



Review

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

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ARTICLE INFO

Article History:

Received 4 January 2019
Received in revised form 12 June 2019
Accepted 21 June 2019

Keywords:

Caffeine
Ergogenic
Low dose
Supplement
Sports drink

ABSTRACT

Caffeine is a popular and widely consumed sporting ergogenic aid. Over the years, the effects of different caffeine doses have been researched, with the general consensus being that 3 to 6 mg/kg of caffeine represents the optimal 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 optimized performance benefit. Following this logic, the aim of this review was to 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 with the currently accepted best practice dose of 3 to 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 use caffeine to enhance their performance, and those conducting research into caffeine and sport.

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Introduction

Of all sporting ergogenic aids, caffeine (1,3,7-trimethylxanthine) is the most popular, with ~75% of athletes consuming it either before or during competition [1,2]. Indeed, caffeine has such a reliable performance-enhancing effect that, for >20 y (1984–2004), high doses were banned for within-competition use by the World Anti-Doping Agency (WADA), and caffeine remains on WADA's active monitoring program. 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].

Although the ergogenic effects of caffeine have been known for >100 y [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 neurochemicals, 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]. 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, its use is pervasive among both professional and amateur athletes [1,2].

C.P. is a former employee of DNAFit LifeSciences, a genetic testing company. C.P. received no financial incentives for the preparation of this manuscript. J.K. has no conflicts of interest to declare.

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This extensive use has resulted in the formulation of best practice guidelines by numerous professional bodies. The International Society of Sports Nutrition's position on caffeine [23], for example, summarizes that caffeine is effective at enhancing performance at dosages considered to be moderate ($\sim 3\text{--}6$ mg/kg), consumed ~ 60 min before 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 ≤ 3 mg/kg, are also ergogenic [24]. In this review, we examine the evidence underpinning this finding, and explore whether low doses (≤ 3 mg/kg) of caffeine before exercise offer comparable ergogenic benefits to the more conventionally recommended intakes ($3\text{--}6$ 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.

Are low doses of caffeine ergogenic?

Although historically, high doses (≤ 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 ($\sim 3\text{--}6$ 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). Although the number of these trials is relatively low, a recent review by Spriet [24] concluded that these lower caffeine doses, when consumed before 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 regard 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 ($3\text{--}6$ 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. First, we could compare the magnitude of improvements seen between studies; for example, determining whether the size of the ergogenic effect is greater in the studies that compare 6 mg/kg with 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 participants [28]. As illustration, consider the array of variables that 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- 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 with 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 4, there were mixed results; 2 reported no additional benefits from 6 mg/kg of caffeine compared with 3 mg/kg of caffeine when examining aerobic endurance performance [39,41]; 1 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 1 found that 5 mg/kg enhanced maximum knee flexion and extension isokinetic torque, whereas 2 mg/kg did not [42]. The remaining studies either did not use a caffeine dose >3 mg/kg in their comparison [43–45], or only used a single caffeine dose (≤ 3 mg/kg), and compared this with placebo [46–52]. We identified additional papers published after Spriet's [24] review that directly examined a low versus high dose of caffeine [22,53–56]. Of these, Arazi et al. [53] reported no difference in performance between a low (2 mg/kg) and high (5 mg/kg) caffeine dose—a finding replicated by Guest et al. [22] with doses of 2 and 4 mg/kg on a 10-kg cycle ergometer time trial—whereas others [53–55] reported mixed results, in part because of the large number of performance tests used. Interestingly, Sabol et al. [56] reported similar improvements in vertical jump performance after ingestion of 2, 4, and 6 mg/kg of caffeine; whereas upper body ballistic exercise performance was only enhanced after 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 used in other trials, it is unclear whether lower doses of caffeine are as ergogenic as higher doses. Recently, Talanian and Spriet [57] suggested that, based on their interpretations of five lower-dose caffeine studies [26,40,43,44,57], the timing of the lower caffeine dose may be a crucial aspect, with ingestion <60 min pre-exercise associated with a greater performance benefit than later ingestion (80–180 min pre-exercise).

