine, particularly since caffeine is reported
277 to lower the sensitivity threshold of central chemoreceptors for CO_2 .⁵⁷ moreover, the fact that

278 adenosine has differential effects on \dot{V}_E depending on the type of adenosine receptor
279 affected,⁵⁸ suggests that the response is most likely due to the effect of caffeine on the A_1
280 receptor subtype.⁵⁸ Either way, given that at least part of the caffeine-induced increase in \dot{V}_E
281 is likely due to the drive to reduce CO_2 , it is difficult to explain how, in the absence of any
282 corresponding change in $\dot{V}O_2$, that response does not affect RER.

283

284 Although this meta-analysis revealed no effect of caffeine on heart rate, it is difficult to
285 reconcile that response with adenosine receptor antagonism, given that adenosine is reported
286 to increase heart rate,^{47,59} most likely by reducing parasympathetic and increasing cardiac
287 sympathetic nervous system tone.⁵⁹ However, exogenous adenosine infusions have been
288 shown to have differential effects on heart rate depending on the dose and the site of
289 infusion.⁴⁷ Moreover, while there is evidence of a small caffeine-induced reduction in resting
290 heart rate,^{31,52} that effect is reported to dissipate as exercise intensity increases,⁵² supporting
291 the findings of this meta-analysis. Nevertheless, and as previously reported,³⁰ caffeine did
292 lead to a reduction in RPE, a response which could be explained by the fact that adenosine
293 has been shown to increase pain, at least in animal models, and most likely via interaction with
294 A_{2B} receptors.⁶⁰ However, given that the RPE scale was developed to reflect also the heart
295 rate response to exercise,³⁹ the findings of this meta-analysis suggest that caffeine may
296 uncouple that relationship.

297

298 Although the effects of caffeine as an adenosine receptor antagonist can explain most of the
299 effects determined in this meta-analysis, there are instances where, depending on the receptor
300 subtype involved, adenosine can elicit contrasting effects to those highlighted above.
301 However, given the clear effects of caffeine on most of the physiological responses
302 examined, it seems unlikely that those effects are important, at least during the exercise
303 conditions examined in this meta-analysis. Finally, it is worth noting that despite the clear
304 effects of caffeine determined in this meta-analysis, there were many instances where studies
305 were unable to detect those effects, most likely due to issues associated with relatively small
306 sample sizes.

307

308 **Conclusion**

309 The results of this meta-analysis reveal clear effects of caffeine on [BLa], [BGI], \dot{V}_E , and
310 RPE during submaximal exercise, independent of any ergogenic response. While those
311 effects can be explained by the antagonistic effects of caffeine on adenosine receptors,
312 differential effects of adenosine on the various receptor subtypes make it difficult to identify
313 the precise mechanisms by which adenosine, and therefore caffeine, influences human
314 physiology. Nevertheless, it is envisaged that the results of this meta-analysis will help to
315 distinguish caffeine-induced physiological responses from those associated with
316 corresponding increases in submaximal endurance performance and, as such, help future
317 researchers to identify the most likely mechanisms by which caffeine exerts its ergogenic
318 effect.

319

320 **Practical Applications**

321 The positive effects of caffeine supplementation on endurance performance are well-
322 established; particularly when consumed in a dose of 3 – 6 mg·kg⁻¹ ingested 30 – 90 minutes
323 prior to exercise.¹ Those performance improvements are accompanied by various

324 physiological responses associated with the corresponding increase in exercise intensity,
325 making it difficult to distinguish performance- from caffeine-related effects. This meta-
326 analysis has revealed clear effects of caffeine on measures of [BLa], [BGI], \dot{V}_E , and RPE,
327 independent of any ergogenic effect, which, given its dietary prevalence, reinforces the
328 importance of caffeine restriction prior to any experimental intervention or physiological
329 profile. For researchers, the results of this meta-analysis reinforce the problems associated
330 with the use of small sample sizes, with several instances where individual investigations
331 failed to find significant effects despite clear evidence to the contrary.

For Peer Review

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477

478 **Figure Legends**

479 **Figure 1.** Forest plots of studies that have investigated the effects of caffeine
480 supplementation on heart rate (upper plot) and ratings of perceived exertion (lower plot)
481 during sustained (5 – 30 minutes) fixed-intensity (60 – 85% $\dot{V}O_{2\max}$) submaximal exercise.
482 Squares represent the raw mean difference, relative to placebo, with associated 95%
483 confidence limits. The size of each square reflects the weighting given to the response. The
484 diamond at the base of each plot represents the overall effect calculated from a random
485 effects model; the width of the diamond representing the 95% confidence interval.

