The Plymouth Student Scientist - Volume 03 - 2010 The Plymouth Student Scientist - Volume 3, No. 2 - 2010

2010

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Marshall, K.

Marshall, K. (2010) 'The effect of different dosages of caffeine on time to exhaustion in prolonged exercise in trained athletes (a meta analysis)', The Plymouth Student Scientist, p. 18-39.

http://hdl.handle.net/10026.1/13911

The Plymouth Student Scientist
University of Plymouth

*The Plymouth Student Scientist, 2010, **3**, (2), 18-39*

The effect of different dosages of caffeine on time to exhaustion in prolonged exercise in trained athletes (a meta analysis)

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Abstract

Background
The world anti doping organisation removed caffeine from the banned list of substances in 2004; yet, research shows over recent years caffeine has become one of the most widely used ergogenic aids by athletes in the UK. This analysis investigates one of the suggested ergogenic benefits of caffeine, increasing time to exhaustion, and whether this effect relates to specific dosages of caffeine ingested before exercise.

Objectives
To assess the effects of two different dosages of caffeine on trained athlete's time to exhaustion in endurance exercise.

Search methods
"caffeine" and "time to exhaustion" were entered into Pubmed, Scirus and Google Scholar. "Humans, randomised, double blind trial" were entered as limiters. The search was completed using the Athens log in through the University of Plymouth on 29 January 2010.

Selection criteria
Randomised, double blind trials which reported the effects of ingesting dosages of caffeine of either 3-6 mg per kg of body weight (mg/kg) or 9-13mg/kg and a placebo for time to exhaustion in prolonged exercise were used in this meta analysis.

Data collection and analysis
The data was extracted by the author using strict inclusion criteria. The mean difference with 95% confidence intervals, fixed effects was analysed using RevMan 5 for time to exhaustion when ingesting either caffeine or the placebo one hour before exercise.

Main results
Thirty studies were available via the University of Plymouth subscription. Six were eligible as having the correct inclusion criteria and measuring the correct endpoints.

Overall, caffeine increased time to exhaustion in comparison to the placebo with a mean increase of **11.94 minutes**

The dose range 3-6mg/kg had a significant effect on time to exhaustion in comparison to the placebo with a mean increase of **11.99 minutes.**

The dose range 9-13mg/kg also had a significant effect on time to exhaustion when compared to the placebo with a mean increase of **11.81 minutes**.

There was no significant difference between the mean differences for the two dose ranges and so the smaller dose (3-6 mg/kg) of caffeine produced a similar effect on time to exhaustion as the larger dose (9-13mg/kg).

Conclusions

Caffeine significantly increased time to exhaustion in comparison to the placebo across all studies. There was no dose- response relationship evident for the effects of caffeine on time to exhaustion. Due to the side effects noted for caffeine doses residing in the higher range (9-13mg/kg), it may be more beneficial for athletes to ingest doses in the lower range (3-6mg/kg), as the adverse effects may surpass the ergogenic benefits.

Background

Overview of caffeine

Caffeine is a drug of wide social acceptance and is used around the world with up to 90% of adults consuming it in their everyday lives (Burke, 2008). Caffeine is a member of the methylxanthine group and enters all tissues, crossing the blood brain barrier and reaching peak concentrations 30-60 minutes after ingestion (Paluska, 2003). Caffeine is metabolised in the liver by cytochrome P450 1A2 and paraxanthine constitutes more than 80% of its metabolites (Graham and Spriet, 1995). It is thought to increase energy, improve performance and reduce fatigue and due to its safety and popularity, caffeine has become one of the most widely used ergogenic aids by athletes (Graham, 2001).

Caffeine and time to exhaustion

This meta analysis focused on one of the suggested ergogenic benefits of caffeine, increasing time to exhaustion following prolonged exercise. It has been suggested that caffeine is of ergogenic benefit when given one hour before endurance exercise lasting between 30-120 minutes (Tarnopolsky and Cupido, 2000). This has been supported by various studies including Costill *et al* (1978) who showed that ingestion of methylxanthine caffeine resulted in increased power output and prolonged work. In another study, in which subjects ingested either a placebo or caffeine (9mg/kg) one hour before exercise, the time to exhaustion increased from 49.2 minutes for the placebo to 71.0 minutes for caffeine (Graham and Spriet, 1995, Graham and Spriet, 1991). However, despite the large numbers of studies suggesting there is an ergogenic effect of caffeine use prior to engaging in endurance exercise, other studies have failed to show significant effects. For example, Powers *et al* (1983) examined time to exhaustion on a cycle ergometer for 7 trained male runners. The subjects received 5mg/kg of caffeine one hour prior to testing and no significant effects were detected for time to exhaustion. Also, in another study, 7 moderately trained male athletes were tested for VO_{2max} and time to exhaustion on a cycle ergometer. After ingesting 3-5mg/kg caffeine one hour prior to testing, caffeine had no effect on exercise performance (Dodd *et al*., 1991).

Different dosages of caffeine and time to exhaustion

The dosages of caffeine investigated in previous studies have ranged from 1-15 mg of caffeine/kg of body mass (Bell and McLellan, 2002). Pasman *et al* (1995) found that 5, 9 or 13 mg/kg of caffeine produced significant but quite similar ergogenic benefits when performing endurance cycling. Bruce *et al* (2000) found that dosages of 6 to 9 mg/kg were equally effective in increasing performance/power in a simulation of 2000m rowing. It has been suggested that dosages between 3-6 mg/kg produce an equivalent ergogenic effect to higher dosages; (Graham, 2001) and so the optimal dose lies in this lower range.