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 ($3\text{--}6$ 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 randomized 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;

Table 1
Studies examining the effects of low doses of pre-exercise caffeine on sports performance*

Study	Participants	Caffeine timing	Exercise	Caffeine dose	Comparison to best practice?	Finding
Graham and Spriet [39]	8 well-trained men	60 min pre-exercise	TTE run at 85% VO _{2max}	0 (placebo), 3, 6, and 9 mg/kg	Yes	Endurance was equally enhanced in both 3- and 6-mg/kg caffeine trials
Kovacs et al. [40]	15 well-trained men	60% of solution 60 min pre-exercise, and 20% at two time points within exercise trial	1-h maximum cycle	0 (placebo), 2.1, 3.2, 4.5 mg/kg	Yes	Performance was enhanced to the greatest extent in 4.5 mg/kg, then 3.2 mg/kg, then 2.1 mg/kg
Jenkins et al. [44]	13 trained male cyclists	60 min pre-exercise	15 min VO ₂ peak performance cycle	0 (placebo), 1, 2, and 3 mg/kg	No	Compared with placebo, only 2 mg/kg significantly enhanced performance
Desbrow et al. [43]	9 trained male cyclists	60 min pre-exercise	120 min steady-state cycle, followed by TT	0 (placebo), 1.5, 3 mg/kg	No	No performance enhancement with caffeine
Irwin et al. [50]	12 trained male cyclists	90 min pre-exercise	Cycle TT	0 (placebo) or 3 mg/kg	No	Caffeine enhanced performance compared with placebo
Desbrow et al. [41]	16 trained cyclists	90 min pre-exercise	60-min cycle at 75% peak sustainable power	0 (placebo), 3, and 6 mg/kg	Yes	No additional benefit of 6 mg/kg compared with 3 mg/kg
Wiles et al. [46]	34 male athletes	60 min pre-exercise	1500-m run	~150–200 mg from coffee (3 g total coffee)	No	Caffeine enhanced performance
Van Nieuwenhoven et al. [47]	98 well-trained men and women	At start, 4.5, 9, and 13.5 km of exercise trial	18-km run	90 mg	No	No effect of caffeine
Bridge and Jones [48]	8 male runners	60 min pre-exercise	8-km race	0 (placebo), 3 mg/kg, or no supplement	No	Caffeine enhanced performance
Schubert et al. [45]	6 male runners	65 min pre-exercise	5-km run TT	0 (placebo, 80 mg, 140 mg)	No	No differences in caffeine consumption trials when compared with placebo
Perez-Lopez et al. [52]	13 elite female volleyball players	60 min pre-exercise	Volleyball-specific tests	0 (placebo) and 3 mg/kg	No	Caffeine enhanced performance
Del Coso et al. [51]	15 male volleyball players	60 min pre-exercise	Volleyball-specific tests	0 (placebo) and 3 mg/kg	No	Caffeine enhanced performance
Strecker et al. [49]	10 male tennis players	90 min pre-exercise	Tennis skill performance	0 (placebo) and 3 mg/kg	No	Caffeine enhanced performance
Astorino et al. [42]	15 active men	60 min pre-exercise	40 maximal knee extensions	0 (placebo), 2, and 5 mg/kg	Yes	Only the 5-mg/kg dose enhanced performance
Talanian and Spriet [57]	15 cyclists (n = 4 women)	40 (~42% total), 20 (~33% total) and 0 (~25%) min pre-TT	Time to completion cycle ergometer test	0 (placebo), ~1.5, ~2.9 mg/kg	No	Higher caffeine dose enhanced TT performance to a greater extent than lower dose
Tallis and Yavuz [55]	10 active men	60 min pre-exercise	Isokinetic concentric and eccentric strength at 60 and 180 deg/s of elbow and knee flexors	0 (placebo), 3, and 6 mg/kg	Yes	No effect of caffeine on elbow flexor (concentric and eccentric) or knee (eccentric) flexor strength. Both caffeine doses increased 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 al. [54]	26 young (8–10 y old) boys	60 min pre-exercise	Handgrip strength and Wingate tests	0, (placebo), 1, 3, and 5 mg/kg	Yes	Grip strength: significantly higher in 3- and 5-mg/kg caffeine trials Wingate: 3 mg/kg produced greatest peak power, whereas 5 mg/kg produced greatest mean power
Arazi et al. [53]	10 female karate athletes	60 min pre-exercise	1 RM leg press, leg press repetitions to failure, vertical jump, RAST test	0 (placebo), 2, and 5 mg/kg	Yes	No significant difference in test performance between groups
Sabol et al. [56]	20 recreationally active men	60 min pre-exercise	Medicine ball throw and vertical jump	0 (placebo), 2, 4, and 6 mg/kg	Yes	No difference between caffeine doses in terms of lower body performance enhancement. Only 6 mg/kg enhanced upper body performance
Guest et al. [22]	101 competitive men	~45 min pre-exercise	10-km cycle ergometer TT	0 (placebo), 2, and 4 mg/kg	Yes	No difference in performance enhancement between caffeine doses; both enhanced performance compared with placebo

