

Central Lancashire Online Knowledge (CLoK)

Title	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
Туре	Article
URL	https://clok.uclan.ac.uk/id/eprint/29558/
DOI	https://doi.org/10.1016/j.nut.2019.06.016
Date	2019
Citation	Pickering, Craig and Kiely, John (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
Creators	Pickering, Craig and Kiely, John

It is advisable to refer to the publisher's version if you intend to cite from the work. https://doi.org/10.1016/j.nut.2019.06.016

For information about Research 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 http://clok.uclan.ac.uk/policies/

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. **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 (≤3 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

1. Introduction

Of all sporting ergogenic aids, caffeine (1,3,7-trimethylxanthine) is the most popular, with approximately 75% of athletes consuming it either before or during competition [1,2]. Indeed, caffeine has such a reliable performance enhancing effect that, for over twenty years (1984-2004), high doses were banned for within-competition use by the World Anti-Doping Agency (WADA), and caffeine remains on their active monitoring programme to this day. The ergogenic effects of caffeine ingestion have been demonstrated across a wide range of sports, including endurance [3] and team sports [4], and across different exercise methods and modalities, including repeated high-intensity efforts [5], muscular endurance [6], maximum strength [7] and anaerobic performance [8].

Whilst the ergogenic effects of caffeine have been known for over 100 years [9], the broad array of potential mechanisms by which caffeine exerts its performance enhancing effects have only more recently been more fully elucidated. The most well-established mechanism is that of caffeine's role as a competitive adenosine receptor antagonist [10], dampening adenosine's downregulation of Central Nervous System arousal [11]. In turn, this promotes the release of a spectrum of neuro-chemicals, including dopamine and the excitatory neurotransmitter glutamate [12], thereby increasing muscle firing rates [13]. Caffeine also stimulates adrenaline secretion [14], alters substrate utilization and metabolism [15], and increases cellular ion release [16]. More recently, the relationship between caffeine, pain, and exercise performance has been explored, with current evidence suggesting that caffeine decreases pain perception, which in turn reduces rating of perceived exertion (RPE) [17] and enhances exercise capacity [18]. Latterly, it has been proposed that caffeine's bitter taste may drive some of its performance enhancing benefits [19], in a similar fashion to the documented effects of the bitter tasting compound quinine [20]; such observations may explain the ergogenic effects of caffeine-infused 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

Nutrition's position stand on caffeine [23], for example, summarizes that caffeine is effective at enhancing performance at dosages considered to be moderate (~3-6 mg/kg), consumed approximately 60 minutes prior to performance, with no additional ergogenic effects seen with higher caffeine doses (>9 mg/kg). Such recommendations have been echoed elsewhere, both in the scientific literature [14,16] and lay press.

Interestingly, however, a number of studies have recently shown that lower doses of caffeine, typically of ≤3 mg/kg, are also ergogenic [24]. In this article, we examine the evidence underpinning this finding, and explore whether low doses (≤3 mg/kg) of caffeine pre-exercise offer comparable ergogenic benefits to the more conventionally recommended intakes (3-6 mg/kg); such an examination is crucial, as athletes are likely interested in whether their caffeine dose offers the *maximal* ergogenic benefits, as opposed to just *an* ergogenic effect. Finally, we note some methodological recommendations that researchers may wish to consider when conducting low dose caffeine research in the future.

2. Are low doses of caffeine ergogenic?

Whilst, historically, high doses (up to 13 mg/kg) of caffeine have been used to induce ergogenic effects [25], more recently there has been an increasing focus on the use of more moderate (~3-6 mg/kg) caffeine doses [26]. The success of these trials in turn has prompted research investigating the efficacy of lower doses of caffeine (≤3 mg/kg). Whilst the number of these trials is relatively low, a recent review by Spriet [24] concluded that these lower caffeine doses, when consumed prior to exercise, likely enhanced athletic performance.

Similarly, a recent meta-analysis of the ergogenic effects of caffeine-containing energy drinks, the majority of which had a dose of ≤3 mg/kg, concluded that ingestion of these drinks improved performance [27].

