



Article

Are low doses of caffeine as ergogenic as higher doses? A critical review highlighting the need for comparison with current best practice in caffeine research

Pickering, Craig and Kiely, John

Available at http://clok.uclan.ac.uk/29558/

Pickering, Craig and Kiely, John ORCID: 0000-0001-9817-0224 (2019) Are low doses of caffeine as ergogenic as higher doses? A critical review highlighting the need for comparison with current best practice in caffeine research. Nutrition, 67-68 . p. 110535. ISSN 0899-9007

It is advisable to refer to the publisher's version if you intend to cite from the work. $\tab{http://dx.doi.org/10.1016/j.nut.2019.06.016}$

For more information about UCLan's research in this area go to http://www.uclan.ac.uk/researchgroups/ and search for <name of research Group>.

For information about Research generally at UCLan please go to http://www.uclan.ac.uk/research/

All outputs in CLoK are protected by Intellectual Property Rights law, including Copyright law. Copyright, IPR and Moral Rights for the works on this site are retained by the individual authors and/or other copyright owners. Terms and conditions for use of this material are defined in the <u>http://clok.uclan.ac.uk/policies/</u>



| 1 | |
|----|--|
| 2 | Title: Are low doses of caffeine as ergogenic as higher doses? A critical review highlighting the need for |
| 3 | comparison to current best practice in caffeine research. |
| 4 | |
| 5 | Short Title: Low versus high caffeine doses |
| 6 | |
| 7 | Authors: Craig Pickering ¹ , John Kiely ¹ |
| 8 | |
| 9 | 1. Institute of Coaching and Performance, University of Central Lancashire, Preston, UK |
| 10 | |
| 11 | Corresponding Author: |
| 12 | Craig Pickering |
| 13 | Institute of Coaching and Performance, University of Central Lancashire, Fylde Road, Preston, PR1 2HE, UK. |
| 14 | Email: craigpickering1014@hotmail.com |
| 15 | Word Count: 4099 |
| 16 | Number of Tables: 1 |
| 17 | Disclosure of potential conflicts of interest |
| 18 | CP is a former employee of DNAFit LifeSciences, a genetic testing company. He received no financial |
| 19 | incentives for the preparation of this manuscript. JK declares that he has no conflict of interest relevant to the |
| 20 | content of this article. |
| 21 | |
| 22 | |
| 23 | |
| 24 | |
| 25 | |
| 26 | |
| 27 | |
| 28 | |

Are low doses of caffeine as ergogenic as higher doses? A critical review highlighting the need for

comparison to current best practice in caffeine research.

| 0 | |
|----|---|
| ~~ | |
| J | т |
| | |

Abstract

Caffeine is a popular and widely utilised sporting ergogenic aid. Over the years, the effects of different caffeine doses have been researched, with the general consensus being that 3-6 mg/kg of caffeine represents the optimal caffeine dose for most people. Recently there has been increased attention placed on lower ($\leq 3 \text{ mg/kg}$) caffeine doses, with some research suggesting these doses are also ergogenic. However, a critical consideration for athletes is not merely whether caffeine is ergogenic at a given dose, but whether the consumed dose provides an optimised performance benefit. Following this logic, we identify a potential oversight in the current research relating to the efficacy of lower caffeine doses. Although low caffeine doses do appear to bestow ergogenic effects, these effects have not been adequately compared to the currently accepted best practice dose of 3-6 mg/kg. This methodological oversight limits the practical conclusions we can extract from the research into the efficacy of lower doses of caffeine, as the relative ergogenic benefits between low and recommended doses remains unclear. Here, we examine existing research with a critical eye, and provide recommendations both for those looking to utilise caffeine to enhance their performance, and those conducting research into caffeine and sport. Key Words: Caffeine, ergogenic, low-dose, supplement, sports drink

| 50 |) |
|----|---|
|----|---|

1. Introduction

62

61

63 Of all sporting ergogenic aids, caffeine (1,3,7-trimethylxanthine) is the most popular, with 64 approximately 75% of athletes consuming it either before or during competition [1,2]. Indeed, caffeine has such 65 a reliable performance enhancing effect that, for over twenty years (1984-2004), high doses were banned for 66 within-competition use by the World Anti-Doping Agency (WADA), and caffeine remains on their active 67 monitoring programme to this day. The ergogenic effects of caffeine ingestion have been demonstrated across a 68 wide range of sports, including endurance [3] and team sports [4], and across different exercise methods and 69 modalities, including repeated high-intensity efforts [5], muscular endurance [6], maximum strength [7] and 70 anaerobic performance [8]. 71 72 Whilst the ergogenic effects of caffeine have been known for over 100 years [9], the broad array of 73 potential mechanisms by which caffeine exerts its performance enhancing effects have only more recently been 74 more fully elucidated. The most well-established mechanism is that of caffeine's role as a competitive adenosine 75 receptor antagonist [10], dampening adenosine's downregulation of Central Nervous System arousal [11]. In 76 turn, this promotes the release of a spectrum of neuro-chemicals, including dopamine and the excitatory 77 neurotransmitter glutamate [12], thereby increasing muscle firing rates [13]. Caffeine also stimulates adrenaline 78 secretion [14], alters substrate utilization and metabolism [15], and increases cellular ion release [16]. More 79 recently, the relationship between caffeine, pain, and exercise performance has been explored, with current 80 evidence suggesting that caffeine decreases pain perception, which in turn reduces rating of perceived exertion 81 (RPE) [17] and enhances exercise capacity [18]. Latterly, it has been proposed that caffeine's bitter taste may 82 drive some of its performance enhancing benefits [19], in a similar fashion to the documented effects of the 83 bitter tasting compound quinine [20]; such observations may explain the ergogenic effects of caffeine-infused

84 85

mouth-rinses [21].