RAST; running-based anaerobic sprint test; RM; repetition maximum; TT, time trial; TTE, time-to-exhaustion; VO_{2 max}, maximal oxygen consumption

Adapted from Spriet [24]. Studies that did not use a pre-exercise caffeine dose, or those that only used a caffeine dose >3 mg/kg, were excluded, and additional relevant papers published since that review have been added.

*For the purposes of this table, a low dose of caffeine is defined as ≤3 mg/kg.

whereas three studies [61–63] reported a positive effect. An obvious distinction between these trials is the dose; the “no-effect” findings occurred after a dose of 200 mg; whereas 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 using a currently accepted optimal caffeine dose in the 200-mg studies would potentially resolve the current ambiguity.

Additionally, there is contemporary debate regarding the effects of regular caffeine consumption on the subsequent ergogenic effects of caffeine, with some studies finding a negative effect of habituation [32], and others reporting 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 et al. [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 after caffeine ingestion; in this case, very low habitual caffeine users (<40 mg/d) did exhibit ergogenic effects; whereas 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 was not 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.

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 [14,23]. Furthermore, it is not suggested that there are any additional ergogenic effects associated with a dose larger than this [25]. However, there is considerable interindividual variation in the ergogenic effects of caffeine ingestion [67]. This phenomenon becomes apparent when caffeine studies report individual participant data. Jenkins et al. [44], for example, examined the effects of lower caffeine doses (1, 2, and 3 mg/kg) compared with placebo on a 15-min maximum cycle. Of the 13 participants, 1 did not exhibit an ergogenic effect at any dose, whereas 4 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 individuals, but with the percentage improvements compared against the placebo trial varying from 105% to 250%. Neither of these studies used 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 interindividual responses to caffeine. Furthermore, some studies report no ergogenic effect of caffeine [68], again illustrating that the individual response to a standardized dose of caffeine is highly variable. The drivers of the variation of wide and varied, but can be grossly summarized as genetic, environmental (i.e., non-genetic), and epigenetic factors [67].

Genetics

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 metabolism speed. Here, individuals with a C allele metabolize caffeine slower than AA genotypes [70]. Potentially, this single nucleotide polymorphism (SNP) might affect 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 et al. [22] suggest that because caffeine is a vasoconstrictor, slow metabolizers experience this vasoconstriction for a longer period of time, inhibiting the delivery of oxygen and nutrients to the working muscle. Conversely, Womack et al. [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 metabolism of caffeine. As such, it is not clear whether caffeine has a reduced ergogenic, or even an ergolytic, effect in C allele carriers, or whether they need to ingest caffeine for a longer amount of time before exercise [73]. Similarly, there is the potential that an SNP in *ADORA2A*, which encodes for a subtype 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].

Environmental factors

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].