Accordingly, in general, the evidence to date supports the perspective that lower doses of caffeine are ergogenic for sports performance, particularly with regards to endurance sport. However, perhaps a more pertinent consideration for athletes is whether these low doses of caffeine are as effective in enhancing performance as the more conventional, higher doses? As athletes consume caffeine primarily to improve performance, and presumably wish to improve their performance to the maximum amount possible, this is an important consideration. If low doses of caffeine are ergogenic, but not as ergogenic as higher doses, then athletes consuming these lower doses may be leaving some potential performance improvements on the table. As such,

the question as to whether or not low (≤3 mg/kg) doses of caffeine exert similar ergogenic effects as more conventional, moderate (3-6 mg/kg) doses seems highly relevant.

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

Instead, a better option might be to have low-dose and high-dose caffeine trials within each study, thereby allowing for a direct comparison between the different caffeine doses. Although seemingly sensible, such an approach is surprisingly uncommon. In a recent review, Spriet [24] concluded that low caffeine doses (≤3 mg/kg), taken before exercise, enhanced athletic performance compared to placebo. However, the vast majority of the studies included in Spriet's [24] review (summarized in table 1) did not directly compare a low dose (≤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 these four, there were mixed results; two reported no additional benefits from 6 mg/kg of caffeine compared to 3mg/kg of caffeine when examining aerobic endurance performance [39,41]; one reported that 4.5 mg/kg enhanced aerobic endurance performance to a greater extent than 3.2 mg/kg, which in turn was more ergogenic than a dose of 2.1 mg/kg [40]; and one found that 5 mg/kg enhanced maximum knee flexion and extension isokinetic torque, whilst 2 mg/kg did not [42]. The remaining studies either did not use a caffeine dose above 3 mg/kg in their comparison [43-45], or only used a single caffeine dose (≤3 mg/kg), and compared this to placebo [46-52]. We identified additional papers published following Spriet's [24] review that directly examined a low versus high dose of caffeine [22,53-56]. Of these, Arazi and colleagues [53] reported no difference in performance between a low (2 mg/kg) and high (5 mg/kg) caffeine dose—a finding replicated by Guest and colleagues [22] with doses of 2 and 4 mg/kg on a 10kg cycle ergometer time trial—whilst others [5355] reported mixed results, in part because of the large number of performance tests utilised. Interestingly, Sabol and colleagues [56] reported similar improvements in vertical jump performance following ingestion of 2, 4, and 6 mg/kg of caffeine, whilst upper body ballistic exercise performance was only enhanced following a dose of 6 mg/kg. Consequently, due to both the equivocal results of the small numbers of trials directly investigating this phenomenon, and the lack of higher caffeine doses utilised in other trials, it is unclear whether lower doses of caffeine are as ergogenic as higher doses. Recently, Talanian & Spriet [57] suggested that, based on their interpretations of five lower-dose caffeine studies [26,40,43,44,57] that the timing of the lower caffeine dose may be a crucial aspect, with ingestion less than 60 minutes pre-exercise associated with a greater performance benefit than later ingestion (80-180 minutes pre-exercise).

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
		00 minutes			168	
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
					NO	
et al. [44]	male cyclists	pre-	VO2 peak	(placebo),		placebo, only 2
		exercise	performance	1, 2, 3		mg/kg significantly
			cycle	mg/kg		enhanced
						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		
0.1.1.	6 1	<i></i>	61 TETE	nt.	N	N. 1100
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
					Tes	
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.

