TITLE
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JOURNAL
International Journal of Sports Physiology and Performance

DATE DEPOSITED
6 September 2017

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Journal:	*International Journal of Sports Physiology and Performance*
Manuscript ID	IJSPP.2017-0312
Manuscript Type:	Invited Brief Review
Keywords:	Ergogenic aids, methylxanthine, endurance exercise, adenosine receptor

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

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Running title: Physiological responses to caffeine

Abstract only word count: 250
Text only word count: 3191
Number of figures: 3
Number of tables: 2

Abstract

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

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

Introduction

Caffeine, a trimethylxanthine, is a ubiquitous socially acceptable drug with no apparent long-term health effects.[1] While there is some evidence that caffeine may improve single[2] and repeated sprint activities,[3] effects are most consistently observed in sustained bouts of high-intensity aerobic exercise.[1] Typical ergogenic doses of 3 – 6 mg·kg^{-1} ingested 30 – 90 minutes prior to exercise have been shown to result in performance increases of up to 6% in events lasting from a few minutes to several hours.[1] The key mechanism by which caffeine is believed to exert its effect is via the antagonism of adenosine receptors, leading to increases in neurotransmitter release, motor unit firing rates, and pain suppression.[4] However, the ubiquitous nature of adenosine receptors, coupled with their ability to produce differential responses depending on the site of action and the receptor subtype involved, has made it difficult to identify the precise mechanisms by which caffeine exerts its ergogenic effect.

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

Methods

Systematic review

The databases of Pubmed, SportDiscus, Science Direct, and Web of Science were searched for peer-reviewed publications (prior to September 2015) containing 'caffeine' in the title and any of the following words in the title or the abstract: 'endurance', 'submaximal', 'aerobic', 'steady state', 'exhaustion', or 'fixed intensity'. Reference lists of those studies that passed the initial screening for potential inclusion in the analysis along with those from relevant review articles[4,27-35] and textbooks[1] were also examined for publications which may have eluded the search of online databases.

Inclusion and exclusion criteria

Studies considered for inclusion in this investigation were limited to those conducted on adult (age: ≥ 18 years) humans, which had adopted double-blind, randomised, crossover designs using a standard effective caffeine dose of 3 – 6 mg·kg^{-1} administered 30 – 90 minutes prior to exercise. Studies examining combinations of supplements were included in the analysis if the experimental design incorporated a caffeine versus placebo comparison.[5,25] In cases where studies had investigated the effects of different caffeine doses,[10,13,18,36] the dose closest to the upper limit of the inclusion range was used in the analysis. Exercise intensities were constrained to those required to elicit 60 – 85% $\dot{V}O_{2max}$, since those intensities span the range typically experienced in prolonged endurance events,[37] and as such, were the most commonly used to evaluate the effects of caffeine on submaximal physiological responses. On those occasions where studies had investigated the effects of caffeine supplementation on several exercise intensities,[19,22,26,36,38] the intensity closest to the middle of the inclusion range was chosen for the analysis. Exercise duration was limited to a minimum of 5 minutes, to provide sufficient time for physiological responses to achieve a steady state; and to a maximum of 30 minutes to reduce any effect that fatigue may have on the results. Studies using bouts of submaximal exercise longer than 30 minutes were included in the analysis if physiological measurements were made within the 5 – 30 minutes inclusion window. In instances where authors had made multiple measurements within the 5 – 30 minutes inclusion window, values closest to the upper limit of 30 minutes were used in the meta-analysis. No inclusion restrictions were placed on potential moderator variables of gender, training status, caffeine habituation, or supplementation method, since previous research has failed to establish whether any of those variables influence the effects of caffeine on endurance performance.[1] However, subgroup meta-analyses were used to investigate potential influences of supplementation method and exercise intensity on the physiological responses to caffeine (see below).