Epigenetics

Habitual caffeine use likely induces long-term epigenetic changes [78,79], which may in turn affect future ergogenic effects, potentially by increasing caffeine metabolism 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, although caffeine is ergogenic, the currently accepted optimal caffeine dose may not be optimal for everyone [67]. Some individuals may benefit from lower doses of caffeine (discussed later), whereas 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 and 6 mg/kg likely is sufficient to realize the optimum ergogenic effects. Indeed, Burke [83] suggested that the dose–response relationship of caffeine on performance appears to plateau at ~3 mg/kg. As such, this dose may represent a target threshold to maximize 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 to 6 mg/kg should be taken as a starting point, from which individual experimentation can be used to refine pretraining and pre-competition caffeine strategies.

When might lower doses of caffeine be more appropriate?

The purpose of this review was 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 after 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 tradeoff between the optimized 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 precompetition anxiety may wish to consume less caffeine before 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 favorable than higher doses. Although 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 [67,73].

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 realize the ergogenic effects, such that if an athlete habitually consumed 3 mg/kg of caffeine pretraining, they might require a caffeine dose closer to 6 mg/kg precompetition [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 do not restore the optimized ergogenic effect of caffeine. In this scenario, habitual use of lower caffeine doses (~3 mg/kg) may facilitate an increased precompetition dose, thereby allowing for both enhancement of regular training, along with competition performance.

Conclusions

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 (3–6 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, although low doses of caffeine do offer a performance benefit, it is 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 using 3 to 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 uses the currently accepted optimal dose of caffeine—even if this dose is not optimal for everyone—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 [65,67], we urge athletes and practitioners to experiment with different caffeine doses, timing, and ingestion methods to uncover the strategies best suiting their unique genetic predispositions, environmental influences, and individual histories.

Novelty statement and practical applications

This critical review has demonstrated that, although lower doses (≤ 3 mg/kg) of caffeine have the potential to be ergogenic, it is 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 use caffeine as a means to enhance performance would be best placed to experiment with various different caffeine doses to determine the optimal dose to enhance their performance, given their own unique biology, history, and performance requirements.

References

- [1] Desbrow B, Leveritt M. Awareness and use of caffeine by athletes competing at the 2005 Ironman Triathlon World Championships. *Int J Sport Nutr Exerc Metab* 2006;6:545–58.
- [2] Del Coso J, Muñoz G, Muñoz-Guerra J. Prevalence of caffeine use in elite athletes following its removal from the World Anti-Doping Agency list of banned substances. *Appl Physiol Nutr Metab* 2011;36:555–61.
- [3] Keisler BD, Armsey TD. Caffeine as an ergogenic aid. *Curr Sports Med Rep* 2006;5:215–9.
- [4] Foskett A, Ali A, Gant N. Caffeine enhances cognitive function and skill performance during simulated soccer activity. *Int J Sport Nutr Exerc Metab* 2009;19:410–23.
- [5] Glaister M, Howatson G, Abraham CS, Lockey RA, Goodwin JE, Foley P, et al. Caffeine supplementation and multiple sprint running performance. *Med Sci Sports Exerc* 2008;40:1835–40.
- [6] Da Silva VL, Messias FR, Zanchi NE, Gerlinger-Romero F, Duncan MJ, Guimaraes-Ferreira L, et al. Effects of acute caffeine ingestion on resistance training performance and perceptual responses during repeated sets to failure. *J Sports Med Phys Fitness* 2015;55:383–9.
- [7] Grgic J, Mikulic P. Caffeine ingestion acutely enhances muscular strength and power but not muscular endurance in resistance-trained men. *Eur J Sport Sci* 2017;17:1029–36.
- [8] Grgic J. Caffeine ingestion enhances Wingate performance: a meta-analysis. *Eur J Sport Sci* 2018;18:219–25.
- [9] Rivers WH, Webber HN. The action of caffeine on the capacity for muscular work. *J Physiol* 1907;36:33.
- [10] Biaggioni IT, Paul SU, Puckett AN, Arzubiaga C. Caffeine and theophylline as adenosine receptor antagonists in humans. *J Pharmacol Exp Ther* 1991;258:588–93.
- [11] Ribeiro JA, Sebastiao AM. Caffeine and adenosine. *J Alzheimers Dis* 2010;20 (suppl 1):3–15.
- [12] Fredholm BB. Adenosine, adenosine receptors and the actions of caffeine. *Pharmacol Toxicol* 1995;76:93–101.
- [13] Kalmar JM. The influence of caffeine on voluntary muscle activation. *Med Sci Sports Exerc* 2005;37:2113–9.
- [14] Graham TE. Caffeine and exercise: metabolism, endurance and performance. *Sports Med* 2001;31:785–807.
- [15] Cruz RS, de Aguiar RA, Turnes T, Guglielmo LG, Beneke R, Caputo F. Caffeine affects time to exhaustion and substrate oxidation during cycling at maximal lactate steady state. *Nutrients* 2015;7:5254–64.
- [16] Sökmén B, Armstrong LE, Kraemer WJ, Casa DJ, Dias JC, Judelson DA, et al. Caffeine use in sports: considerations for the athlete. *J Strength Cond Res* 2008;22:978–86.
- [17] Doherty M, Smith PM, Hughes MG, Davison R. Caffeine lowers perceptual response and increases power output during high-intensity cycling. *J Sports Sci* 2004;22:637–43.