Given that caffeine's effects have been extensively researched, and consistently, reliably and
repeatedly demonstrated to improve—and only very rarely shown to harm [22]—exercise performance, it's use
is pervasive amongst both professional and amateur athletes alike [1,2]. This extensive use has resulted in the

89 formulation of best practice guidelines by numerous professional bodies. The International Society of Sports 90 Nutrition's position stand on caffeine [23], for example, summarizes that caffeine is effective at enhancing 91 performance at dosages considered to be moderate (~3-6 mg/kg), consumed approximately 60 minutes prior to 92 performance, with no additional ergogenic effects seen with higher caffeine doses (>9 mg/kg). Such 93 recommendations have been echoed elsewhere, both in the scientific literature [14,16] and lay press. 94 Interestingly, however, a number of studies have recently shown that lower doses of caffeine, typically of ≤ 3 95 mg/kg, are also ergogenic [24]. In this article, we examine the evidence underpinning this finding, and explore 96 whether low doses ($\leq 3 \text{ mg/kg}$) of caffeine pre-exercise offer comparable ergogenic benefits to the more 97 conventionally recommended intakes (3-6 mg/kg); such an examination is crucial, as athletes are likely 98 interested in whether their caffeine dose offers the maximal ergogenic benefits, as opposed to just an ergogenic 99 effect. Finally, we note some methodological recommendations that researchers may wish to consider when 100 conducting low dose caffeine research in the future. 101 102 2. Are low doses of caffeine ergogenic? 103 104 Whilst, historically, high doses (up to 13 mg/kg) of caffeine have been used to induce ergogenic effects 105 [25], more recently there has been an increasing focus on the use of more moderate (~3-6 mg/kg) caffeine doses 106 [26]. The success of these trials in turn has prompted research investigating the efficacy of lower doses of 107 caffeine ($\leq 3 \text{ mg/kg}$). Whilst the number of these trials is relatively low, a recent review by Spriet [24] concluded 108 that these lower caffeine doses, when consumed prior to exercise, likely enhanced athletic performance. 109 Similarly, a recent meta-analysis of the ergogenic effects of caffeine-containing energy drinks, the majority of 110 which had a dose of $\leq 3 \text{ mg/kg}$, concluded that ingestion of these drinks improved performance [27]. 111 Accordingly, in general, the evidence to date supports the perspective that lower doses of caffeine are ergogenic 112 for sports performance, particularly with regards to endurance sport. However, perhaps a more pertinent 113 consideration for athletes is whether these low doses of caffeine are as effective in enhancing performance as 114 the more conventional, higher doses? As athletes consume caffeine primarily to improve performance, and 115 presumably wish to improve their performance to the maximum amount possible, this is an important 116 consideration. If low doses of caffeine are ergogenic, but not as ergogenic as higher doses, then athletes 117 consuming these lower doses may be leaving some potential performance improvements on the table. As such,

118 the question as to whether or not low ($\leq 3 \text{ mg/kg}$) doses of caffeine exert similar ergogenic effects as more 119 conventional, moderate (3-6 mg/kg) doses seems highly relevant.

120

121 There are two ways by which we could determine whether low doses of caffeine are as ergogenic as 122 higher doses. Firstly, we could compare the magnitude of improvements seen between studies; for example, 123 determining whether the size of the ergogenic effect is greater in those studies that utilise 6 mg/kg compared to 124 2 mg/kg. This superficially simple approach, however, is surprisingly problematic, because the magnitude of 125 caffeine-derived performance enhancement is highly variable between both trials and subjects [28]. As 126 illustration, consider the array of variables which interact to modulate caffeine ergogenesis; genotype 127 [22,29,30], training status [31], habitual caffeine use [32], sex [33], caffeine source [34], age [35], expectancy 128 [36], exercise type [37], and time of day of exercise [38]. Given the extensive differences between study 129 methodologies and recruited populations, it seems unlikely that such a comparison would provide the desired, 130 and necessary, conceptual clarity.

131

132 Instead, a better option might be to have low-dose and high-dose caffeine trials within each study, 133 thereby allowing for a direct comparison between the different caffeine doses. Although seemingly sensible, 134 such an approach is surprisingly uncommon. In a recent review, Spriet [24] concluded that low caffeine doses 135 $(\leq 3 \text{ mg/kg})$, taken before exercise, enhanced athletic performance compared to placebo. However, the vast 136 majority of the studies included in Spriet's [24] review (summarized in table 1) did not directly compare a low 137 dose (\leq 3 mg/kg) of caffeine with a higher dose (>3 mg/kg). In fact, only 4 of the 14 studies did so [39-42]. Of 138 these four, there were mixed results; two reported no additional benefits from 6 mg/kg of caffeine compared to 139 3mg/kg of caffeine when examining aerobic endurance performance [39,41]; one reported that 4.5 mg/kg 140 enhanced aerobic endurance performance to a greater extent than 3.2 mg/kg, which in turn was more ergogenic 141 than a dose of 2.1 mg/kg [40]; and one found that 5 mg/kg enhanced maximum knee flexion and extension 142 isokinetic torque, whilst 2 mg/kg did not [42]. The remaining studies either did not use a caffeine dose above 3 143 mg/kg in their comparison [43-45], or only used a single caffeine dose (≤ 3 mg/kg), and compared this to 144 placebo [46-52]. We identified additional papers published following Spriet's [24] review that directly 145 examined a low versus high dose of caffeine [22,53-56]. Of these, Arazi and colleagues [53] reported no 146 difference in performance between a low (2 mg/kg) and high (5 mg/kg) caffeine dose—a finding replicated by 147 Guest and colleagues [22] with doses of 2 and 4 mg/kg on a 10kg cycle ergometer time trial—whilst others [53148 55] reported mixed results, in part because of the large number of performance tests utilised. Interestingly, Sabol 149 and colleagues [56] reported similar improvements in vertical jump performance following ingestion of 2, 4, 150 and 6 mg/kg of caffeine, whilst upper body ballistic exercise performance was only enhanced following a dose 151 of 6 mg/kg. Consequently, due to both the equivocal results of the small numbers of trials directly investigating 152 this phenomenon, and the lack of higher caffeine doses utilised in other trials, it is unclear whether lower doses 153 of caffeine are as ergogenic as higher doses. Recently, Talanian & Spriet [57] suggested that, based on their 154 interpretations of five lower-dose caffeine studies [26,40,43,44,57] that the timing of the lower caffeine dose 155 may be a crucial aspect, with ingestion less than 60 minutes pre-exercise associated with a greater performance 156 benefit than later ingestion (80-180 minutes pre-exercise).

- 157
- 158

| Study | Subjects | Caffeine | Exercise | Caffeine | Comparison | Finding |
|-------------|----------------|-------------|------------|------------|------------|---------------------|
| | | Timing | | Dose | to best | |
| | | | | | practice? | |
| | | | | | | |
| Graham | 8 well-trained | 60 minutes | TTE run at | 0 | Yes | Endurance was |
| and | males | pre- | 85% | (placebo), | | equally enhanced |
| Spriet | | exercise | VO2max | 3, 6, & 9 | | in both 3 and 6 |
| [39] | | | | mg/kg | | mg/kg caffeine |
| | | | | | | trials |
| Kovacs | 15 well- | 60% of | 1-hour | 0 | Yes | Performance was |
| et al. [40] | trained males | solution 60 | maximum | (Placebo), | | enhanced to the |
| | | minutes | cycle | 2.1, 3.2, | | greatest extent in |
| | | pre- | | 4.5 mg/kg | | 4.5 mg/kg, then 3.2 |
| | | exercise, | | | | mg/kg, then 2.1 |
| | | and 20% at | | | | mg/kg. |
| | | two time | | | | |
| | | points | | | | |
| | | within | | | | |