Data extraction

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

Meta-analysis

From an initial search result of 483 studies, 26 met the inclusion criteria for the meta-analysis (Table 1). Meta-analyses were conducted using specialist software (Review Manager Version 5.3. The Nordic Cochrane Centre, Copenhagen: The Cochrane Collaboration, 2014). Meta-analyses were completed using a random-effects model and data are presented as raw mean difference (*D*) with associated 95% confidence limits (CL_{95}). The choice to use *D* rather than a standardized mean difference was based on the fact that each physiological response was measured on the same scale.[40] Moreover, the advantage of using *D* is that it provides an outcome to the analysis which is intuitively meaningful to the reader.[40] Heterogeneity between studies was examined using the I^2 statistic, which describes the percentage of variability in mean difference estimates due to heterogeneity rather than chance. When I^2 was > 25% (25 – 50% represents moderate heterogeneity[41]), a subgroup meta-analysis was completed to investigate the source of heterogeneity. In line with recommendations regarding tests for heterogeneity,[42] CL_{95} for I^2 were calculated using the method outlined by Higgins & Thompson.[43] Subgroup meta-analyses were performed, when appropriate, to investigate the influence of the following potential moderator variables: 1) exercise intensity (constrained to comparisons between the upper ['high intensity'] and lower ['low intensity'] half of the inclusion range); and 2) supplementation method (capsule versus drink formats). Of the remaining potential moderator variables, no comparisons were made to investigate the effects of: 1) exercise mode: since most had used either cycling (n = 17) or running (n = 5) and there was no rationale to expect any differential effects of caffeine; 2) gender: since only one study (2) had used solely female participants; 3) training status: since between-study inconsistences in the way that this variable was reported/measured did not allow quantification with adequate precision; 4) caffeine dose: since most studies (*n* = 21) had used doses of 5 – 6 mg·kg^{-1}; and 5) administration time: since most studies had administered the supplement 60 minutes prior to exercise (*n* = 21). Heterogeneity between subgroups was also evaluated using the I^2 statistic. Statistical significance was accepted at $p < 0.05$ for all analyses.

Results

Heart rate

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

Oxygen uptake

The effects of caffeine on $\dot{V}O_2$ during submaximal exercise are presented in Figure 2. Relative to placebo, caffeine had no significant effect on $\dot{V}O_2$ (*D* = -0.00 L·min^{-1}; CL_{95}[-0.04, +0.03]; *p* = 0.92; *n* = 203) and the level of heterogeneity across the 20 studies that were analysed was low (I^2 = 24%; CL_{95}[0, 56]).

Respiratory exchange ratio

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

Minute ventilation

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

Rating of perceived exertion

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

Blood lactate

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

Blood glucose

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

Discussion

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

The key mechanism by which caffeine is believed to interact with human tissue, and thereby influence endurance performance, is via the antagonism of adenosine receptors.[4,31] If this is the case, it should be possible to resolve all of the responses determined in this meta-analysis by that mechanism. Adenosine is a ubiquitous endogenous extracellular signalling molecule, the concentration of which increases during exercise due to the hydrolysis of adenosine triphosphate.[44,45] Adenosine exerts its effect via its interaction with G-protein coupled cell membrane receptors, widely expressed throughout the body, and of which there are four subtypes (A_1, A_{2A}, A_{2B}, and A_3).[44,45] Although adenosine has the highest affinity for the A_1 and A_{2A} receptor subtypes,[45] the ability of adenosine receptors to activate and inhibit the same signalling cascades[44,45] has made it difficult to identify the precise mechanism by which adenosine exerts its effects. Nevertheless, there is evidence that adenosine signalling affects glucose homeostasis and lipid metabolism,[44] central nervous system function,[46] and cardiovascular and respiratory responses;[47] all of which could explain the physiological responses observed in this meta-analysis.

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

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

One finding from this meta-analysis that is particularly difficult to explain is the lack of any effect of caffeine on RER. Goedecke et al.[55] reported a strong positive correlation ($r = 0.63$) between RER and [BLa] during exercise at 70% $\dot{V}O_{2max}$. As such, it is surprising that despite the fact that caffeine supplementation resulted in a significant increase in [BLa], there was no corresponding increase in RER; in fact, the pattern of the response was towards a reduction in RER. Nevertheless, caffeine did result in an increase in $\dot{V}_{E,}$, a response which could be explained by the buffering response associated with the disruption of acid-base balance, as indicated by the caffeine-induced increase in [BLa].[56] Then again, it is possible to explain the increase in $\dot{V}_E$ by a direct stimulatory effect of caffeine, particularly since caffeine is reported to lower the sensitivity threshold of central chemoreceptors for CO_2;[57] moreover, the fact that adenosine has differential effects on $\dot{V}_E$ depending on the type of adenosine receptor affected,[58] suggests that the response is most likely due to the effect of caffeine on the A_1 receptor subtype.[58] Either way, given that at least part of the caffeine-induced increase in $\dot{V}_E$ is likely due to the drive to reduce CO_2, it is difficult to explain how, in the absence of any corresponding change in $\dot{V}O_2$, that response does not affect RER.