- [18] Gonglach AR, Ade CJ, Bemben MG, Larson RD, Black CD. Muscle pain as a regulator of cycling intensity: effect of caffeine ingestion. *Med Sci Sports Exerc* 2016;48:287–96.
- [19] Wickham KA, Spriet LL. Administration of caffeine in alternate forms. *Sports Med* 2018;48(suppl 1):79–91.
- [20] Gam S, Guelfi KJ, Fournier PA. New insights into enhancing maximal exercise performance through the use of a bitter tastant. *Sports Med* 2016;46:1385–90.
- [21] Beaven CM, Maulder P, Pooley A, Kiduff L, Cook C. Effects of caffeine and carbohydrate mouth rinses on repeated sprint performance. *Appl Physiol Nutr Metab* 2013;38:633–7.
- [22] Guest N, Corey P, Pescovi J, El-Sohemy A. Caffeine, CYP1 A2 genotype, and endurance performance in athletes. *Med Sci Sports Exerc* 2018;50:1570–8.
- [23] Goldstein ER, Ziegenfuss T, Kalman D, Kreider R, Campbell B, Wilborn C, et al. International society of sports nutrition position stand: caffeine and performance. *J Int Soc Sports Nutr* 2010;7:5.
- [24] Spriet LL. Exercise and sport performance with low doses of caffeine. *Sports Med* 2014;44:175–84.
- [25] Pasmán WJ, Van Baak MA, Jeukendrup AE, de Haan A. The effect of different dosages of caffeine on endurance performance time. *Int J Sports Med* 1995;16:225–30.
- [26] Cox GR, Desbrow B, Montgomery PG, Anderson ME, Bruce CR, Macrides TA, et al. Effect of different protocols of caffeine intake on metabolism and endurance performance. *J Appl Physiol* 2002;93:990–9.
- [27] Souza DB, Del Coso J, Casonatto J, Polito MD. Acute effects of caffeine-containing energy drinks on physical performance: a systematic review and meta-analysis. *Eur J Nutr* 2017;56:13–27.
- [28] Ganió MS, Klau JF, Casa DJ, Armstrong LE, Maresh CM. Effect of caffeine on sport-specific endurance performance: a systematic review. *J Strength Cond Res* 2009;23:315–24.
- [29] Womack CJ, Saunders MJ, Bechtel MK, Bolton DJ, Martin M, Luden ND, et al. The influence of a CYP1 A2 polymorphism on the ergogenic effects of caffeine. *J Int Soc Sports Nutr* 2012;9:7.
- [30] Loy BD, O'Connor PJ, Lindheimer JB, Covert SF. Caffeine is ergogenic for adenosine A_{2A} receptor gene (ADORA2A) T allele homozygotes: a pilot study. *J Caffeine Res* 2015;5:73–81.
- [31] Collomp K, Ahmaidi S, Chatard JC, Audran M, Prefaut C. Benefits of caffeine ingestion on sprint performance in trained and untrained swimmers. *Eur J Appl Physiol Occup Physiol* 1992;64:377–80.
- [32] Beaumont R, Cordery P, Funnell M, Mears S, James L, Watson P. Chronic ingestion of a low dose of caffeine induces tolerance to the performance benefits of caffeine. *J Sports Sci* 2017;35:1920–7.
- [33] Sabblah S, Dixon D, Bottoms L. Sex differences on the acute effects of caffeine on maximal strength and muscular endurance. *Comp Exerc Physiol* 2015;11:89–94.
- [34] Hodgson AB, Randell RK, Jeukendrup AE. The metabolic and performance effects of caffeine compared to coffee during endurance exercise. *PLoS One* 2013:e59561.
- [35] Tallis J, James RS, Cox VM, Duncan MJ. 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* 2017;21:1–9.
- [36] Saunders B, de Oliveira LF, da Silva RP, de Salles Painelli V, Gonçalves LS, Yamaguchi G, et al. Placebo in sports nutrition: a proof-of-principle study involving caffeine supplementation. *Scand J Med Sci Sports* 2017;27:1240–7.
- [37] Davis JK, Green JM. Caffeine and anaerobic performance. *Sports Med* 2009;39:813–32.
- [38] Mora-Rodríguez R, Pallarés JG, López-Gullón JM, Lopez-Samanes A, Fernandez-Elias VE, Ortega JF. Improvements on neuromuscular performance with caffeine ingestion depend on the time-of-day. *J Sci Med Sport* 2015;18:338–42.