How caffeine may increase time to exhaustion

There have been three main mechanisms proposed for explaining how caffeine can increase time to exhaustion in prolonged exercise. Firstly, there is the glycogen sparing hypothesis suggesting that when caffeine is ingested before exercise, there is increased fatty acid mobilisation and oxidation. This then results in muscle glycogen being preserved and so helps to prolong time to exhaustion (Costill *et al*., 1978). This theory was first thought to result from caffeine causing increased levels

of epinephrine to be released from the adrenal medulla (Costill *et al*., 1978). However, due to recent research showing inconsistencies in this theory, it is thought that caffeine's ergogenic benefits are not dependent on epinephrine, preserving glycogen or enhanced fat metabolism (Graham et al., 1998, Graham and Spriet, 1995, Jackman et al., 1996)

Secondly, there is the theory that caffeine increases calcium release from the sarcoplasmic reticulum, which enhances muscular contraction and endurance *in vitro* (Plaskett and Cafarelli, 2001). However, the concentration of caffeine needed to generate calcium release that would have significant ergogenic effects *in vivo* could cause adverse advents that may compromise performance (Kalmar and Cafarelli, 1999).

The primary mechanism of action of caffeine is that it acts as an A_1 and A_{2a} adenosine receptor antagonist (Fredholm et al., 1999). The resultant cascade of cellular events that follow adenosine receptor blockade include increased dopamine and noradrenaline release, have been suggested as key regulatory mechanisms to explain the ergogenic effects of caffeine (such as time to exhaustion) (Bell and McLellan, 2002).

Why is it important to do this meta analysis?

One study carried out by Chester and Wojek (2008) in the UK in found that out of 480 sports competitors, a third of track and field athletes and sixty percent of cyclists reported taking caffeine before competing. The results showed that the use of caffeine as an ergogenic aid in the UK is high. Also, it is thought there is now a more widespread use and greater acceptance of caffeine in competitive sport especially at elite level (Chester and Wojek, 2008).

These results are significant because in 2004, the World Anti Doping Agency (WADA, 2009) removed caffeine from the prohibited list of substances and onto the monitored list. The reasons behind this decision were such factors as caffeine being metabolised at different rates in individuals. Also, some experts believe that as caffeine is ubiquitous in beverages and food, if the threshold was reduced to unmask cheaters, there might be a serious risk of sanctioning athletes for social or diet consumption of caffeine (WADA, 2009).

Since caffeine has been removed from the list of banned substances, there have been greater opportunities for athletes to use caffeine as a training and competitive aid. This means that some athletes may be gaining unfair advantages over others which could go undetected.

This meta analysis is therefore important to show whether caffeine does have an overall positive effect on time to exhaustion as the results from different studies are inconsistent. It also investigated whether a dose response relationship of caffeine on time to exhaustion exists. The results of this meta analysis could also provide evidence to whether caffeine does significantly impact on this area of performance and whether the decision of WADA to classify caffeine down to a monitored substance was correct.

Objectives

1. To determine the overall effect of caffeine on time to exhaustion in prolonged exercise in trained athletes.
2. To determine whether caffeine's effect on time to exhaustion varies according to the dose ingested.

Methods

Criteria for considering studies for this meta analysis

Identification of studies by electronic searches
Studies were found by searching Pubmed, Scirus and Google Scholar using the key words "caffeine" and "ergogenic effects" with the limits of "humans, randomised double blind trial." Many of the studies looked at caffeine and time to exhaustion so the search was narrowed to this topic. The search did yield a large number of studies, but was restricted due to the limitations of subscription by the University of Plymouth to certain journals.

Selection of studies
One of the main aims of this meta analysis was to keep the participants and methodologies as similar as possible. The studies all had to reach strict inclusion criteria and if the study did not fulfil all of the criteria listed, it was excluded.

Types of study
Only randomised, double blind trials were used in the meta analysis. The studies were limited to those that used humans.

Types of participants
Men and women ≥ 19 years of age who trained regularly in their discipline were included in the analysis. In all studies, the subjects abstained from caffeine for ≥12 hours to make sure limited caffeine was present in the body before the test. As the subjects were recruited to the studies on the basis of their ability in their sport rather than uniformity in their caffeine habits, the habitual use of caffeine for the participants had to be stated. Participants must have participated in both caffeine and placebo trials in order to act as their own controls.

Types of interventions
Studies were included if they tested the effect of ingesting caffeine doses in the ranges of (3-6mg/kg) or (9-13 mg/kg) in controlled exercise tests (using cycle ergometers or treadmills) lasting 25 minutes or more. The efficacy of caffeine on time to exhaustion was compared against a placebo in each study. The studies had to specify they were testing time to volitional exhaustion and researchers did not stop the tests themselves. Also, studies were included if they were looking at the effect of one dose of caffeine before exercise, not repeated dosages.