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

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

Conclusion

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

Practical Applications

The positive effects of caffeine supplementation on endurance performance are well-established; particularly when consumed in a dose of 3 – 6 $mg \cdot kg^{-1}$ ingested 30 – 90 minutes prior to exercise.[1] Those performance improvements are accompanied by various physiological responses associated with the corresponding increase in exercise intensity, making it difficult to distinguish performance- from caffeine-related effects. This meta-analysis has revealed clear effects of caffeine on measures of [BLa], [BGl], $\dot{V}_E$, and RPE, independent of any ergogenic effect, which, given its dietary prevalence, reinforces the importance of caffeine restriction prior to any experimental intervention or physiological profile. For researchers, the results of this meta-analysis reinforce the problems associated with the use of small sample sizes, with several instances where individual investigations failed to find significant effects despite clear evidence to the contrary.

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Figure Legends

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

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

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

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

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

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

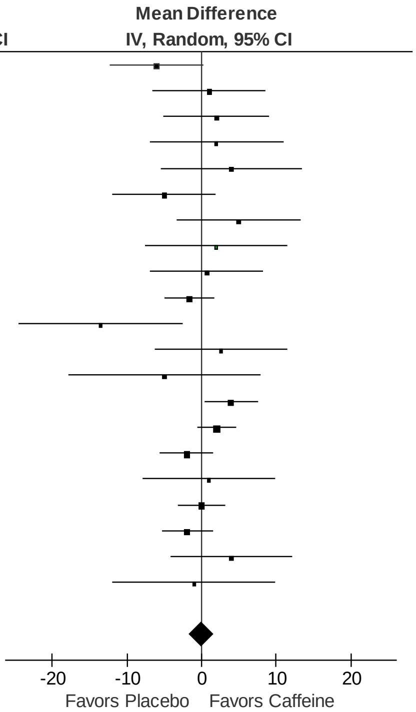
Table 2. Summary of subgroup meta-analyses examining the possible influence of exercise intensity (low intensity: 60 – 72.5% $\dot{V}O_{2max}$ vs high intensity: 72.5 – 85% $\dot{V}O_{2max}$) and supplementation method (capsule vs drink formats) on the effect of caffeine supplementation on various physiological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