| | | exercise | | | | |
|-------------|-----------------|------------|--------------|------------|-----|---------------------|
| | | trial. | | | | |
| Jenkins | 13 trained | 60 minutes | 15 minutes | 0 | No | Compared to |
| et al. [44] | male cyclists | pre- | VO2 peak | (placebo), | | placebo, only 2 |
| | , j | exercise | performance | 1, 2, 3 | | mg/kg significantly |
| | | | cycle | mg/kg | | enhanced |
| | | | cycle | ing ng | | performance |
| | | | | | | _ |
| Desbrow | 9 trained male | 60 minutes | 120 min | 0 | No | No performance |
| et al. [43] | cyclists | pre- | steady state | (placebo), | | enhancement with |
| | | exercise | cycle, | 1.5, 3 | | caffeine |
| | | | followed by | mg/kg | | |
| | | | TT. | | | |
| Irwin et | 12 trained | 90 minutes | Cycle TT | 0 | No | Caffeine enhances |
| al. [50] | male cyclists | pre- | | (placebo) | | performance |
| | | exercise | | or 3 | | compared to |
| | | | | mg/kg | | placebo |
| Desbrow | 16 trained | 90 minutes | 60 min cycle | 0 | Yes | No additional |
| et al. [41] | cyclists | pre- | at 75% peak | (placebo), | | benefit of 6 mg/kg |
| | | exercise | sustainable | 3, 6 | | compared to 3 |
| | | | power | mg/kg | | mg/kg |
| Wiles et | 34 male | 60 minutes | 1500m run | ~150-200 | No | Caffeine enhanced |
| al. [46] | athletes | pre- | | mg from | | performance. |
| | | exercise | | coffee (3g | | |
| | | | | total | | |
| | | | | coffee) | | |
| Van | 98 well trained | At start, | 18km run | 90 mg | No | No effect of |
| Nieuwen | male and | 4.5, 9 and | | | | caffeine |
| hoven et | females | 13.5 km of | | | | |
| al. [47] | | exercise | | | | |
| | | trial | | | | |
| | | | | | | |

| Bridge & | 8 male runners | 60 minutes | 8km race | 0 | No | Caffeine enhanced |
|-------------|-----------------|------------|----------------|------------|-----|--------------------|
| Jones | | pre- | | (Placebo), | | performance. |
| [48] | | exercise | | 3 mg/kg, | | |
| | | | | or no | | |
| | | | | suppleme | | |
| | | | | nt. | | |
| Schubert | 6 male runners | 65 minutes | 5km run TT | 0 | No | No differences in |
| et al. [45] | | pre- | | (placebo), | | caffeine |
| | | exercise | | 80 mg, | | consumption trials |
| | | | | 140 mg) | | when compared to |
| | | | | | | placebo. |
| Perez- | 13 elite female | 60 minutes | Volleyball | 0 | No | Caffeine enhanced |
| Lopez et | volleyball | pre- | specific tests | (placebo) | | performance. |
| al. [52] | players | exercise | | and 3 | | |
| | | | | mg/kg | | |
| Del Coso | 15 male | 60 minutes | Volleyball | 0 | No | Caffeine enhanced |
| et al. [51] | volleyball | pre- | specific tests | (placebo) | | performance. |
| | players | exercise | | and 3 | | |
| | | | | mg/kg | | |
| Strecker | 10 male tennis | 90 minutes | Tennis skill | 0 | No | Caffeine enhanced |
| et al. [49] | players | pre- | performance | (placebo) | | performance. |
| | | exercise | | and 3 | | |
| | | | | mg/kg | | |
| Astorino | 15 active | 60 minutes | 40 maximal | 0 | Yes | Only the 5mg/kg |
| et al. [42] | males | pre- | knee | (placebo), | | dose enhanced |
| | | exercise | extensions | 2, 5 | | performance. |
| | | | | mg/kg | | |
| Talanian | 15 cyclists | 40 (~42% | Time to | 0 | No | Higher caffeine |
| & Spriet | (n=4 female) | total), 20 | completion | (placebo), | | dose enhanced |
| [57] | | (~33% | cycle | | | time-trial |

| | | total) and 0 | ergometer | ~1.5, ~2.9 | | performance to a |
|-----------|--------------|--------------|--------------|------------|-----|----------------------|
| | | (~25%) | test | mg/kg | | greater extent than |
| | | minutes | | | | lower dose. |
| | | pre-time | | | | |
| | | trial | | | | |
| Tallis & | 10 active | 60 minutes | Isokinetic | 0 | Yes | No effect of |
| Yavuz | males | pre- | concentric | (placebo), | | caffeine on elbow |
| [55] | | exercise | and | 3 and 6 | | flexor (concentric |
| | | | eccentric | mg/kg | | and eccentric) or |
| | | | strength at | | | knee (eccentric) |
| | | | 60 & 180 | | | flexor strength. |
| | | | deg/s of | | | Both caffeine |
| | | | elbow and | | | doses increased |
| | | | knee flexors | | | concentric force in |
| | | | | | | knee extensors at |
| | | | | | | 180 deg/s, with no |
| | | | | | | difference between |
| | | | | | | doses. Only the |
| | | | | | | higher (6 mg/kg) |
| | | | | | | dose enhanced |
| | | | | | | force during |
| | | | | | | repeated |
| | | | | | | contractions. |
| Turley et | 26 young (8- | 60 minutes | Hand grip | 0, | Yes | Grip strength – |
| al. [54] | 10y) boys | pre- | and Wingate | (placebo), | | significantly higher |
| | | exercise | tests | 1, 3 and 5 | | in 3 and 5 mg/kg |
| | | | | mg/kg | | caffeine trials. |
| | | | | | | Wingate – 3 mg/kg |
| | | | | | | produced greatest |
| | | | | | | peak power, whilst |

| | | | | | | 5 mg/kg produced |
|----------|-----------------|------------|----------------|-------------|-----|--------------------|
| | | | | | | greatest mean |
| | | | | | | power. |
| Arazi et | 10 female | 60 minutes | 1RM leg | 0 | Yes | No significant |
| al. [53] | karate athletes | pre- | press, leg | (placebo), | | difference in test |
| | | exercise | press | 2 and 5 | | performance |
| | | | repetitions to | mg/kg | | between groups. |
| | | | failure, | | | |
| | | | vertical | | | |
| | | | jump, RAST | | | |
| | | | test. | | | |
| Sabol et | 20 | 60 minutes | Medicine | 0 | Yes | No difference |
| al [56] | recreationally | pre- | ball throw | (placebo), | | between caffeine |
| | active males | exercise | and vertical | 2, 4, and 6 | | doses in terms of |
| | | | jump | mg/kg | | lower body |
| | | | | | | performance |
| | | | | | | enhancement. Only |
| | | | | | | 6 mg/kg enhanced |
| | | | | | | upper body |
| | | | | | | performance. |
| Guest et | 101 | ~45 | 10km cycle | 0 | Yes | No difference in |
| al [22] | competitive | minutes | ergometer | (placebo), | | performance |
| | males | pre- | time trial | 2 and 4 | | enhancement |
| | | exercise | | mg/kg | | between caffeine |
| | | | | | | doses; both |
| | | | | | | enhanced |
| | | | | | | performance |
| | | | | | | compared to |
| | | | | | | placebo. |