Outcomes measured
The primary outcome measured was the overall mean difference in time to exhaustion between caffeine and placebo trials for prolonged exercise. The exercise test had to be performed at a steady rate at the level of 80-85% VO_2 max

for each individual. The secondary outcomes measured were the differences in time to exhaustion for prolonged exercise for two different dose ranges of caffeine 3-6mg/kg and 9-13mg/kg. These two dose ranges were used as these have been the most widely investigated and discussed in previous research.

Data collection and analysis

Data extraction and management

The studies that matched the inclusion criteria were put into an inclusion table stating their main characteristics. Some studies investigated the effect of more than one dose of caffeine. If the doses investigated lay in the specified ranges of 3-6mg/kg or 9-13mg/kg, they were used in the analysis individually.

Measures of treatment effect

The mean, standard deviation and number of participants for both caffeine and placebo groups for all the doses were entered into RevMan 5. Firstly, RevMan calculated a weighted mean average in order to show the effects of individual studies as a contribution to the total. As the data was continuous (each individual's outcome was a measurement of numerical quantity) fixed effects models using inverse variance and 95% confidence intervals were used to calculate the mean difference between caffeine and placebo trials for time to exhaustion. The results were presented in forest plots. In a forest plot, the area of the block indicates the weight assigned to the study (Figures 1-3). The larger the area of the block, the greater weight the study has in the meta analysis. Therefore, a large block would dominate the calculation of the pooled result more than a smaller block. The horizontal line either side of the block depicts the 95% confidence interval. The confidence interval indicates where 95% of the results from the study would be expected to lie (Cochrane, 2010). RevMan was then used to calculate heterogeneity by measuring I^2.

This whole process was repeated for two more analyses. The first used dosages in the range of 3-6mg/kg. The second used dosages in the range of 9-13mg/kg. The overall mean differences calculated for time to exhaustion for the two dose ranges were then compared using a one way ANOVA (unstacked) on Mini Tab 15.

A funnel plot was also constructed for the overall effect of all caffeine doses on time to exhaustion. This was in order to assess publication bias. Cochrane (2010) advises that tests for funnel plot asymmetry should only be used when there are at least 10 studies included in the meta-analysis. If there are fewer studies the power of the tests are too low to distinguish chance from real asymmetry. This is why a funnel plot was only carried out for comparison one.

Results

Description of studies

Results of the search

The search yielded 52 studies but due to limitations in the subscription of the University of Plymouth to scientific journals, only 30 were available for the meta analysis.

Included studies
Six studies which matched all the inclusion criteria were included in the meta analysis. All the studies tested the effects of caffeine on time to exhaustion in prolonged exercise, although the main aim of the studies differed as seen in Table 1. The main characteristics of the included studies are outlined in Table 2. There were 11 individual trials for different doses of caffeine within the 6 studies as shown in Figure 1. A total of 202 participants, both male and female aged between 19-34 years were used in the analysis. Six trials with 122 participants contributed to the low dose comparison (3-6mg/kg) (Figure 2) and 5 trials with 80 participants to the high dose comparison (9-13mg/kg) (Figure 3).

Excluded studies
Twenty four studies were excluded because they did not match the inclusion criteria. The reasons for exclusion from the analysis are shown in Table 3.

Effects of interventions

Comparison 1: Overall effect across all studies of caffeine on time to exhaustion
Trial results were divided into 2 groups based on the results for mean difference and the 95% confidence intervals shown in Figure 1. It was clear there was no significant difference within group 1 (trials 1,3,4,6 and 11) and within group 2 (trials 2, 5,7,8,9 and 10) (Figure 1). The mean differences from group 1 were significantly higher than the mean differences of group 2. This indicates that the results from group 1 showed a greater positive effect of caffeine on time to exhaustion than group 2.

The overall standardised mean increase in time to exhaustion calculated using the fixed effects model was 11.94 minutes in favour of caffeine ($P< 0.00001$). There was significant heterogeneity ($I^2 = 78\%$, $P < 0.00001$).

Comparison 2: Effect of 3-6mg/kg of caffeine on time to exhaustion in prolonged exercise
Trial results were divided into 2 groups based on the results for mean difference and the 95% confidence intervals shown in Figure 2. It was clear there was no significant difference within group 1 (trials 1, 4, 5) and within group 2 (trials 2, 3 and 6) (Figure 2). The mean differences from group 2 were significantly higher than the mean differences from group 1. This indicates that the trials from group 2 showed a greater positive effect of caffeine on time to exhaustion than group 1.

The overall standardised mean increase in time to exhaustion calculated using the fixed effects model was 11.99 minutes in favour of caffeine ($P<0.00001$). There was significant heterogeneity ($I^2 = 85\%$) ($P = 0.00001$).

Comparison 3: Effect of 9-13mg/kg of caffeine on time to exhaustion in prolonged exercise
Trial results were divided into two groups based on the results for mean difference and the 95% confidence intervals shown in Figure 3. It was clear there was no significant difference within group 1 (trials 1 and 3) and within group 2 (trials 2, 4 and 5) (Figure 3). The mean differences from group 2 were significantly higher than the mean differences from group 1. This indicates that the trials from group 2 showed a greater positive effect of caffeine on time to exhaustion than group 1.

The overall standardised mean increase in time to exhaustion calculated using the fixed effects model was 11.81 minutes in favour of caffeine (P< 0.00001) (Figure 3). There was significant heterogeneity (I^2= 67%) (P=0.02).