- [39] Graham TE, Spriet LL. Metabolic, catecholamine, and exercise performance responses to various doses of caffeine. *J Appl Physiol* 1995;78:867–74.
- [40] Kovacs EM, Stegen JH, Brouns F. Effect of caffeinated drinks on substrate metabolism, caffeine excretion, and performance. *J Appl Physiol* 1998;85:709–15.
- [41] Desbrow B, Biddulph C, Devlin B, Grant GD, Anoopkumar-Dukie S, Leveritt MD. The effects of different doses of caffeine on endurance cycling time trial performance. *J Sports Sci* 2012;30:115–20.
- [42] Astorino TA, Terzi MN, Roberson DW, Burnett TR. Effect of two doses of caffeine on muscular function during isokinetic exercise. *Med Sci Sports Exerc* 2010;42:2205–10.
- [43] Desbrow B, Barrett CM, Minahan CL, Grant GD, Leveritt MD. Caffeine, cycling performance, and exogenous CHO oxidation: a dose-response study. *Med Sci Sports Exerc* 2009;41:1744–51.
- [44] Jenkins NT, Triukh JL, Singhal A, O'Connor PJ, Cureton KJ. Ergogenic effects of low doses of caffeine on cycling performance. *Int J Sport Nutr Exerc Metab* 2008;18:328–42.
- [45] Schubert MM, Astorino TA. The effects of caffeinated “energy shots” on time trial performance. *Nutrients* 2013;5:2062–75.
- [46] Wiles JD, Bird SR, Hopkins J, Riley M. Effect of caffeinated coffee on running speed, respiratory factors, blood lactate and perceived exertion during 1500-m treadmill running. *Br J Sports Med* 1992;26:116–20.
- [47] Van Nieuwenhoven MA, Brouns FJ, Kovacs EM. The effect of two sports drinks and water on GI complaints and performance during an 18-km run. *Int J Sports Med* 2005;26:281–5.
- [48] Bridge CA, Jones MA. The effect of caffeine ingestion on 8 km run performance in a field setting. *J Sports Sci* 2006;24:433–9.
- [49] Strecker E, Foster B, Taylor K, Bell L, Pascoe D, et al. The effect of caffeine ingestion on tennis skill performance and hydration status. *Med Sci Sports Exerc* 2007;39:S175. <https://insights.ovid.com/mespe/200705001/00005768-200705001-01134>.
- [50] Irwin C, Desbrow B, Ellis A, O'Keefe B, Grant G, Leveritt M. Caffeine withdrawal and high-intensity endurance cycling performance. *J Sports Sci* 2011;29:509–15.
- [51] Del Coso J, Pérez-López A, Abian-Vicen J, Salinero JJ, Lara B, Valades D. Enhancing physical performance in male volleyball players with a caffeine-containing energy drink. *Int J Sports Physiol Perform* 2014;9:1013–8.
- [52] Perez-Lopez A, Salinero JJ, Abian-Vicen J, Valades D, Lara B, Hernandez C, et al. Caffeinated energy drinks improve volleyball performance in elite female players. *Med Sci Sports Exerc* 2015;47:850–6.
- [53] Arazi H, Hoseinihaji M, Eghbali E. The effects of different doses of caffeine on performance, rating of perceived exertion and pain perception in teenagers female karate athletes. *Braz J Pharm Sci* 2016;52:685–92.
- [54] Turley KR, Eusse PA, Thomas MM, Townsend JR, Morton AB. Effects of different doses of caffeine on anaerobic exercise in boys. *Pediatr Exerc Sci* 2015;27:50–6.
- [55] Tallis J, Yavuz HC. 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* 2017;43:274–81.
- [56] Sabol F, Grgic J, Mikulic P. The effects of three different doses of caffeine on jumping and throwing performance: a randomized, double-blind, crossover study. *Int J Sports Physiol Perform* 2019:1–35.
- [57] Talanian JL, Spriet LL. Low and moderate doses of caffeine late in exercise improve performance in trained cyclists. *Appl Physiol Nutr Metab* 2016;41:850–5.
- [58] Henry D, Hill S. Comparing treatments. *BMJ* 1995;310:1279.