Table 1 – A summary of studies examining the impact of low doses of pre-exercise caffeine on sports
performance. For the purposes of this table, a low dose of caffeine is defined as 3mg/kg or less. (Adapted from
Spriet [24]; studies that did not utilise a pre-exercise caffeine dose, or those that only used a caffeine dose
greater than 3mg/kg, were excluded, and additional relevant papers published since that review have been
added). 1RM; one repetition maximum. RAST; running-based anaerobic sprint test.

166

167 **3.** A potential solution?

168

169 This is not to suggest that these methodological shortcomings are the fault of researchers. Commonly, 170 investigations are designed to explore phenomena tangentially bordering, but not directly targeting, this 171 experimental question. However, based on our interpretation of the research, it is clear that, to decisively answer 172 this question, additional trials that directly compare low caffeine doses with those falling into line with the 173 currently accepted optimal dose (3-6 mg/kg), are required. Such research would remove much of the existing 174 ambiguity permeating caffeine research. An equivalent approach is considered best-practice in the realm of 175 medical drug development, where randomised controlled trials are designed to directly compare new drugs with 176 the best currently available treatment as the optimal approach [58]. Accordingly, it is not sufficient to 177 demonstrate that a new intervention is more effective than placebo, but that it produces better results than the 178 currently accepted best treatment.

179

180 An illustrative example is that of research into caffeinated chewing gum, an increasing popular 181 ergogenic aid in sport [19]. Studies investigating the ergogenic effects of caffeinated gum on aerobic endurance 182 performance are currently equivocal. As per a recent review [19]. two studies [59,60] reported no ergogenic 183 effect of caffeinated gum on aerobic endurance performance, whilst three studies [61-63] reported a positive 184 effect. An obvious distinction between these trials is the dose; the "no effect" findings occurred following a dose 185 of 200 mg, whilst the positive effect trials employed a dose of 300 mg. If we assume an average subject mass of 186 ~80 kg, then 200 mg of caffeine would be classed as a low dose, and 300 mg would fall within the 187 recommended optimal threshold. Here, the inclusion of a trial utilising a currently accepted optimal caffeine 188 dose in the 200 mg studies would potentially resolve the current ambiguity.

189

190 Additionally, there is contemporary debate regarding the impact of regular caffeine consumption on the 191 subsequent ergogenic effects of caffeine, with some studies finding a negative impact of habituation [32], whilst 192 others report none [64]. One potential outcome is that regular caffeine use requires a subsequently larger 193 caffeine dose to exert performance benefits [65]. As such, the dose of caffeine used in experimental trials 194 substantially influences study conclusions, particularly when exploring the effects of habitual use. Recently, 195 Evans and colleagues [66] explored the influence of caffeinated gum, supplying 200 mg of caffeine, on repeated 196 sprint performance in team sport athletes. The initial finding was that caffeine did not confer any ergogenic 197 effects; however, further analysis demonstrated that habitual caffeine use modified the performance 198 enhancement seen following caffeine ingestion; in this case, very low habitual caffeine users (<40 mg/d) did 199 exhibit ergogenic effects, whilst more moderate habitual users (>130 mg/d) did not. Such findings may be 200 interpreted as evidence that habitual use reduced caffeine's ergogenic effects. However, an obvious question 201 emerges; what if the dose of caffeine used was within the currently accepted guidelines, as opposed to <3202 mg/kg? As this wasn't explored, the answer remains unclear. Again, this is not an attack on the authors, who 203 were exploring a different research question, but it nevertheless underscores the point that increasingly robust 204 conclusions could be inferred from caffeine research if the currently accepted optimal dose was included.

205

206

4. How robust is the currently accepted optimal dose?

207

208 For the purposes of this review, we have defined the currently accepted optimal dose of caffeine as 209 between 3 and 6 mg/kg. This figure is based on a number of different reviews and positions stands [14,23]. 210 Furthermore, it is not suggested that there are any additional ergogenic effects associated with a dose above this 211 [25]. However, there is considerable inter-individual variation in the ergogenic effects of caffeine ingestion [68]. 212 This phenomenon becomes apparent when caffeine studies report individual subject data. Jenkins et al. [44], for 213 example, examined the effects of lower caffeine doses (1, 2, and 3 mg/kg) compared to placebo on a 15-minute 214 maximum cycle. Of the 13 subjects, one did not exhibit an ergogenic effect at any dose, whilst four found 215 caffeine ergogenic at every dose, but to different extents. Graham and Spriet [39] demonstrated that 9 mg/kg of 216 caffeine improved time-to-exhaustion in seven subjects, but with the percentage improvements compared 217 against the placebo trial varying from 105-250%. Neither of these studies utilised the currently accepted optimal 218 caffeine dose, so whether the findings would have been replicated under those conditions remains unclear. 219 Nevertheless, the results serve to illustrate the extent of inter-individual responses to caffeine. Furthermore,

224

4.1 Genetic

225 Variation within CYP1A2, the gene encoding for cytochrome P450 1A2—the enzyme responsible for 226 95% of all caffeine metabolism [69]—has been shown to affect caffeine metabolization speed. Here, individuals 227 with a C allele metabolise caffeine slower than AA genotypes [70]. Potentially, this single nucleotide 228 polymorphism (SNP) might impact caffeine ergogenicity, with C allele carriers exhibiting lower [29] or no [22] 229 ergogenic effects. However, these findings are currently tentative, with other studies reporting the opposite [71], 230 or no effect [72] of this polymorphism on performance. The mechanism underpinning this reduced ergogenic 231 effect in C allele carriers is currently unclear. Guest and colleagues [22] suggest that, because caffeine is a 232 vasoconstrictor, slow metabolisers experience this vasoconstriction for a longer period of time, inhibiting the 233 delivery of oxygen and nutrients to the working muscle. Conversely, Womack and colleagues [29] suggest that 234 the downstream metabolites of caffeine (paraxanthine, theobromine, and theophylline) confer their own 235 ergogenic effect; in this case, the presence of these metabolites would be lower in C allele carriers than AA 236 genotypes at a given time point due to the slower metabolization of caffeine. As such, it's not clear whether 237 caffeine has a reduced ergogenic, or even an ergolytic, effect in C allele carriers, or whether they need to ingest 238 caffeine a greater amount of time before exercise [73]. Similarly, there is the potential that a SNP in ADORA2A, 239 which encodes for a sub-type of adenosine receptor, may underpin some of the individual variation in response 240 to caffeine, in terms of ergogenicity [30], anxiety [74], and sleep disturbances [75].