Comparison 4: Comparing the mean differences for the two dose ranges 3-6mg/kg and 9-13mg/kg
The overall mean differences calculated for doses 3-6mg/kg and 9-13mg/kg were not significantly different (Figure 4). This shows that the effects of the two different doses on time to exhaustion are not significantly different.

The data for comparison 1 was plotted using a funnel plot (figure 5). This was asymmetrical and 95% of the trials did not lie within the funnel defined by the straight lines. This demonstrated publication bias.

Discussion

Overall completeness and applicability of evidence
From the results it can be concluded that all caffeine doses significantly increase time to exhaustion when taken one hour before prolonged exercise. This is supported by other studies such as Costill *et al* (1978) who reported caffeine ingested one hour before exhaustive exercise significantly enhanced performance among competitive cyclists. Additional research offers further support for this idea and demonstrates that caffeine improves time to exhaustion and performance during prolonged, moderate to high intensity exercise lasting 30-120 minutes (Graham, 2001, Greer *et al*., 2000, Jackman *et al*., 1996).

In this meta analysis, varying the dose of caffeine had no effect on time to exhaustion as there was no significant difference between ingesting either 3-6mg/kg or 9-13mg/kg (P = 0.946). This idea is additionally supported by Plaskett and Cafarelli (2001) who found no dose response relation for caffeine and time to exhaustion . One study found cycling time to be increased by an average of 27% for all caffeine dosages used. However, for each dose investigated (5, 9, 13 mg/kg) no dose-response relation was found (Pasman et al., 1995). These results are also in agreement with another study that concluded no dose response relation exists between caffeine and time to exhaustion (Cadarette et al., 1983). However, there is a significant difference between time to exhaustion for placebo and caffeine trials.

It appears once caffeine gets to a certain level in the blood, the P450 enzymes in the liver that metabolize caffeine become saturated (Schepsis and Busconi, 2006). This is believed to be around 9mg/kg and so doses above this would not cause an increase in time to exhaustion.

Nonetheless, some researchers do suggest that a dose response relationship does exist (Handel, 1983, James, 1991). The reason for this inconsistency may be due to one factor that could have acted as a confounding variable in this analysis- habitual caffeine use. Participants were recruited to studies on the basis of their athletic ability rather than their caffeine habits. The daily caffeine ingestion of participants ranged from non users to consuming up to 500mg/kg a day (Graham *et al*., 1998). This could have impacted on the results as one study showed when subjects received the same dose of caffeine relative to their body mass, the magnitude and

duration of the ergogenic effect was different between users and nonusers of the drug (Bell and McLellan, 2002). The authors suggested that this was due to caffeine acting as an A_1 and A_{2a} adenosine antagonist (Fredholm, 1995) and regular consumption of caffeine was associated with the up regulation of adenosine receptors in the vascular and neural tissues of the brain (Fredholm *et al*., 1999). Therefore, the same concentration of caffeine may block a greater percentage of adenosine receptors for nonusers and lead to a greater ergogenic effect. Contrary to this view, another study reported that there was no direct relationship between caffeine habits and the ergogenic response to 9mg/kg of caffeine. However, those subjects that were the lightest users of caffeine had their poorest response after the higher doses and complained of confusion (Graham and Spriet, 1995). Thus, one might expect that lower doses of caffeine (3-6mg/kg) produce greater ergogenic effects for non users and higher doses of caffeine (9-13mg/kg) have greater ergogenic benefits for users. Future research could investigate the dose-response relationship between caffeine and exercise for users and non users as these values have yet to be clarified. The same method could be used as described by Bell and McLellan (2002) but the caffeine dose could be varied instead of the hours between caffeine ingestion and exercise.

Reasons why Graham (2001) may support the idea that the optimal dose of caffeine for time to exhaustion lies in the lower range (3-6mg/kg) may be due to side effects reported for higher doses. Some known side effects of caffeine are dizziness, headaches, hunger sensations, insomnia and diuresis (McDuff and Baron, 2005). Pasman *et al* (1995) reported that side effects were worse during and after the exercise tests for participants ingesting high doses of caffeine (9 and 13 mg/kg). Therefore, ingestion of lower doses of caffeine may be better for athletes as the adverse effects from higher doses may surpass the ergogenic benefits (Paluska, 2003). Studies have also shown doses as low as 2mg/kg to be of ergogenic benefit for sports performance (Cox *et al*., 2002, Kovacs *et al*., 1998). Future research could investigate whether a lower dose than 3mg/kg of caffeine has a positive effect on time to exhaustion.

Quality of the evidence variation

In an attempt to account for the inconsistencies in research for caffeine and time to exhaustion, Conlee (1991) listed a number of experimental factors that are important to control in these types of studies. These include: caffeine dose, type of exercise, exercise intensity, pre-exercise feedings, subject training status, previous caffeine use and individual differences in metabolism. Variation in these factors and/or failure to control for these may be responsible for contradictory results reported in this area of research (Conlee, 1991). The strengths of this meta analysis were that the majority of these factors were controlled. For example, caffeine doses were split into two ranges 3-6mg/kg and 9-13mg/kg and participants were all trained in their disciplines. One study has shown that the effect of caffeine is independent of the exercise modality, as in one study trained runners exercised longer on both a bicycle and treadmill after caffeine ingestion (Graham and Spriet, 1991). This supports that exercise modality was not a limiting factor in this analysis and even though some tests used cycle ergometers (Graham *et al*, 1998) and others treadmills (Bell and McLellan, 2002) the validity of the results should not be affected. There were also different withdrawal periods from caffeine before the trials e.g. Graham *et al* (1998) 24 hours and Van Soeren and Graham (1998) 48 hours.