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

Note: Values in square parentheses represent 95% confidence limits

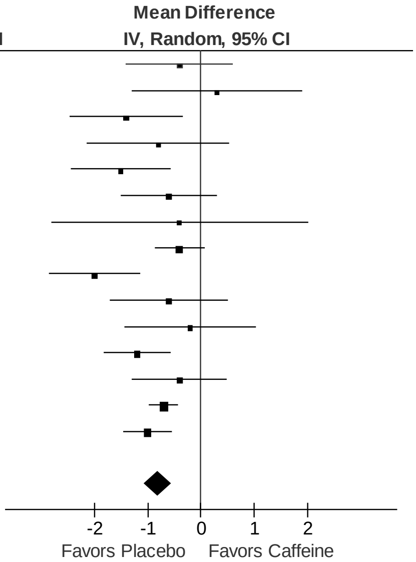
Study or Subgroup	Caffeine Mean	Caffeine SD	Caffeine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Acker-Hewitt et al. (2012)	140	6	10	146	8	10	4.2%	-6.00 [-12.20, 0.20]
Anderson et al. (2000)	153	9	8	152	6	8	3.1%	1.00 [-6.50, 8.50]
Bell & McLellan (2002)	169	10	13	167	8	13	3.5%	2.00 [-4.96, 8.96]
Bell & McLellan (2002)	174	8	8	172	10	8	2.3%	2.00 [-6.87, 10.87]
Bell et al. (1998)	181	9	8	177	10	8	2.1%	4.00 [-5.32, 13.32]
Black et al. (2015)	156	11	14	161	7	14	3.6%	-5.00 [-11.83, 1.83]
Black et al. (2015)	146	12	14	141	10	14	2.7%	5.00 [-3.18, 13.18]
Bruce et al. (2000)	161	11	8	159	8	8	2.1%	2.00 [-7.43, 11.43]
Casal & Leon (1985)	149.8	8.1	9	149.1	8.1	9	3.1%	0.70 [-6.78, 8.18]
Cruz et al. (2015)	161.9	3.6	8	163.5	3.1	8	9.9%	-1.60 [-4.89, 1.69]
Daniels et al. (1998)	132.5	13.9	10	146	10.9	10	1.6%	-13.50 [-24.45, -2.55]
Demura et al. (2007)	146.7	10.8	10	144.1	9.3	10	2.3%	2.60 [-6.23, 11.43]
Doherty et al. (2004)	141	18	11	146	12	11	1.2%	-5.00 [-17.78, 7.78]
Graham et al. (2000)	158	4	10	154	4	10	9.3%	4.00 [0.49, 7.51]
Jenkins et al. (2008)	181	3.4	13	179	3.1	13	12.8%	2.00 [-0.50, 4.50]
McClaran & Wetter (2007)	146	3.5	9	148	4	9	9.4%	-2.00 [-5.47, 1.47]
Roy et al. (2001)	146	11	12	145	11	12	2.3%	1.00 [-7.80, 9.80]
Stadheim et al. (2013)	156	4	10	156	3	10	10.5%	0.00 [-3.10, 3.10]
Stadheim et al. (2014)	142.7	3.4	8	144.6	3.4	8	9.8%	-1.90 [-5.23, 1.43]
Tarnopolsky et al. (1989)	157.3	6.5	6	153.3	7.7	6	2.7%	4.00 [-4.06, 12.06]
Toner et al. (1982)	152	12	8	153	10	8	1.6%	-1.00 [-11.82, 9.82]
Total (95% CI)			**207**			**207**	**100.0%**	**-0.01 [-1.43, 1.42]**

Heterogeneity: $Tau^2 = 2.53$; $Chi^2 = 27.22$, $df = 20$ ($P = 0.13$); $I^2 = 27\%$
Test for overall effect: $Z = 0.01$ ($P = 0.99$)



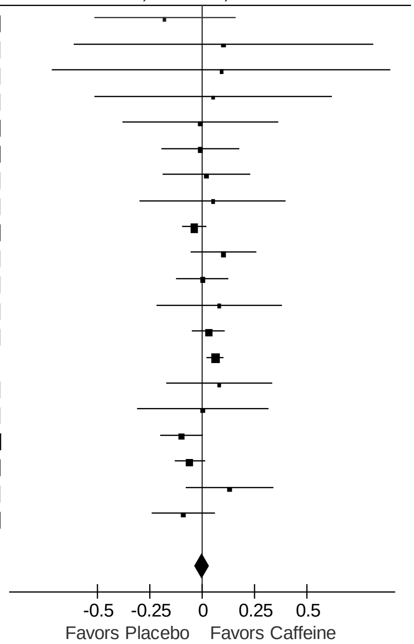
Study or Subgroup	Caffeine Mean	Caffeine SD	Caffeine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Acker-Hewitt et al. (2012)	11.3	1.4	10	11.7	0.8	10	4.8%	-0.40 [-1.40, 0.60]
Anderson et al. (2000)	11.1	1.9	8	10.8	1.3	8	2.2%	0.30 [-1.30, 1.90]
Bell & McLellan (2002)	15.4	1.3	8	16.8	0.8	8	4.4%	-1.40 [-2.46, -0.34]
Bell & McLellan (2002)	16.2	1.4	13	17	2	13	3.0%	-0.80 [-2.13, 0.53]
Black et al. (2015)	12.6	1.3	14	14.1	1.2	14	5.4%	-1.50 [-2.43, -0.57]
Black et al. (2015)	13.4	1	14	14	1.4	14	5.7%	-0.60 [-1.50, 0.30]
Bruce et al. (2000)	10.8	2.4	8	11.2	2.5	8	1.0%	-0.40 [-2.80, 2.00]
Casal & Leon (1985)	11.7	0.5	9	12.1	0.5	9	12.8%	-0.40 [-0.86, 0.06]
Costill et al. (1978)	12.1	0.8	9	14.1	1	9	6.3%	-2.00 [-2.84, -1.16]
Demura et al. (2007)	15	1.3	10	15.6	1.2	10	4.2%	-0.60 [-1.70, 0.50]
Doherty et al. (2004)	12.5	1.3	11	12.7	1.6	11	3.5%	-0.20 [-1.42, 1.02]
Giles & MacLaren (1984)	10.5	0.6	6	11.7	0.5	6	9.3%	-1.20 [-1.82, -0.58]
McClaran & Wetter (2007)	13.4	1	9	13.8	0.9	9	5.9%	-0.40 [-1.28, 0.48]
Stadheim et al. (2013)	14.1	0.3	10	14.8	0.3	10	18.3%	-0.70 [-0.96, -0.44]
Stadheim et al. (2014)	11.8	0.4	8	12.8	0.5	8	13.2%	-1.00 [-1.44, -0.56]
Total (95% CI)			**147**			**147**	**100.0%**	**-0.82 [-1.07, -0.58]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 21.69$, $df = 14$ ($P = 0.09$); $I^2 = 35\%$
Test for overall effect: $Z = 6.53$ ($P < 0.00001$)