241

242 *4.2 Environmental*

Alongside these genetic drivers are environmental determinants of individual variation in the response to caffeine, which include age [35], training status [31], habitual caffeine use [32,65], diet [76], medication use [77], and personal belief as to whether caffeine enhances performance [36].

246

247 *4.3 Epigenetics*

Habitual caffeine use likely induces long-term epigenetic changes [78,79], which may in turn affect future ergogenic effects, potentially by increasing caffeine metabolization speed [80]. For example, habitual caffeine use increases CYP1A2 activity [81], thereby increasing caffeine clearance, which may alter the
expected ergogenic effects of caffeine ingestion. Additionally, long-term exposure to caffeine may alter its
stimulatory effects, partly mediated by inhibition of genes affecting the adenosine pathway [82].

253

254 Accordingly, whilst caffeine is ergogenic, the currently accepted optimal caffeine dose may not be 255 optimal for everyone [68]. Some individuals may benefit from lower doses of caffeine (discussed below), whilst 256 others may need higher doses. Nevertheless, at present the abundance of evidence does suggest that, for most 257 people, most of the time, a caffeine dose of between 3-6 mg/kg likely is sufficient to realise the optimum 258 ergogenic effects. Indeed, Burke [83] suggested that the dose-response relationship of caffeine on performance 259 appears to plateau at around 3 mg/kg. As such, this dose may represent a target threshold to maximise caffeine's 260 ergogenic effects, although higher doses are indeed ergogenic, and in some cases may be required, such as in 261 habitual users [65]. Sensibly, the recommendations of 3-6 mg/kg should be taken as a starting point, from which 262 individual experimentation can be used to refine pre-training and pre-competition caffeine strategies.

- 263
- 264

5. When might lower doses of caffeine be more appropriate?

265

266 The purpose of this article is not to discount the ergogenic potential of lower doses of caffeine; indeed, 267 available evidence suggests that these lower doses can enhance performance [24]. Furthermore, the use of lower 268 doses of caffeine may be preferential in certain situations. Higher doses of caffeine, for example, appear to be 269 more likely to induce negative side-effects, such as anxiety [84] and sleep disturbances [85]. From a sporting 270 perspective, both of these outcomes have the potential to negatively impact performance [86,87]. Furthermore, 271 sleep disturbances following caffeine ingestion may reduce recovery from exercise and/or competition, and 272 subsequently harm physical performance the following day [87]. In these cases, individual athletes need to make 273 informed, strategic decisions negotiating the trade-off between the optimised ergogenic effects seen with higher 274 doses of caffeine against the potential for increased anxiety or compromised sleep. Here, the context is critical; 275 arguably, the athlete would be more concerned with sleep disturbances if there is a high priority competitive 276 bout in the proceeding few days, such as during the heats at the Olympic Games, as opposed to an Olympic 277 Final, when no subsequent performance is required. Conversely, athletes predisposed to greater pre-competition 278 anxiety may wish to consume less caffeine prior to important competitions than they would for lower level 279 competitions and training, as caffeine may exacerbate this anxiety-promoting predisposition.

Similarly, differences in genotype may predispose individuals to respond well to lower doses of caffeine. Preliminary evidence suggests, for example, that moderate doses of caffeine (4 mg/kg) are harmful to endurance performance in *CYP1A2* genotypes [22]. However, a dose of 2 mg/kg showed no performance decrement, suggesting that lower doses for these individuals may be more favourable than higher doses. Whilst further clarification is required, the potential for genetically-guided caffeine recommendations to be made, with certain genotypes potentially responding better to lower caffeine doses, remains a future possibility [68,73].

287

288 Regular ingestion of lower doses of caffeine may also guard against habituation to higher doses, which 289 has been shown to negatively affect the ergogenic benefits of a caffeine dose [32,65], although this remains 290 equivocal [64]. There is the potential that regular ingestion of caffeine increases the amount of caffeine required 291 to realise the ergogenic effects, such that if an athlete habitually consumed 3 mg/kg of caffeine pre-training, 292 they might require a caffeine dose closer to 6 mg/kg pre-competition [65]. This may increase the potential for 293 adverse side effects, and, if the habitual dose increases over time, might take the athlete to a point in which 294 further increases in dose don't restore the optimised ergogenic effect of caffeine. In this scenario, habitual use of 295 lower caffeine doses (~3 mg/kg) may facilitate an increased pre-competition dose, thereby allowing for both 296 enhancement of regular training, along with competition performance.

297

6. Conclusions

299

300 In summary, the existing research is clear that low doses of caffeine are ergogenic [24]. However, to 301 derive more robust conclusions there is an evident need within these studies for a direct comparison with the 302 currently accepted optimal caffeine dose (>3 to 6 mg/kg). The majority of studies that support the ergogenic 303 benefits of low doses of caffeine do not compare these low doses to the caffeine doses more typically considered 304 to be ergogenic. As a result, whilst low doses of caffeine do offer a performance benefit, it's not clear that this 305 performance benefit is greater than, or indeed equal to, that offered by caffeine doses between 3 and 6 mg/kg. 306 The addition of a caffeine trial utilising 3-6 mg/kg of caffeine would therefore greatly aid in the interpretation of 307 such findings, and so should be considered in future research. 308