3. A potential solution?

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

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

Additionally, there is contemporary debate regarding the impact of regular caffeine consumption on the subsequent ergogenic effects of caffeine, with some studies finding a negative impact of habituation [32], whilst others report none [64]. One potential outcome is that regular caffeine use requires a subsequently larger caffeine dose to exert performance benefits [65]. As such, the dose of caffeine used in experimental trials substantially influences study conclusions, particularly when exploring the effects of habitual use. Recently, Evans and colleagues [66] explored the influence of caffeinated gum, supplying 200 mg of caffeine, on repeated sprint performance in team sport athletes. The initial finding was that caffeine did not confer any ergogenic effects; however, further analysis demonstrated that habitual caffeine use modified the performance enhancement seen following caffeine ingestion; in this case, very low habitual caffeine users (<40 mg/d) did exhibit ergogenic effects, whilst more moderate habitual users (>130 mg/d) did not. Such findings may be interpreted as evidence that habitual use reduced caffeine's ergogenic effects. However, an obvious question emerges; what if the dose of caffeine used was within the currently accepted guidelines, as opposed to <3 mg/kg? As this wasn't explored, the answer remains unclear. Again, this is not an attack on the authors, who were exploring a different research question, but it nevertheless underscores the point that increasingly robust conclusions could be inferred from caffeine research if the currently accepted optimal dose was included.

4. How robust is the currently accepted optimal dose?

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

some studies report no ergogenic effect of caffeine [67], again illustrating that the individual response to a standardised dose of caffeine is highly variable. The drivers of the variation of wide and varied, but can be grossly summarised as genetic, environmental (i.e. non-genetic), and epigenetic factors [68].

223

224

225

226

227

228

229

230

231

232

233

234

235

236

237

238

239

240

220

221

222

4.1 Genetic

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

241

242

243

244

245

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

248

249

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].

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

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

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

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

6. Conclusions

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

We hope that the points raised here enable athletes, coaches, support staff, and perhaps even researchers to better critique the studies underpinning their caffeine strategies and recommendations. Moving forward, we also recommend that caffeine researchers include a trial that utilizes the currently accepted optimal dose of caffeine – even if this dose is not optimal for everyone – in order to enable more direct comparisons between studies, and thereby enabling firmer conclusions to be made. Finally, as per our previous explorations of caffeine use in sport [65,68], we urge athletes and practitioners to experiment with different caffeine doses, timing, and ingestion methods in order to uncover the strategies best suiting their unique genetic predispositions, environmental influences, and individual histories.

Novelty Statement & Practical Applications

This critical review has demonstrated that, whilst lower doses (≤3 mg/kg) of caffeine have the potential to be ergogenic, it's not clear whether such doses are as ergogenic as higher doses. The main cause of this uncertainty is due to a lack of trials directly comparing low and high doses of caffeine. As such, athletes, coaches and practitioners looking to utilise caffeine as a means to enhance performance would be best placed to experiment with various different caffeine doses in order to determine the optimal dose to enhance their performance, given their own unique biology, history, and performance requirements.

Compliance with Ethical Standards

327 Funding

No sources of funding were used to assist in the preparation of this article.

References:

- 1. Desbrow B, Leveritt M. (2006). Awareness and use of caffeine by athletes competing at the 2005 Ironman Triathlon World Championships. Int J Sport Nutr Exerc Metab 16(5):545-58.
- Del Coso J, Muñoz G, Muñoz-Guerra J. (2011). Prevalence of caffeine use in elite athletes following
 its removal from the World Anti-Doping Agency list of banned substances. Appl Physiol Nutr Metab
 36(4):555-61
 - 3. Keisler BD, Armsey TD. (2006). Caffeine as an ergogenic aid. Curr Sports Med Rep 5(4):215-9.

- Foskett A, Ali A, Gant N. (2009). Caffeine enhances cognitive function and skill performance during
 simulated soccer activity. Int J Sport Nutr Exerc Metab 19(4):410-23.
- 5. Glaister M, Howatson G, Abraham CS, et al. (2008). Caffeine supplementation and multiple sprint running performance. Med Sci Sports Exerc 40(10):1835-40.
- Da Silva VL, Messias FR, Zanchi NE, et al. (2015). Effects of acute caffeine ingestion on resistance
 training performance and perceptual responses during repeated sets to failure. J Sports Med Phys
 Fitness 55(5):383-9.
- Grgic J, Mikulic P. (2017). Caffeine ingestion acutely enhances muscular strength and power but not
 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.
- 9. Rivers WH, Webber HN. (1907). The action of caffeine on the capacity for muscular work. J Physiol 36(1):33
- 351 10. Biaggioni IT, Paul SU, Puckett AN, et al. (1991). Caffeine and theophylline as adenosine receptor 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 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 31(11):785-807.
- 360 15. Cruz RS, de Aguiar RA, Turnes T, et al. (2015). Caffeine affects time to exhaustion and substrate 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 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 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