However, research has reported the length of caffeine abstinence does not affect the ergogenic benefits of caffeine and would not be a limiting factor. For example, one study found that withdrawing from caffeine for 0,2,12,24 or 48 hours before ingesting 5mg/kg of caffeine did not alter metabolic responses to steady state exercise (Hetzler *et al*., 1994). In another study, participants were instructed to habituate to coffee drinking and then withdraw for either 0, 2 or 4 days before ingesting 6mg/kg of caffeine and completing an exercise test. The days of withdrawal had no effect on the magnitude of caffeine's ergogenic impact on endurance exercise (Van Soeren and Graham, 1998).

It is difficult to control for training status as no two individuals will have an identical level of fitness. However, in this analysis, each study contained practice trials in order to identify the power output needed for each participant to be exercising at their individual 80-85% VO_2 max. For example, Graham *et al* (1998) had a pre experimental protocol in which each subject performed a practice trial consisting of 20-30 minutes running on a treadmill at a workload predicted to require 85% of the VO_2max. The O_2 consumption was then measured to confirm the selection was correct. In another study, a pre experimental test was completed in order to find each individual's relationship between VO_2 and power output. From this relationship the power output equivalent to 80% VO_2 max was used in subsequent trials on the same ergometer (Bell and McLellan, 2002). As long as each individual was exercising at their individual 80-85% VO_2 max, reliable comparisons could be made between study participants for time to exhaustion.

Therefore, the original objectives were fulfilled to a large extent in this meta analysis as it was found all doses of caffeine increased time to exhaustion, and there was no significant difference between the effects for caffeine doses of 3-6mg/kg and 9-13mg/kg. Nonetheless, it can be argued that the objectives were not completely fulfilled as not all the factors stated by Conlee (1991) were controlled for and this may have led to inconsistencies and increased heterogeneity. Heterogeneity will always exist in a systematic review as there is clinical and methodological diversity due to different studies being brought together (Cochrane, 2010). The I_2 test was used in this analysis which expresses the amount of heterogeneity as a percentage with 25%, 50% and 75% being used to describe heterogeneity as low, moderate and high (Higgins *et al*., 2003). There was significant heterogeneity in this analysis due to the values all being high (comparison 1= 78%, comparison 2 = 85%, comparison 3= 67%). One factor already discussed that may have contributed to the high heterogeneity was the varied caffeine habits of the participants. Also, there may have been too much variation between individuals meaning the results were too diverse to be compared. This may have been because both males and females were used with ages ranging between 19-34 years which is quite a large variation. It has also been found that women using oral contraceptives may have a rate of caffeine metabolism that is relatively slowed (Gilbert, 1992). There is a distinct lack of studies investigating only females and the effect of caffeine on time to exhaustion as most investigate only males or both genders. Further research needs to be carried out to see whether there are specific gender differences with caffeine metabolism. Only six studies matched all the inclusion criteria for the analysis and so only 202 participants were included. If a larger range of data had been analysed, the level of heterogeneity may have been further reduced.

For most humans, the mean elimination half life of caffeine is from 3-7 hours with more than 90% of caffeine being removed from the body in 12 hours (James, 1991). However, the half life can be influenced by a variety of factors and this demonstrates how there may be considerable individual and group variation in metabolism which may have contributed to heterogeneity. One cause of the variation in the rate of caffeine metabolism is inherited metabolic differences (Wilson and Temple, 2004). Other factors such as the use of certain drugs and smoking can also influence caffeine's metabolic rate (Weinberg and Bealer, 2002). These factors were not consistently controlled across studies used in this meta analysis and so future research should employ tighter control for these factors and should consider them when creating exclusion criteria for their study.

Publication bias

The significant publication bias found in this meta analysis may have been due to different factors (Figure 5). Firstly, there were no large studies present with the highest number of participants for an individual study being 21. Larger studies are generally thought to be more precise and lead to less bias. Secondly, not only were small studies used, they all showed a positive effect of caffeine on time to exhaustion. No negative results were included which may be due to studies showing these types of results remaining unpublished and so the reviewer could not obtain these articles. Due to the absence of this unpublished data, the meta analysis may have significantly over estimated the intervention effect (Cochrane, 2010). A deeper, stronger study could be created by contacting authors in hopes of attaining raw unpublished data. A second researcher could also be used to extract the data from studies and then make decisions on discrepancies. Another way to reduce bias would be to have the reviewer extracting the data blinded to the possible outcomes.

Conclusions

In conclusion, the ergogenic effect of caffeine increasing time to exhaustion was reported for all caffeine dosages. For the lower (3-6mg/kg) and higher dose (9-13mg/kg) ranges investigated, no dose response relation was found. Although, 3-6mg/kg may be recognised as a more suitable dose for athletes as doses in the higher range may cause side effects which may have a negative impact on performance.