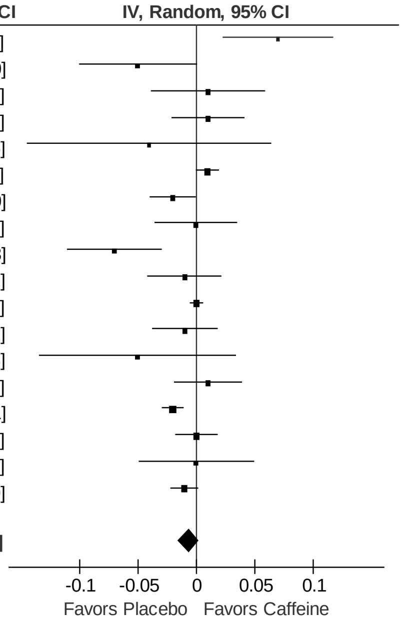
Study or Subgroup	Caffeine Mean	Caffeine SD	Caffeine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Acker-Hewitt et al. (2012)	3.23	0.4	10	3.41	0.36	10	1.0%	-0.18 [-0.51, 0.15]
Anderson et al. (2000)	2.3	0.41	8	2.2	0.94	8	0.2%	0.10 [-0.61, 0.81]
Bell & McLellan (2002)	3.1	0.9	8	3.01	0.73	8	0.2%	0.09 [-0.71, 0.89]
Bell & McLellan (2002)	3.44	0.71	13	3.39	0.75	13	0.4%	0.05 [-0.51, 0.61]
Bell et al. (1998)	3.27	0.34	8	3.28	0.41	8	0.8%	-0.01 [-0.38, 0.36]
Black et al. (2015)	1.88	0.22	14	1.89	0.27	14	3.1%	-0.01 [-0.19, 0.17]
Black et al. (2015)	1.39	0.28	14	1.37	0.28	14	2.5%	0.02 [-0.19, 0.23]
Bruce et al. (2000)	3.56	0.31	8	3.51	0.39	8	0.9%	0.05 [-0.30, 0.40]
Casal & Leon (1985)	2.93	0.06	9	2.97	0.06	9	15.9%	-0.04 [-0.10, 0.02]
Costill et al. (1978)	3.34	0.18	9	3.24	0.15	9	4.2%	0.10 [-0.05, 0.25]
Cruz et al. (2015)	2.72	0.12	8	2.72	0.13	8	6.1%	0.00 [-0.12, 0.12]
Demura et al. (2007)	1.95	0.33	10	1.87	0.35	10	1.3%	0.08 [-0.22, 0.38]
Graham et al. (2000)	3.14	0.08	10	3.11	0.09	10	11.9%	0.03 [-0.04, 0.10]
Jenkins et al. (2008)	3.84	0.05	13	3.78	0.05	13	20.2%	0.06 [0.02, 0.10]
McClaran & Wetter (2007)	2.66	0.27	9	2.58	0.27	9	1.8%	0.08 [-0.17, 0.33]
Olcina et al.(2008)	2.26	0.47	20	2.26	0.53	20	1.2%	0.00 [-0.31, 0.31]
Stadheim et al. (2013)	3.18	0.07	10	3.28	0.14	10	8.5%	-0.10 [-0.20, -0.00]
Stadheim et al. (2014)	3.13	0.08	8	3.19	0.06	8	12.9%	-0.06 [-0.13, 0.01]
Tarnopolsky et al. (1989)	4.44	0.21	6	4.31	0.15	6	2.5%	0.13 [-0.08, 0.34]
Toner et al. (1982)	2.96	0.15	8	3.05	0.15	8	4.5%	-0.09 [-0.24, 0.06]
Total (95% CI)			**203**			**203**	**100.0%**	**-0.00 [-0.04, 0.03]**