- 368 19. Wickham KA, Spriet LL. (2018). Administration of Caffeine in Alternate Forms. Sports Med 48(S1):79-91.
- 370 20. Gam S, Guelfi KJ, Fournier PA. (2016). New insights into enhancing maximal exercise performance 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 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 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.
- 25. Pasman WJ, Van Baak MA, Jeukendrup AE, et al. (1995). The effect of different dosages of caffeine 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 metabolism and endurance performance. J Appl Physiol 93(3):990-9.
- 27. Souza DB, Del Coso J, Casonatto J, et al. (2017). Acute effects of caffeine-containing energy drinks on 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.
- Womack CJ, Saunders MJ, Bechtel MK, et al. (2012). The influence of a CYP1A2 polymorphism on 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 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 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 tolerance to the performance benefits of caffeine. J Sports Sci 35(19):1920-1927.
- 33. Sabblah S, Dixon D, Bottoms L. (2015). Sex differences on the acute effects of caffeine on maximal strength and muscular endurance. Comparative Exercise Physiology 11(2):89-94.

- 398 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.
- Tallis J, James RS, Cox VM, et al. (2017). Is the ergogenicity of caffeine affected by increasing age?
 The direct effect of a physiological concentration of caffeine on the power output of maximally
- stimulated edl and diaphragm muscle isolated from the mouse. J Nutr Health Aging 21(4):1-9
- 36. Saunders B, Oliveira LF, Silva RP, et al. (2017). Placebo in sports nutrition: a proof- of- principle study involving caffeine supplementation. Scand J Med Sci Sports 27(11):1240-1247 doi: 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 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 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, caffeine excretion, and performance. J Appl Physiol 85(2):709-15.
- 41. Desbrow B, Biddulph C, Devlin B, et al. (2012). The effects of different doses of caffeine on endurance cycling time trial performance. J Sports Sci 30(2):115-20.
- 42. Astorino TA, Terzi MN, Roberson DW, et al. (2010). Effect of two doses of caffeine on muscular 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 CHO oxidation: a dose-response study. Med Sci Sports Exerc 41(9):1744-51.
- 44. Jenkins NT, Trilk JL, Singhal A, et al. (2008). Ergogenic effects of low doses of caffeine on cycling 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 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 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 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.
- 50. Irwin C, Desbrow B, Ellis A, et al. (2011). Caffeine withdrawal and high-intensity endurance cycling performance. J Sports Sci 29(5):509-15.
- 51. Del Coso J, Pérez-López A, Abian-Vicen J, et al. (2014). Enhancing physical performance in male 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 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.
- 54. Turley KR, Eusse PA, Thomas MM, et al. (2015). Effects of different doses of caffeine on anaerobic exercise in boys. Pediatr Exerc Sci 27(1):50-6.
- 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 enhance cycling to exhaustion. J Strength Cond Res 26(3):844-50.
- 454 60. Oberlin-Brown KT, Siegel R, Kilding AE, et al. (2016). Oral presence of carbohydrate and caffeine in
 455 chewing 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 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 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 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 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 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 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 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
- Wendler C, Poulsen R, Fang X. (2014). Caffeine induces both short-term and long-term effects on gene
 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 Letters 152(1):11-8.
- 503 81. Djordjevic N, Ghotbi R, Bertilsson L, et al. (2008). Induction of CYP1A2 by heavy coffee 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 putative link to epigenetics. J Alzheimers Dis 24(S2):161-71.
- 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 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 caffeine. Clin Pharmacol Ther 20(6):682-9.
- 512 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 Behav 90(2-3):274-84.