As caffeine use is in on the increase in UK athletes and significant effects have been shown for all doses and time to exhaustion in this analysis, it could be argued that caffeine should no longer remain on the WADA monitored list and be re classified as a banned substance for competitive athletes.

Acknowledgements

Many thanks to Professor Waleed Al-Murrani BVM&S, Dip, PhD (Quant, Genetics, & Biostatistics) at the School of Biomedical & Biological Sciences at the University of Plymouth who provided guidance in statistical analysis and interpretation in this meta analysis.

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Included studies, excluded studies, additional studies

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Table 1- Shows the main aims of the 6 studies used in this meta analysis. Even though the aims vary, all studies measured the same outcome, the effect of caffeine on time to exhaustion.

Authors	Year	Title	Aim
Graham et al	1998	Metabolic and exercise endurance effects of coffee and caffeine ingestion.	The main aim of the study was to exam the impact of ingestion of the same dose of caffeine as a capsule of in coffee.
Bell and McLellan	2002	Exercise endurance 1, 3, and 6 hours after caffeine ingestion in caffeine users and non users.	The purpose of this study was to examine the duration of caffeine's ergogenic effect and see whether it differs between users and nonusers of the drug.
Van Soeren and Graham,	1998	Effect of caffeine on metabolism, exercise endurance and catecholamine responses after withdrawal.	In this study the main aim was to look at the effects of acute caffeine ingestion on exercise performance, hormonal (epinephrine, norepinephrine, insulin), and metabolic (free fatty acids, glycerol, glucose, lactate, expired gases) parameters during short-term withdrawal from dietary caffeine.
Graham and Spriet	1995	Metabolic, catecholamine and exercise performances to various doses of caffeine.	The main aim was to investigate the exercise responses of well-trained endurance athletes to various doses of caffeine to evaluate the impact of the drug on exercise metabolism and endurance capacity.
Pasman et al	1995	The effect of different dosages of caffeine on endurance performance time.	The main aim was to investigate the effect of different dosages of caffeine (0-5-9-13 mg.kg body weight^{-1}) on endurance performance.
Graham and Spriet,	1991	Performance and metabolic responses to high caffeine doses during prolonged exercise.	The aim was to analyse the performance and metabolic responses to high caffeine doses during prolonged exercise.

Table 2- Characteristics of included studies. Note: RDB= Randomised double blind trial. M= male. F = female.
In all studies, the participants took part in both caffeine and placebo trials and so acted as their own controls. No co interventions were used.

Study	RDB	M/F	Mean Age (yrs)	Subjects	Method of measuring Exhaustion Time	Placebo	Habitual use of caffeine	Method of caffeine and timing of intake
1. Metabolic and exercise endurance effects on caffeine and caffeine ingestion **Graham et al, 1998**	RDB	8 M 1 F	27.8 22	Trained endurance runners	Ran on treadmill until voluntary exhaustion. Power output equivalent to ~85% of $VO_{2\,max}$	Dextrose capsules	Abstain from caffeine 24 hours before trial. Caffeine habits before 1 abstainer and 2 very light users (<100 mg/day) to moderate users(<500 mg/day).	**4.45 mg /kg** of body weight of caffeine capsule. Intake= 1 hr before trial.
2. Exercise Endurance 1, 3, and 6 Hours After Caffeine Ingestion in Caffeine Users and Non-users **Bell and McLellan, 2002**	RDB	15 M 6 F	32±7 yrs	All trained in aerobic activities and had a cycle ergometer $VO_{2\,max}$ of 51 ± 8 ml · kg^{-1} · min^{-1}.	Ride to exhaustion at 80% $VO_{2\,max}$ 60 and 100 revolutions/min on cycle ergometer	Placebo not stated.	Refrain from products containing caffeine for 12 h before each trial. 13 caffeine users (ingesting ≥ 300 mg caffeine day) and 8 nonusers (ingesting < 50 mg caffeine day)	**5 mg/kg** of caffeine capsule ingested with Gatorade. Intake =1 hr before trial.
3. Effect of caffeine on metabolism, exercise endurance, and catecholamine responses after withdrawal	RDB	6 M	36.7 ± 4.2	Recreational athletes cycling or running 5 times a week for at least one year	Time to exhaustion measured 80-85% $VO_{2\,max}$ on a cycle ergometer	Placebo-dextrose tablets.	Subjects required to abstain from caffeine for 48 hours before trial. Average daily caffeine consumption from all sources equivalent to 761.3 ± 11.8 mg/day	caffeine **6 mg/kg** Intake=1 hr before trial