486

487 **Figure 2.** Forest plots of studies that have investigated the effects of caffeine
488 supplementation on oxygen uptake (upper plot), respiratory exchange ratio (middle plot), and
489 minute ventilation (lower plot) during sustained (5 – 30 minutes) fixed-intensity (60 – 85%
490 $\dot{V}O_{2\max}$) submaximal exercise. Squares represent the raw mean difference, relative to placebo,
491 with associated 95% confidence limits. The size of each square reflects the weighting given
492 to the response. The diamond at the base of each plot represents the overall effect calculated
493 from a random effects model; the width of the diamond representing the 95% confidence
494 interval.

495

496 **Figure 3.** Forest plots of studies that have investigated the effects of caffeine
497 supplementation on blood lactate (upper plot) and blood glucose (lower plot) concentrations
498 during sustained (5 – 30 minutes) fixed-intensity (60 – 85% $\dot{V}O_{2\max}$) submaximal exercise.
499 Squares represent the raw mean difference, relative to placebo, with associated 95%
500 confidence limits. The size of each square reflects the weighting given to the response. The
501 diamond at the base of each plot represents the overall effect calculated from a random
502 effects model; the width of the diamond representing the 95% confidence interval.

Table 1. The effects of caffeine supplementation (3-6 mg·kg⁻¹), administered 30 – 90 minutes prior to a sustained (≥ 5 minutes) fixed-intensity bout of submaximal (60 – 85% $\dot{V}O_{2max}$) exercise, on selected physiological responses.