Heterogeneity: Tau² = 0.00; Chi² = 25.17, df = 19 (P = 0.16); I² = 24%
Test for overall effect: Z = 0.10 (P = 0.92)



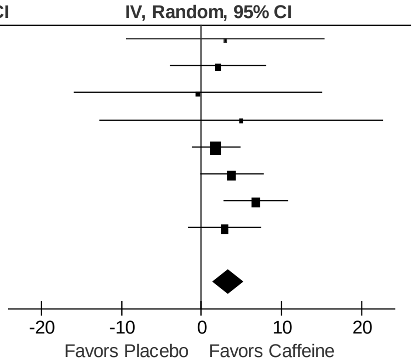
Study or Subgroup	Caffeine Mean	Caffeine SD	Caffeine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Acker-Hewitt et al. (2012)	0.96	0.07	10	0.89	0.03	10	2.7%	0.07 [0.02, 0.12]
Anderson et al. (2000)	0.84	0.04	8	0.89	0.06	8	2.5%	-0.05 [-0.10, -0.00]
Black et al. (2015)	0.97	0.06	14	0.96	0.07	14	2.6%	0.01 [-0.04, 0.06]
Black et al. (2015)	0.94	0.03	14	0.93	0.05	14	4.9%	0.01 [-0.02, 0.04]
Bruce et al. (2000)	0.94	0.09	8	0.98	0.12	8	0.7%	-0.04 [-0.14, 0.06]
Casal & Leon (1985)	0.85	0.01	9	0.84	0.01	9	10.9%	0.01 [0.00, 0.02]
Cruz et al. (2015)	0.93	0.02	8	0.95	0.02	8	7.6%	-0.02 [-0.04, -0.00]
Demura et al. (2007)	0.95	0.04	10	0.95	0.04	10	4.1%	0.00 [-0.04, 0.04]
Giles & MacLaren (1984)	0.85	0.04	6	0.92	0.03	6	3.5%	-0.07 [-0.11, -0.03]
Graham et al. (2000)	0.93	0.03	10	0.94	0.04	10	4.9%	-0.01 [-0.04, 0.02]
Jenkins et al. (2008)	0.99	0.01	13	0.99	0.001	13	11.8%	0.00 [-0.01, 0.01]
McClaran & Wetter (2007)	0.93	0.03	9	0.94	0.03	9	5.5%	-0.01 [-0.04, 0.02]
Olcina et al.(2008)	1.09	0.13	20	1.14	0.14	20	1.0%	-0.05 [-0.13, 0.03]
Roy et al. (2001)	0.94	0.04	12	0.93	0.03	12	5.4%	0.01 [-0.02, 0.04]
Stadheim et al. (2013)	0.96	0.01	10	0.98	0.01	10	11.0%	-0.02 [-0.03, -0.01]
Tarnopolsky et al. (1989)	0.97	0.01	6	0.97	0.02	6	8.2%	0.00 [-0.02, 0.02]
Toner et al. (1982)	0.94	0.05	8	0.94	0.05	8	2.5%	0.00 [-0.05, 0.05]
Van Soeren & Graham (1998)	0.83	0.01	6	0.84	0.01	6	10.2%	-0.01 [-0.02, 0.00]
Total (95% CI)			**181**			**181**	**100.0%**	**-0.01 [-0.01, 0.00]**