Van Soren and Graham, 1998								
4. Metabolic, catecholamine and exercise performance responses to varying doses of caffeine **Graham and Spriet, 1995**	RDB	8M	19-34 yrs	Well trained distance runners	Ran on treadmill where speed and slope equivalent to ~ 85% VO_{2max} to voluntary exhaustion	3,6,9 mg/kg body weight dextrose gelatine capsules	Subjects withdrew from all dietary sources of caffeine for 48 h before each of four tests. Daily ingestion of caffeine ranged from 0 – 940 mg/day with two being nonusers and three others consuming < 200mg/day.	Gelatine capsules **3mg/kg** **6 mg/kg** **9 mg/kg** of caffeine. Intake=1 hr before exercise.
5. The effect of different dosages of caffeine on endurance performance time **Pasman et al, 1995**	RDB	9 M and 1 F	22.1 ±2.8	Well trained cyclists	Cycled until exhaustion at 80% Wmax on electromagnetically braked cycle ergometer	Placebo (0mg CAF kg body weight) capsules	During pre testing days, refrain from caffeine consumption, no caffeine present in body before exercise test. Varying Caffeine consumption of subjects 5 subjects= 100-250mg caffeine day 4 subjects above 250mg caffeine per day	Capsules containing: **5 mg/kg** **9 mg/kg** **13 mg/kg** of caffeine. Intake=1 hr before exercise.
6. Performance and metabolic responses to high caffeine dose during prolonged exercise **Graham and Spriet, 1991**	RDB	1 F 6 M	28.3 ± 2.3	Seven trained distance runners	Ran or cycled to exhaustion at 85%VO_{2max}	Placebo, 9mg/kg placebo (dextrose)	2 ingested 450-720mg/day 3 ingested 120-150mg/day 2 nonusers <20mg.day Not asked to fast before trials as not typical race prep. Instructed to eat as they would for race.	Caffeine **9mg/kg** Ingestion = 1 hr before trial,

Table 3- Characteristics of excluded studies

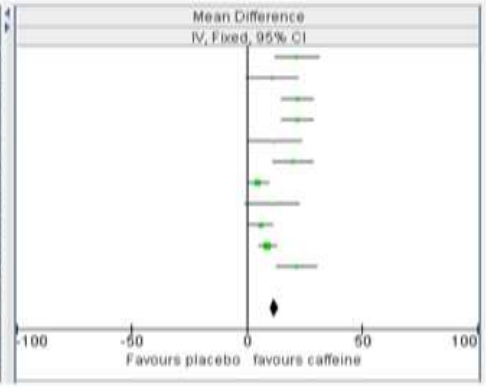
Excluded study	**Reason for exclusion**
Study	**Reason for exclusion**
Bangsbo *et al*, 1992	The study looked at the effect of increasing caffeine doses over a 6 week period on exercise performance.
Bell *et al*, 2001	The study looked at con intervention of caffeine ingestion with ephedrine.
Bell and McLellan, 2003	The study looked at the effect of ingesting repeated doses of caffeine.
Bruce *et al*, 2000	The study investigated the effect of caffeine doses on 2000m rowing performance, not time to exhaustion.
Conway *et al*, 2003	The study looked at the effect of divided caffeine doses on exercise instead of a single dose.
Cox *et al,* 2002.	The study did not measure the effect of one caffeine dose alone.
Doherty and Smith, 2005	The study only measured rate of perceived exertion and not time to exhaustion.
Falk *et al*, 1989	The participants in the study did a 40km march before the trial and so did not rest for 1 hour before the exercise test.
Graham *et al*, 2000	The study did not measure time to exhaustion.
Greer *et al*, 2000	The study investigated the effect of caffeine in a co intervention with theophylline
Jackman *et al*, 1996	The study investigated only short term intense exercise lasting 4 minutes and under.
LeBlanc *et al*, 1985	The study only measured the effect of caffeine on resting metabolic rate.
McClaran and Wetter, 2007	The study did not measure the effect of caffeine on time to exhaustion.
McNaughton, 1986	The study did not measure a constant rate of prolonged exercise. Exercise increased with intensity over time
Meyers *et al*, 2005	The study looks at the effect of caffeine on motor

	unit firing and not time to exhaustion.
Norager *et al,* 2005	The study uses 75 yr old participants who are out of the age range and also not trained athletes.
Plaskett and Cafarelli, 2001	This study did not state whether they used trained athletes.
Powers *et al*, 1983	This was a single blind trial and so could not be used in the analysis.
Spriet *et al,* 1992	The study used a single blind approach with the first trial always being placebo and the second always being caffeine.
Talia *et al*, 2001	The study looks the effect of ingesting caffeine and a co intervention e.g. fat and carbohydrates.
Toner *et al*, 1982	The study did not use only trained athletes but a combination on trained and untrained athletes.
Wemple *et al*, 1997	The study did not investigate the effect of caffeine on time to exhaustion.
Williams *et al*, 1988	The study investigated the effect of caffeine on short term high intensity exercise.
Yeo *et al*, 2005	The study did not measure the effect of caffeine on time to exhaustion.