Author(s)	n	Exercise mode	Exercise duration and intensity	Training status	Gender	Dose (mg·kg ⁻¹)	Pre-test supplementation time (mins)	Supplementation method	Physiological responses*
Acker-Hewitt et al. ⁵	10	Cycling	20 mins @ 60% $\dot{V}O_{2max}$	Cyclists	M	6	60	Capsule	↑ RER; no Δ in [BGI], [BLa], HR, RPE, \dot{V}_E , or $\dot{V}O_2$
Anderson et al. ⁶	8	Rowing	6 mins @ ~74% $\dot{V}O_{2max}$	Rowers	F	6	60	Capsule	no Δ in [BLa], HR, RER, RPE, \dot{V}_E , or $\dot{V}O_2$
Bell & McLellan ¹⁴	13	Cycling	80% $\dot{V}O_{2max}$ to exh	Active	M&F	5	60	Capsule	↑ [BGI] ^{††} , [BLa] ^{††} , HR, & $\dot{V}O_2$; ↓ RPE; no Δ in RER
Bell & McLellan ¹⁴	8 [†]	Cycling	80% $\dot{V}O_{2max}$ to exh	Active	M&F	5	60	Capsule	↑ [BGI], [BLa], HR, & $\dot{V}O_2$; ↓ RPE; no Δ in RER
Bell et al. ⁷	8	Cycling	85% $\dot{V}O_{2max}$ to exh	Healthy	M	5	90	Capsule	↑ [BLa], no Δ in [BGI], HR, RPE, \dot{V}_E , or $\dot{V}O_2$
Black et al. ¹⁵	14	Cycling	30 mins @ 60% $\dot{V}O_{2max}$	Active	M&F	5	60	Capsule	↑ [BLa]; no Δ in HR, RPE, RER, or $\dot{V}O_2$
Black et al. ¹⁵	14	Arm cranking	30 mins @ 60% $\dot{V}O_{2max}$	Active	M&F	5	60	Capsule	↑ [BLa]; no Δ in HR, RPE, RER, or $\dot{V}O_2$
Bruce et al. ⁸	8	Rowing	6 mins @ 75% $\dot{V}O_{2max}$	Rowers	M	6	60	Capsule	no Δ in HR, RER, RPE, \dot{V}_E , or $\dot{V}O_2$
Casal & Leon ⁹	9	Running	45 mins @ 75% $\dot{V}O_{2max}$	Runners	M	~6 (400 mg)	60	Drink [‡]	no Δ in HR, RER, RPE, \dot{V}_E , or $\dot{V}O_2$
Costill et al. ²⁴	9	Cycling	80% $\dot{V}O_{2max}$ to exh	Cyclists	M&F	~5 (330 mg)	60	Drink [‡]	↓ RER & RPE; no Δ in [BGI], [BLa], HR, or $\dot{V}O_2$
Cruz et al. ¹²	8	Cycling	~73% $\dot{V}O_{2max}$ to exh	Active	M	6	60	Capsule	↑ [BGI], [BLa], \dot{V}_E ; ↓ RER; no Δ in HR, or $\dot{V}O_2$
Daniels et al. ⁶¹	10	Cycling	55 mins @ 65% $\dot{V}O_{2max}$	Cyclists	M&F	6	45	Capsule	no Δ in HR
Demura et al. ¹⁶	10	Cycling	60 mins @ 60% $\dot{V}O_{2max}$	Healthy	M	6	60	Drink [‡]	↓ RPE; no Δ in [BLa], HR, RER, or $\dot{V}O_2$
Doherty et al. ³⁸	11	Cycling	6 mins @ 70% $\dot{V}O_{2max}$	Cyclists	M	5	60	Drink ^{**}	no Δ in HR or RPE
Giles & Maclaren ²⁵	6	Running	120 mins @ 65% $\dot{V}O_{2max}$	Runners	M	5	60	Drink [‡]	↑ $\dot{V}O_2$; ↓ RER & RPE; no Δ in [BGI], or [BLa]
Graham & Spriet ¹⁸	8	Running	85% $\dot{V}O_{2max}$ to exh	Runners	M	6	60	Capsule	↑ [BGI]; no Δ in [BLa], RER, or $\dot{V}O_2$
Graham et al. ⁶²	9	Running	85% $\dot{V}O_{2max}$ to exh	Runners	M&F	4.45	60	Capsule	no Δ in [BGI] or [BLa]
Graham et al. ⁶²	9	Running	85% $\dot{V}O_{2max}$ to exh	Runners	M&F	4.45	60	Drink [‡]	no Δ in [BGI] or [BLa]
Graham et al. ¹⁷	10	Cycling	60 mins @ 70% $\dot{V}O_{2max}$	Healthy	M	6	60	Capsule	↑ [BGI] & [BLa]; no Δ in HR, RER, or $\dot{V}O_2$
Greer et al. ¹⁹	7	Cycling	45 mins @ 70% $\dot{V}O_{2max}$	Active	M	6	90	Capsule	no Δ in [BGI], [BLa], RER, or $\dot{V}O_2$
Jenkins et al. ¹³	13	Cycling	15 mins @ 80% $\dot{V}O_{2max}$	Cyclists	M	3	60	Capsule	↑ [BLa] & \dot{V}_E ; no Δ in HR, RER, or $\dot{V}O_2$
McClaran & Wetter ¹⁰	9	Cycling	5 mins @ ~63% $\dot{V}O_{2max}$	Active	M	3	30	Capsule	↓ HR & RER; no Δ in RPE, \dot{V}_E , or $\dot{V}O_2$
Olcina et al. ²⁰	20	Cycling	30 mins @ 75% $\dot{V}O_{2max}$	Untrained	M	5	60	Capsule	no Δ in [BLa], RER, or $\dot{V}O_2$
Roy et al. ²¹	12	Cycling	60 mins @ 65% $\dot{V}O_{2max}$	Trained	M&F	6	75	Capsule	↑ [BLa]; no Δ in [BGI], HR, RER, or $\dot{V}O_2$
Stadheim et al. ²⁶	10	X-C skiing	5 mins @ 70% $\dot{V}O_{2max}$	X-C skiers	M	6	~60	Drink ^{**}	↑ [BGI]; ↓ RER & RPE; no Δ in [BLa], HR, or $\dot{V}O_2$
Stadheim et al. ³⁶	8	X-C skiing	5 mins @ 65% $\dot{V}O_{2max}$	X-C skiers	M	4.5	~60	Drink ^{**}	↑ [BLa]; ↓ RPE; no Δ in HR, or $\dot{V}O_2$
Tarnopolsky et al. ¹¹	6	Running	90 mins @ 70% $\dot{V}O_{2max}$	Runners	M	6	60	Drink ^{**}	no Δ in [BGI], [BLa], HR, RER, RPE, \dot{V}_E , or $\dot{V}O_2$
Toner et al. ²²	8	Cycling	5 mins @ 73.2% $\dot{V}O_{2max}$	Mixed	M	~4.6 (350 mg)	60	Drink [‡]	no Δ in HR, RER, or $\dot{V}O_2$
Van Soeren & Graham ²³	6	Cycling	85% $\dot{V}O_{2max}$ to exh	Active	M	6	60	Capsule	no Δ in [BGI], [BLa], RER, or $\dot{V}O_2$