| 309 | We hope that the points raised here enable athletes, coaches, support staff, and perhaps even | | | | | | |
|-----|--|--|--|--|--|--|--|
| 310 | researchers to better critique the studies underpinning their caffeine strategies and recommendations. Moving | | | | | | |
| 311 | forward, we also recommend that caffeine researchers include a trial that utilizes the currently accepted optimal | | | | | | |
| 312 | dose of caffeine – even if this dose is not optimal for everyone – in order to enable more direct comparisons | | | | | | |
| 313 | between studies, and thereby enabling firmer conclusions to be made. Finally, as per our previous explorations | | | | | | |
| 314 | of caffeine use in sport [65,68], we urge athletes and practitioners to experiment with different caffeine doses, | | | | | | |
| 315 | timing, and ingestion methods in order to uncover the strategies best suiting their unique genetic predispositions, | | | | | | |
| 316 | environmental influences, and individual histories. | | | | | | |
| 317 | | | | | | | |
| 318 | Novelty Statement & Practical Applications | | | | | | |
| 319 | This critical review has demonstrated that, whilst lower doses ($\leq 3 \text{ mg/kg}$) of caffeine have the potential to be | | | | | | |
| 320 | ergogenic, it's not clear whether such doses are as ergogenic as higher doses. The main cause of this uncertainty | | | | | | |
| 321 | is due to a lack of trials directly comparing low and high doses of caffeine. As such, athletes, coaches and | | | | | | |
| 322 | practitioners looking to utilise caffeine as a means to enhance performance would be best placed to experiment | | | | | | |
| 323 | with various different caffeine doses in order to determine the optimal dose to enhance their performance, given | | | | | | |
| 324 | their own unique biology, history, and performance requirements. | | | | | | |
| 325 | | | | | | | |
| 326 | Compliance with Ethical Standards | | | | | | |
| 327 | Funding | | | | | | |
| 328 | No sources of funding were used to assist in the preparation of this article. | | | | | | |
| 329 | | | | | | | |
| 330 | References: | | | | | | |
| 331 | | | | | | | |
| 332 | 1. Desbrow B, Leveritt M. (2006). Awareness and use of caffeine by athletes competing at the 2005 | | | | | | |
| 333 | Ironman Triathlon World Championships. Int J Sport Nutr Exerc Metab 16(5):545-58. | | | | | | |
| 334 | 2. Del Coso J, Muñoz G, Muñoz-Guerra J. (2011). Prevalence of caffeine use in elite athletes following | | | | | | |
| 335 | its removal from the World Anti-Doping Agency list of banned substances. Appl Physiol Nutr Metab | | | | | | |
| 336 | 36(4):555-61 | | | | | | |
| 337 | 3. Keisler BD, Armsey TD. (2006). Caffeine as an ergogenic aid. Curr Sports Med Rep 5(4):215-9. | | | | | | |

| 338 | 4. | Foskett A, Ali A, Gant N. (2009). Caffeine enhances cognitive function and skill performance during |
|-----|-----|--|
| 339 | | simulated soccer activity. Int J Sport Nutr Exerc Metab 19(4):410-23. |
| 340 | 5. | Glaister M, Howatson G, Abraham CS, et al. (2008). Caffeine supplementation and multiple sprint |
| 341 | | running performance. Med Sci Sports Exerc 40(10):1835-40. |
| 342 | 6. | Da Silva VL, Messias FR, Zanchi NE, et al. (2015). Effects of acute caffeine ingestion on resistance |
| 343 | | training performance and perceptual responses during repeated sets to failure. J Sports Med Phys |
| 344 | | Fitness 55(5):383-9. |
| 345 | 7. | Grgic J, Mikulic P. (2017). Caffeine ingestion acutely enhances muscular strength and power but not |
| 346 | | muscular endurance in resistance-trained men. Eur J Sport Sci 17(8):1029-1036. |
| 347 | 8. | Grgic J. (2018). Caffeine ingestion enhances Wingate performance: a meta-analysis. Eur J Sport Sci |
| 348 | | 18(2):219-225. |
| 349 | 9. | Rivers WH, Webber HN. (1907). The action of caffeine on the capacity for muscular work. J Physiol |
| 350 | | 36(1):33 |
| 351 | 10. | Biaggioni IT, Paul SU, Puckett AN, et al. (1991). Caffeine and theophylline as adenosine receptor |
| 352 | | antagonists in humans. J Pharmacol Exp Ther 258(2):588-93. |
| 353 | 11. | Ribeiro JA, Sebastiao AM. (2010). Caffeine and adenosine. J Alzheimers Dis 20(S1):3-15. |
| 354 | 12. | Fredholm BB. (1995). Adenosine, adenosine receptors and the actions of caffeine. Pharmacol Toxicol |
| 355 | | 76(2):93-101. |
| 356 | 13. | Kalmar JM. (2005). The influence of caffeine on voluntary muscle activation. Med Sci Sports Exerc |
| 357 | | 37(12):2113-9. |
| 358 | 14. | Graham TE. (2001). Caffeine and exercise: Metabolism, endurance and performance. Sports Med |
| 359 | | 31(11):785-807. |
| 360 | 15. | Cruz RS, de Aguiar RA, Turnes T, et al. (2015). Caffeine affects time to exhaustion and substrate |
| 361 | | oxidation during cycling at maximal lactate steady state. Nutrients 7(7):5254-64. |
| 362 | 16. | Sökmen B, Armstrong LE, Kraemer WJ, et al. (2008). Caffeine use in sports: considerations for the |
| 363 | | athlete. J Strength Cond Res 22(3):978-86. |
| 364 | 17. | Doherty M, Smith PM, Hughes MG, et al. (2004). Caffeine lowers perceptual response and increases |
| 365 | | power output during high-intensity cycling. J Sports Sci 1;22(7):637-43. |
| 366 | 18. | Gonglach AR, Ade CJ, Bemben MG, et al. (2016). Muscle pain as a regulator of cycling intensity: |
| 367 | | effect of caffeine ingestion. Med Sci Sports Exerc 48(2):287-96 |

369 48(S1):79-91. 370 20. Gam S, Guelfi KJ, Fournier PA. (2016). New insights into enhancing maximal exercise performance 371 through the use of a bitter tastant. Sports Med 46(10):1385-90. 372 21. Beaven CM, Maulder P, Pooley A, et al. (2013). Effects of caffeine and carbohydrate mouth rinses on 373 repeated sprint performance. Appl Physiol Nutr Metab 38(6):633-7. 374 22. Guest N, Corey P, Vescovi J, et al. (2018). Caffeine, CYP1A2 genotype, and endurance performance in 375 athletes. Med Sci Sports Exerc 50(8):1570-8. 376 23. Goldstein ER, Ziegenfuss T, Kalman D, et al. (2010). International society of sports nutrition position 377 stand: caffeine and performance. J Int Soc Sports Nutr 7(1):5. 378 24. Spriet LL. (2014). Exercise and sport performance with low doses of caffeine. Sports Med 44(2):175-379 84. 380 25. Pasman WJ, Van Baak MA, Jeukendrup AE, et al. (1995). The effect of different dosages of caffeine 381 on endurance performance time. Int J Sports Med 16(4):225-30. 382 26. Cox GR, Desbrow B, Montgomery PG, et al. (2002). Effect of different protocols of caffeine intake on 383 metabolism and endurance performance. J Appl Physiol 93(3):990-9. 384 27. Souza DB, Del Coso J, Casonatto J, et al. (2017). Acute effects of caffeine-containing energy drinks on 385 physical performance: a systematic review and meta-analysis. Eur J Nutr 56(1):13-27. 386 28. Ganio MS, Klau JF, Casa DJ, et al. (2009). Effect of caffeine on sport-specific endurance performance: 387 a systematic review. J Strength Cond Res 23(1):315-24. 388 29. Womack CJ, Saunders MJ, Bechtel MK, et al. (2012). The influence of a CYP1A2 polymorphism on 389 the ergogenic effects of caffeine. J Int Soc Sports Nutr 9(1):7. 390 30. Loy BD, O'Connor PJ, Lindheimer JB, et al. (2015). Caffeine is ergogenic for adenosine A2A receptor 391 gene (ADORA2A) T allele homozygotes: a pilot study. J Caffeine Res 5(2):73-81. 392 31. Collomp K, Ahmaidi S, Chatard JC, et al. (1992). Benefits of caffeine ingestion on sprint performance 393 in trained and untrained swimmers. Eur J Appl Physiol Occup Physiol 64(4):377-80. 394 32. Beaumont R, Cordery P, Funnell M, et al. (2017). Chronic ingestion of a low dose of caffeine induces 395 tolerance to the performance benefits of caffeine. J Sports Sci 35(19):1920-1927. 396 33. Sabblah S, Dixon D, Bottoms L. (2015). Sex differences on the acute effects of caffeine on maximal 397 strength and muscular endurance. Comparative Exercise Physiology 11(2):89-94.