Heterogeneity: Tau² = 0.00; Chi² = 54.75, df = 17 (P < 0.00001); I² = 69%
Test for overall effect: Z = 1.33 (P = 0.18)



Study or Subgroup	Caffeine Mean	Caffeine SD	Caffeine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Acker-Hewitt et al. (2012)	77.4	15.9	10	74.4	11.8	10	2.0%	3.00 [-9.27, 15.27]
Anderson et al. (2000)	53.8	6.1	8	51.7	6.1	8	8.4%	2.10 [-3.88, 8.08]
Bell et al. (1998)	108.5	17.7	8	108.9	13.5	8	1.3%	-0.40 [-15.83, 15.03]
Bruce et al. (2000)	99	17	8	94	19	8	1.0%	5.00 [-12.67, 22.67]
Casal & Leon (1985)	81.8	3.4	9	80	3	9	34.0%	1.80 [-1.16, 4.76]
Cruz et al. (2015)	80	3.6	8	76.2	4.3	8	19.8%	3.80 [-0.09, 7.69]
Jenkins et al. (2008)	104.7	5.5	13	97.9	4.8	13	19.0%	6.80 [2.83, 10.77]
McClaran & Wetter (2007)	59.5	6	9	56.6	3.4	9	14.7%	2.90 [-1.61, 7.41]
Total (95% CI)			**73**			**73**	**100.0%**	**3.36 [1.63, 5.08]**

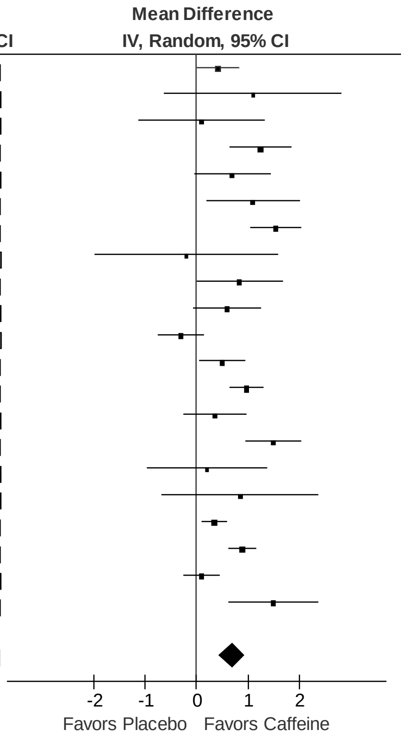
Heterogeneity: Tau² = 0.00; Chi² = 4.48, df = 7 (P = 0.72); I² = 0%
Test for overall effect: Z = 3.81 (P = 0.0001)