Note: [BGI] = blood glucose concentration; [BLa] = blood lactate concentration; HR = heart rate; RER = respiratory exchange ratio; RPE = rating of perceived exertion; \dot{V}_E = minute ventilation; $\dot{V}O_2$ = rate of oxygen consumption; $\dot{V}O_{2max}$ = maximal rate of oxygen consumption; exh = exhaustion; X-C = cross country; M = male; F = female; ↑ = significant ($p < 0.05$) increase relative to placebo; ↓ = significant ($p < 0.05$) decrease relative to placebo; no Δ = no significant ($p \geq 0.05$) change relative to placebo; * = all measurements made within the first 30 minutes of exercise; † = caffeine naive; ‡ = dose added to decaffeinated coffee; ** = dose added to artificially sweetened water/lemonade/juice; †† = based on a sample size of 11;

Table 2. Summary of subgroup meta-analyses examining the possible influence of exercise intensity (low intensity: 60 – 72.5% $\dot{V}O_{2\max}$ vs high intensity: 72.5 – 85% $\dot{V}O_{2\max}$) and supplementation method (capsule vs drink formats) on the effect of caffeine supplementation on various physiological responses during fixed-intensity (60 – 85% $\dot{V}O_{2\max}$) submaximal exercise.

Responses	No of studies	Sample size	Mean difference	<i>p</i>	Heterogeneity <i>I</i> ² (%)	Subgroup differences <i>I</i> ² (%)	<i>p</i>
Heart rate (b.min ⁻¹)							
<i>Low intensity</i>	13	132	-0.57 [-2.81, +1.68]	0.62	47 [0, 72]	0	0.33
<i>High intensity</i>	8	75	+0.83 [-0.88, +2.54]	0.34	0 [0, 68]	0	
<i>Capsule</i>	14	145	-0.02 [-2.08, +2.03]	0.98	45 [0, 71]	0	0.79
<i>Drink</i>	7	62	-0.40 [-2.38, +1.58]	0.69	0 [0, 71]	0	
Respiratory exchange ratio							
<i>Low intensity</i>	11	109	-0.00 [-0.02, +0.01]	0.58	67 [38, 83]	0	0.92
<i>High intensity</i>	7	72	-0.01 [-0.02, 0.00]	0.32	64 [18, 84]	0	
<i>Capsule</i>	12	132	-0.00 [-0.01, +0.01]	0.42	50 [3, 74]	0	0.57
<i>Drink</i>	6	49	-0.01 [-0.03, +0.01]	0.27	84 [67, 92]	0	
Ratings of perceived exertion							
<i>Low intensity</i>	9	92	-0.8 [-1.0, -0.6]	< 0.00001	0 [0, 65]	0	0.78
<i>High intensity</i>	6	55	-0.9 [-1.6, -0.2]	0.02	64 [13, 85]	0	
<i>Capsule</i>	8	84	-0.8 [-1.1, -0.4]	0.0001	0 [0, 68]	0	0.65
<i>Drink</i>	7	63	-0.9 [-1.2, -0.5]	< 0.00001	59 [5, 82]	0	
Blood lactate (mmol·L ⁻¹)							
<i>Low intensity</i>	12	116	+0.64 [+0.40, +0.88]	< 0.00001	64 [33, 81]	0	0.70
<i>High intensity</i>	9	92	+0.76 [+0.22, +1.30]	0.006	83 [69, 91]	0	
<i>Capsule</i>	15	159	+0.87 [+0.62, +1.12]	< 0.00001	55 [19, 75]	80	0.02
<i>Drink</i>	6	49	+0.33 [-0.07, +0.73]	0.11	82 [62, 92]	0	
Blood glucose (mmol·L ⁻¹)							
<i>Low intensity</i>	7	62	+0.32 [+0.15, +0.49]	0.0002	72 [39, 87]	49	0.16
<i>High intensity</i>	8	67	+0.51 [+0.31, +0.71]	< 0.00001	68 [33, 85]	0	
<i>Capsule</i>	11	98	+0.42 [+0.25, +0.59]	< 0.00001	78 [61, 88]	0	0.90
<i>Drink</i>	4	31	+0.40 [+0.20, +0.60]	0.0001	41 [0, 80]	0	

Note: Values in square parentheses represent 95% confidence limits