- [59] Ryan EJ, Kim CH, Muller MD, Bellar DM, Barkley JE, Bliss MV, et al. Low-dose caffeine administered in chewing gum does not enhance cycling to exhaustion. *J Strength Cond Res* 2012;26:844–50.
- [60] Oberlin-Brown KT, Siegel R, Kilding AE, Laursen PB. Oral presence of carbohydrate and caffeine in chewing gum: independent and combined effects on endurance cycling performance. *Int J Sports Physiol Perform* 2016;11:164–71.
- [61] Ryan EJ, Kim CH, Fickes EJ, Williamson M, Muller MD, Barkley JE, et al. Caffeine gum and cycling performance: a timing study. *J Strength Cond Res* 2013;27:259–64.
- [62] Lane SC, Hawley JA, Desbrow B, Jones AM, Blackwell JR, Ross ML, et al. Single and combined effects of beetroot juice and caffeine supplementation on cycling time trial performance. *Appl Physiol Nutr Metab* 2013;39:1050–7.
- [63] Paton C, Costa V, Guglielmo L. Effects of caffeine chewing gum on race performance and physiology in male and female cyclists. *J Sports Sci* 2015;33:1076–83.
- [64] Gonçalves L, de Salles Painelli V, Yamaguchi G, Oliveira LF, Saunders B, da Silva RP, et al. Dispelling the myth that habitual caffeine consumption influences the performance response to acute caffeine supplementation. *J Appl Physiol* 2017;123:213.
- [65] Pickering C, Kiely J. What should we do about habitual caffeine use in athletes? *Sports Med* 2018;49:833–42.
- [66] Evans M, Tierney P, Gray N, Hawe G, Macken M, Egan B. Acute ingestion of caffeinated chewing gum improves repeated sprint performance of team sports athletes with low habitual caffeine consumption. *Int J Sport Nutr Exerc Metab* 2018;28:221–7.
- [67] Pickering C, Kiely J. Are the current guidelines on caffeine use in sport optimal for everyone? Inter-individual variation in caffeine ergogenicity, and a move towards personalised sports nutrition. *Sports Med* 2018;48:7–16.
- [68] Skinner TL, Jenkins DG, Coombes JS, Taaffe DR, Leveritt MD. Dose response of caffeine on 2000-m rowing performance. *Med Sci Sports Exerc* 2010;42:571–6.
- [69] Gu L, Gonzalez FJ, Kalow W, Tang BK. Biotransformation of caffeine, paraxanthine, theobromine and theophylline by cDNA-expressed human CYP1A2 and CYP2E1. *Pharmacogenetics* 1992;2:73–7.
- [70] Sachse C, Brockmüller J, Bauer S, Roots I. Functional significance of a C→A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. *Br J Clin Pharmacol* 1999;47:445–9.
- [71] Pataky MW, Womack CJ, Saunders MJ, Goffe JL, D'Lugos AC, El-Sohemy A, et al. Caffeine and 3-km cycling performance: effects of mouth rinsing, genotype, and time of day. *Scand J Med Sci Sports* 2015;26:613–9.
- [72] Salinero JJ, Lara B, Ruiz-Vicente D, Areces F, Puente-Torres C, Gallo-Salazar C, et al. CYP1A2 genotype variations do not modify the benefits and drawbacks of caffeine during exercise: a pilot study. *Nutrients* 2017;9:269.
- [73] Pickering C. Caffeine, CYP1 A2 genotype, and sports performance: Is timing important? *Ir J Med Sci* 2019;188:349–50.
- [74] Alsene K, Deckert J, Sand P, de Wit H. Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology* 2003;28:1694.
- [75] Retej JV, Adam M, Khatami R, Luhmann UF, Jung HH, Berger W, et al. A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clin Pharmacol Ther* 2007;81:692–8.
- [76] Lampe JW, King IB, Li S, Grate MT, Barale KV, Chen C, et al. Brassica vegetables increase and apiceous vegetables decrease cytochrome P450 1A2 activity in humans: changes in caffeine metabolite ratios in response to controlled vegetable diets. *Carcinogenesis* 2000;21:1157–62.