19. Wickham KA, Spriet LL. (2018). Administration of Caffeine in Alternate Forms. Sports Med

368

- 34. Hodgson AB, Randell RK, Jeukendrup AE. (2013). The metabolic and performance effects of caffeine
 compared to coffee during endurance exercise. PLoS One 8(4):e59561.
- 400 35. Tallis J, James RS, Cox VM, et al. (2017). Is the ergogenicity of caffeine affected by increasing age?
 401 The direct effect of a physiological concentration of caffeine on the power output of maximally
 402 stimulated edl and diaphragm muscle isolated from the mouse. J Nutr Health Aging 21(4):1-9
- 403 36. Saunders B, Oliveira LF, Silva RP, et al. (2017). Placebo in sports nutrition: a proof- of- principle
- 404 study involving caffeine supplementation. Scand J Med Sci Sports 27(11):1240-1247 doi:
 405 10.1111/sms.12793.
- 406 37. Davis JK, Green JM. (2009). Caffeine and anaerobic performance. Sports Med 39(10):813-32.
- 407 38. Mora-Rodríguez R, Pallarés JG, López-Gullón JM, et al. (2015). Improvements on neuromuscular
 408 performance with caffeine ingestion depend on the time-of-day. J Sci Med Sport 18(3):338-42.
- 409 39. Graham TE, Spriet LL. (1995). Metabolic, catecholamine, and exercise performance responses to
 410 various doses of caffeine. J Appl Physiol 78(3):867-74
- 411 40. Kovacs EM, Stegen JH, Brouns F. (1998). Effect of caffeinated drinks on substrate metabolism,
 412 caffeine excretion, and performance. J Appl Physiol 85(2):709-15.
- 413 41. Desbrow B, Biddulph C, Devlin B, et al. (2012). The effects of different doses of caffeine on
 414 endurance cycling time trial performance. J Sports Sci 30(2):115-20.
- 415 42. Astorino TA, Terzi MN, Roberson DW, et al. (2010). Effect of two doses of caffeine on muscular
 416 function during isokinetic exercise. Med Sci Sports Exerc 42(12):2205-10.
- 417 43. Desbrow B, Barrett CM, Minahan CL, et al. (2009). Caffeine, cycling performance, and exogenous
 418 CHO oxidation: a dose-response study. Med Sci Sports Exerc 41(9):1744-51.
- 419 44. Jenkins NT, Trilk JL, Singhal A, et al. (2008). Ergogenic effects of low doses of caffeine on cycling
 420 performance. Int J Sport Nutr Exerc Metab 18(3):328-42.
- 421 45. Schubert MM, Astorino TA. (2013). The effects of caffeinated "energy shots" on time trial
 422 performance. Nutrients 5(6):2062-75.
- 423 46. Wiles JD, Bird SR, Hopkins J, et al. (1992). Effect of caffeinated coffee on running speed, respiratory
 424 factors, blood lactate and perceived exertion during 1500-m treadmill running. Br J Sports Med
 425 26(2):116-20.
- 426 47. Van Nieuwenhoven MA, Brouns FJ, Kovacs EM. (2005). The effect of two sports drinks and water on
 427 GI complaints and performance during an 18-km run. Int J Sports Med 26(04):281-5.

- 428 48. Bridge CA, Jones MA. (2006). The effect of caffeine ingestion on 8 km run performance in a field
 429 setting. J Sports Sci 24(4):433-9.
- 430 49. Strecker E, Foster B, Taylor K, et al. (2006). The effect of caffeine ingestion on tennis skill
 431 performance. Med Sci Sports Exerc 38(5):S175.
- 432 50. Irwin C, Desbrow B, Ellis A, et al. (2011). Caffeine withdrawal and high-intensity endurance cycling
 433 performance. J Sports Sci 29(5):509-15.
- 434 51. Del Coso J, Pérez-López A, Abian-Vicen J, et al. (2014). Enhancing physical performance in male
 435 volleyball players with a caffeine-containing energy drink. Int J Sports Physiol Perform 9(6):1013-8.
- 436 52. Perez-Lopez A, Salinero JJ, Abian-Vicen J, et al. (2015). Caffeinated energy drinks improve volleyball
 437 performance in elite female players. Med Sci Sports Exerc 47(4):850-6.
- 438 53. Arazi H, Hoseinihaji M, Eghbali E. (2016). The effects of different doses of caffeine on performance,
 439 rating of perceived exertion and pain perception in teenagers female karate athletes. Braz J Pharm Sci
 440 52(4):685-92.
- 441 54. Turley KR, Eusse PA, Thomas MM, et al. (2015). Effects of different doses of caffeine on anaerobic
 442 exercise in boys. Pediatr Exerc Sci 27(1):50-6.
- 55. Tallis J, Yavuz HC. (2017). The effects of low and moderate doses of caffeine supplementation on
 upper and lower body maximal voluntary concentric and eccentric muscle force. Appl Physiol Nutr
 Metab 43(3):274-81.
- 56. Sabol F, Grgic J, Mikulic P. (2019) The effects of three different doses of caffeine on jumping and
 throwing performance: a randomized, double-blind, crossover study. Int J Sports Physiol Perform doi:
 10.1123/ijspp.2018-0884
- 57. Talanian JL, Spriet, LL. (2016). Low and moderate doses of caffeine late in exercise improve
 performance in trained cyclists. Appl Physiol Nutr Metab 41(8):850-5.
- 451 58. Henry D, Hill S. (1995). Comparing treatments. BMJ 310(6990):1279.
- 452 59. Ryan EJ, Kim CH, Muller MD, et al. (2012). Low-dose caffeine administered in chewing gum does not
 453 enhance cycling to exhaustion. J Strength Cond Res 26(3):844-50.
- 45460. Oberlin-Brown KT, Siegel R, Kilding AE, et al. (2016). Oral presence of carbohydrate and caffeine in455chewing gum: independent and combined effects on endurance cycling performance. Int J Sports
- 456 Physiol Perform 11(2):164-71.