Study or Subgroup	Caffeine Mean	Caffeine SD	Caffeine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Acker-Hewitt et al. (2012)	2.17	0.4	10	1.75	0.5	10	6.5%	0.42 [0.02, 0.82]
Bell & McLellan (2002)	5.7	1.8	8	4.6	1.7	8	1.5%	1.10 [-0.62, 2.82]
Bell & McLellan (2002)	5.4	1.2	11	5.3	1.7	11	2.5%	0.10 [-1.13, 1.33]
Bell et al. (1998)	9	0.7	8	7.75	0.5	8	5.3%	1.25 [0.65, 1.85]
Black et al. (2015)	3.7	1	14	3	1	14	4.4%	0.70 [-0.04, 1.44]
Black et al. (2015)	4.5	1.4	14	3.4	1	14	3.7%	1.10 [0.20, 2.00]
Cruz et al. (2015)	7.55	0.52	8	6.01	0.47	8	5.9%	1.54 [1.05, 2.03]
Demura et al. (2007)	4.7	1.75	10	4.9	2.29	10	1.4%	-0.20 [-1.99, 1.59]
Giles & MacLaren (1984)	3.62	0.62	6	2.78	0.83	6	4.0%	0.84 [0.01, 1.67]
Graham & Spriet (1995)	4.26	0.69	8	3.66	0.64	8	4.9%	0.60 [-0.05, 1.25]
Graham et al. (1998)	2.8	0.3	9	3.1	0.6	9	6.2%	-0.30 [-0.74, 0.14]
Graham et al. (1998)	2.9	0.6	9	2.4	0.3	9	6.2%	0.50 [0.06, 0.94]
Graham et al. (2000)	3.17	0.45	10	2.2	0.24	10	6.9%	0.97 [0.65, 1.29]
Greer et al. (2000)	4.14	0.65	8	3.78	0.59	8	5.2%	0.36 [-0.25, 0.97]
Jenkins et al. (2008)	9.7	0.7	13	8.2	0.7	13	5.6%	1.50 [0.96, 2.04]
Olcina et al.(2008)	4.12	1.82	20	3.92	1.95	20	2.7%	0.20 [-0.97, 1.37]
Roy et al. (2001)	3.75	2.15	12	2.9	1.6	12	1.9%	0.85 [-0.67, 2.37]
Stadheim et al. (2013)	3.5	0.25	10	3.15	0.29	10	7.3%	0.35 [0.11, 0.59]
Stadheim et al. (2014)	2.42	0.32	8	1.53	0.21	8	7.2%	0.89 [0.62, 1.16]
Tarnopolsky et al. (1989)	2.58	0.35	6	2.48	0.26	6	6.8%	0.10 [-0.25, 0.45]
Van Soeren & Graham (1998)	4.6	0.9	6	3.1	0.6	6	3.8%	1.50 [0.63, 2.37]
Total (95% CI)			**208**			**208**	**100.0%**	**0.69 [0.46, 0.93]**

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 77.14$, df = 20 ($P < 0.00001$); $I^2 = 74\%$

Test for overall effect: $Z = 5.76$ ($P < 0.00001$)



Study or Subgroup	Caffeine Mean	Caffeine SD	Caffeine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Acker-Hewitt et al. (2012)	4.3	0.49	10	4.16	0.53	10	5.0%	0.14 [-0.31, 0.59]
Bell & McLellan (2002)	3.1	0.5	11	3.2	0.7	11	4.2%	-0.10 [-0.61, 0.41]
Bell & McLellan (2002)	4	0.5	8	3.3	0.3	8	5.6%	0.70 [0.30, 1.10]
Bell et al. (1998)	4.73	0.11	8	4.23	0.09	8	11.3%	0.50 [0.40, 0.60]
Cruz et al. (2015)	4.42	0.28	8	3.92	0.28	8	7.8%	0.50 [0.23, 0.77]
Giles & MacLaren (1984)	4.68	0.69	6	4.2	0.63	6	2.4%	0.48 [-0.27, 1.23]
Graham & Spriet (1995)	5.89	0.41	8	4.74	0.25	8	6.7%	1.15 [0.82, 1.48]
Graham et al. (1998)	4.3	0.5	9	4	0.4	9	5.3%	0.30 [-0.12, 0.72]
Graham et al. (1998)	4.7	0.5	9	4.3	0.5	9	4.8%	0.40 [-0.06, 0.86]
Graham et al. (2000)	5.57	0.15	10	5.07	0.15	10	10.7%	0.50 [0.37, 0.63]
Greer et al. (2000)	3.85	0.27	8	3.84	0.14	8	9.1%	0.01 [-0.20, 0.22]
Roy et al. (2001)	5.6	0.65	12	5.45	0.65	12	4.1%	0.15 [-0.37, 0.67]
Stadheim et al. (2013)	4.8	0.1	10	4.5	0.1	10	11.4%	0.30 [0.21, 0.39]
Tarnopolsky et al. (1989)	5.19	0.36	6	4.5	0.21	6	6.7%	0.69 [0.36, 1.02]
Van Soeren & Graham (1998)	3.89	0.22	6	3.5	0.52	6	4.9%	0.39 [-0.06, 0.84]
Total (95% CI)			**129**			**129**	**100.0%**	**0.42 [0.29, 0.55]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 55.50$, df = 14 ($P < 0.00001$); $I^2 = 75\%$

Test for overall effect: $Z = 6.36$ ($P < 0.00001$)