- [77] Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. *Eur J Clin Pharmacol* 1985;28:425–8.
- [78] Ping J, Wang JF, Liu L, Yan YE, Liu F, Lei YY, et al. Prenatal caffeine ingestion induces aberrant DNA methylation and histone acetylation of steroidogenic factor 1 and inhibits fetal adrenal steroidogenesis. *Toxicology* 2014;321:53–61.
- [79] Wendler C, Poulsen R, Fang X. Caffeine induces both short-term and long-term effects on gene expression and DNA methylation in the mouse heart. *FASEB J* 2014;28:542–3.
- [80] Jin B, Park DW, Nam KW, Ph GT, Lee YS, Ryu DY. CpG methylation of the mouse CYP1A2 promoter. *Toxicol Letters* 2004;152:11–8.
- [81] Djordjevic N, Ghotbi R, Bertilsson L, Jankovic S, Akillu E. Induction of CYP1A2 by heavy coffee consumption in Serbs and Swedes. *Eur J Clin Pharmacol* 2008;64:381–5.
- [82] Marques S, Batalha VL, Lopes LV, Outeiro TF. Modulating Alzheimer's disease through caffeine: a putative link to epigenetics. *J Alzheimers Dis* 2011;24 (suppl 2):161–71.
- [83] Burke LM. Caffeine and sports performance. *Appl Physiol Nutr Metab* 2008;33:1319–34.
- [84] Evans SM, Griffiths RR. Dose-related caffeine discrimination in normal volunteers: Individual differences in subjective effects and self-reported cues. *Behav Pharmacol* 1991;2:345–56.
- [85] Karacan I, Thornby JL, Anch AM, Booth GH, Williams RL, Salis PJ. Dose-related sleep disturbances induced by coffee and caffeine. *Clin Pharmacol Ther* 1976;20:682–9.
- [86] Woodman T, Hardy L. The relative impact of cognitive anxiety and self-confidence upon sport performance: a meta-analysis. *J Sports Sci* 2003;21:443–57.
- [87] Reilly T, Edwards B. Altered sleep–wake cycles and physical performance in athletes. *Physiol Behav* 2007;90:274–84.