- 457 61. Ryan EJ, Kim CH, Fickes EJ, et al. (2013). Caffeine gum and cycling performance: a timing study. J
 458 Strength Cond Res 27(1):259-64.
- 459 62. Lane SC, Hawley JA., Desbrow B, et al. (2013). Single and combined effects of beetroot juice and
 460 caffeine supplementation on cycling time trial performance. Appl Physiol Nutr Metab 39(9):1050-7.
- 461 63. Paton C, Costa V, Guglielmo L. (2015). Effects of caffeine chewing gum on race performance and
 462 physiology in male and female cyclists. J Sports Sci 33(10):1076-83.
- 463 64. Gonçalves L, de Salles Painelli V, Yamaguchi G, et al. (2017). Dispelling the myth that habitual
 464 caffeine consumption influences the performance response to acute caffeine supplementation. J Appl
 465 Physiol 123(1):213
- 466 65. Pickering C, Kiely J. (2018). What should we do about habitual caffeine use in athletes? Sports Med
 467 https://doi.org/10.1007/s40279-018-0980-7
- 468 66. Evans M, Tierney P, Gray N, et al. (2018). Acute ingestion of caffeinated chewing gum improves
 469 repeated sprint performance of team sports athletes with low habitual caffeine consumption. Int J Sport
 470 Nutr Exerc Metab 28(3):221-227. doi: 10.1123/ijsnem.2017-0217
- 471 67. Skinner TL, Jenkins DG, Coombes JS, et al. (2010). Dose response of caffeine on 2000-m rowing
 472 performance. Med Sci Sports Exerc 42(3):571-6.
- 473 68. Pickering C, Kiely J. (2018). Are the current guidelines on caffeine use in sport optimal for everyone?
 474 Inter-individual variation in caffeine ergogenicity, and a move towards personalised sports nutrition.
 475 Sports Med 48(1):7-16.
- 476 69. Gu L, Gonzalez FJ, Kalow W, et al. (1992). Biotransformation of caffeine, paraxanthine, theobromine
 477 and theophylline by cDNA-expressed human CYP1A2 and CYP2E1. Pharmacogenetics 2(2):73-7.
- 478 70. Sachse C, Brockmöller J, Bauer S, et al. (1999). Functional significance of a C→ A polymorphism in
 479 intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol 47(4):445-9.
- 480 71. Pataky MW, Womack CJ, Saunders MJ, et al. (2015). Caffeine and 3- km cycling performance:
- 481 Effects of mouth rinsing, genotype, and time of day. Scand J Med Sci Sports 26(6):613-9.
- 482 72. Salinero JJ, Lara B, Ruiz-Vicente D, et al. (2017). CYP1A2 genotype variations do not modify the
 483 benefits and drawbacks of caffeine during exercise: a pilot study. Nutrients 9(3):269.
- 484 73. Pickering C. (2018). Caffeine, CYP1A2 genotype, and sports performance: is timing important? Ir J
 485 Med Sci doi: 10.1007/s11845-018-1811-4

- 486 74. Alsene K, Deckert J, Sand P, et al. (2003). Association between A2a receptor gene polymorphisms and
 487 caffeine-induced anxiety. Neuropsychopharmacology 28(9):1694.
- 488 75. Retey JV, Adam M, Khatami R, et al. (2007). A genetic variation in the adenosine A2A receptor gene
 489 (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. Clin Pharmacol Ther
 490 81(5):692-8.
- 491 76. Lampe JW, King IB, Li S, et al. (2000). Brassica vegetables increase and apiaceous vegetables
 492 decrease cytochrome P450 1A2 activity in humans: changes in caffeine metabolite ratios in response to
 493 controlled vegetable diets. Carcinogenesis 21(6):1157-62.
- 494 77. Abernethy DR, Todd EL. (1985). Impairment of caffeine clearance by chronic use of low-dose
 495 oestrogen-containing oral contraceptives. Eur J Clin Pharmacol 28(4):425-8.
- 496 78. Ping J, Wang JF, Liu L, et al. (2014). Prenatal caffeine ingestion induces aberrant DNA methylation
 497 and histone acetylation of steroidogenic factor 1 and inhibits fetal adrenal steroidogenesis. Toxicology
 498 321:53-61
- 499 79. Wendler C, Poulsen R, Fang X. (2014). Caffeine induces both short-term and long-term effects on gene
 500 expression and DNA methylation in the mouse heart. FASEB 28(S1):542-3.
- 501 80. Jin B, Park DW, Nam KW, et al. (2004). CpG methylation of the mouse CYP1A2 promoter. Toxicol
 502 Letters 152(1):11-8.
- 503 81. Djordjevic N, Ghotbi R, Bertilsson L, et al. (2008). Induction of CYP1A2 by heavy coffee
 504 consumption in Serbs and Swedes. Eur J Clin Pharmacol 64(4):381-5.
- 505 82. Marques S, Batalha VL, Lopes LV, et al. (2011). Modulating Alzheimer's disease through caffeine: a
 506 putative link to epigenetics. J Alzheimers Dis 24(S2):161-71.
- 507 83. Burke LM. (2008). Caffeine and sports performance. Appl Physiol Nutr Metab 33(6):1319-34.
- 508 84. Evans SM, Griffiths RR. (1991). Dose-related caffeine discrimination in normal volunteers: individual
 509 differences in subjective effects and self-reported cues. Behav Pharmacol 2(4&5):345-356.
- 510 85. Karacan I, Thornby JI, Anch AM, et al. (1976). Dose- related sleep disturbances induced by coffee and
 511 caffeine. Clin Pharmacol Ther 20(6):682-9.
- 86. Woodman T, Hardy L. (2003). The relative impact of cognitive anxiety and self-confidence upon sport
 performance: A meta-analysis. J Sports Sci 21(6):443-57.
- 514 87. Reilly T, Edwards B. (2007). Altered sleep–wake cycles and physical performance in athletes. Physiol
 515 Behav 90(2-3):274-84.