FIGURES

Figure 1 (comparison 1)*

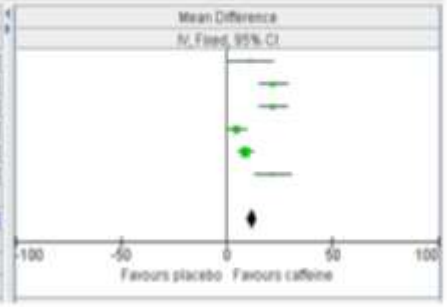
	Study or Subgroup	caffeine Mean	caffeine SD	caffeine Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1	a) Graham and Spriet,1991	71	11	7	49.2	7.2	7	4.1%	21.80 [12.06, 31.54]
2	a) Pasman et al, 1995	58	11	9	47	13	9	3.2%	11.00 [-0.13, 22.13]
3	a)Graham and Spriet, 1995	71.4	9	8	49.4	4.2	8	8.3%	22.00 [15.12, 28.88]
4	b) Graham and Spriet,1995	71.4	9	8	49.4	4.2	8	8.3%	22.00 [15.12, 28.88]
5	b) Pasman et al, 1995	59	12	9	47	13	9	2.9%	12.00 [0.44, 23.56]
6	b)Graham and Spriet, 1991	59.3	9.9	7	39.2	6.5	7	5.1%	20.10 [11.33, 28.87]
7	Bell + McLellan,2002	29.8	8.6	21	24	6.5	21	10.4%	4.80 [0.19, 9.41]
8	c) Pasman et al, 1995	58	12	9	47	13	9	2.9%	11.00 [-0.56, 22.56]
9	c)Graham and Spriet,1995	55.6	6.2	8	49.4	4.2	8	14.5%	6.20 [1.01, 11.39]
10	Graham et al, 1998	41	5	9	32	3	9	27.0%	9.00 [5.19, 12.81]
11	Van Soeren + Graham, 1998	81.1	6.7	6	59.5	8.4	6	5.3%	21.60 [13.00, 30.20]
	Total (95% CI)			101			101	100.0%	11.94 [9.96, 13.92]
	Heterogeneity: Chi² = 44.78, df = 10 (P < 0.00001); I² = 78%								
	Test for overall effect: Z = 11.93 (P < 0.00001)								



Forest plot of comparison 1: All caffeine doses vs Placebo, outcome: time to exhaustion (mins). All caffeine doses showed a more significant increase on time to exhaustion in comparison to the placebo.

Figure 2 (Comparison 2)*

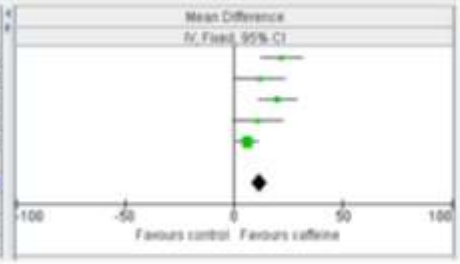
	Study or Subgroup	caffeine Mean	caffeine SD	caffeine Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1	a) Pasman et al, 1995	58	11	9	47	13	9	4.5%	11.00 [-0.13, 22.13]
2	a)Graham and Spriet, 1995	71.4	9	8	49.4	4.2	8	11.7%	22.00 [15.12, 28.88]
3	b) Graham and Spriet,1995	71.4	9	8	49.4	4.2	8	11.7%	22.00 [15.12, 28.88]
4	Bell + McLellan,2002	28.8	8.6	21	24	6.5	21	26.2%	4.80 [0.19, 9.41]
5	Graham et al, 1998	41	5	9	32	3	9	38.3%	9.00 [5.18, 12.81]
6	Van Soeren + Graham, 1998	81.1	6.7	6	59.5	8.4	6	7.5%	21.60 [13.00, 30.20]
	Total (95% CI)			81			81	100.0%	11.99 [9.63, 14.35]
	Heterogeneity: Chi² = 32.78, df = 5 (P < 0.00001); I² = 85%								
	Test for overall effect: Z = 9.97 (P < 0.00001)								



Forest plot of comparison 2: 3-6mg/kg of caffeine vs Placebo, outcome: time to exhaustion (mins). Ingesting caffeine doses within the range of 3-6mg/kg had a significant increase on time to exhaustion in comparison to the placebo.

Figure 3 (Comparison 3)*

	Study or Subgroup	caffeine Mean	caffeine SD	caffeine Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1	a) Graham and Spriet,1991	71	11	7	49.2	7.2	7	13.9%	21.80 [12.08, 31.54]
2	b) Pasman et al, 1995	58	12	9	47	13	9	9.9%	12.00 [0.44, 23.56]
3	b)Graham and Spriet, 1991	59.3	9.9	7	39.2	6.5	7	17.2%	20.10 [11.33, 28.87]
4	c) Pasman et al, 1995	58	12	9	47	13	9	9.9%	11.00 [-0.56, 22.56]
5	c)Graham and Spriet,1995	55.6	6.2	8	49.4	4.2	8	49.1%	6.20 [1.01, 11.39]
	Total (95% CI)			40			40	100.0%	11.81 [8.17, 15.45]
	Heterogeneity: Chi² = 11.98, df = 4 (P = 0.02); I² = 67%								
	Test for overall effect: Z = 6.37 (P < 0.00001)								



Forest plot of comparison 3: 9-13mg/kg of caffeine vs Placebo, outcome: time to exhaustion (mins). Ingesting caffeine doses within the range of 9-13mg/kg had a more significant increase on time to exhaustion than the placebo.

* Total= the number of participants for each intervention group.

```
                                Individual 95% CIs For Mean Based on
                                Pooled StDev
Level       N    Mean  StDev  -------+---------+---------+---------+--
3-6mg/kg    3  11.990  2.360   (---------------*---------------)
9-13mg/kg   3  11.810  3.640  (---------------*---------------)
                                -------+---------+---------+---------+--
                                     9.0      12.0      15.0      18.0

Pooled StDev = 3.068
```

Figure 4- A one way ANOVA (unstacked) for doses 3-6mg/kg and 9-13mg/kg. The mean differences and the 95% confidence intervals for each dose are not significantly different as they both overlap each other. The overall p value for the test was **0.946** which further shows the two doses are not significantly different.

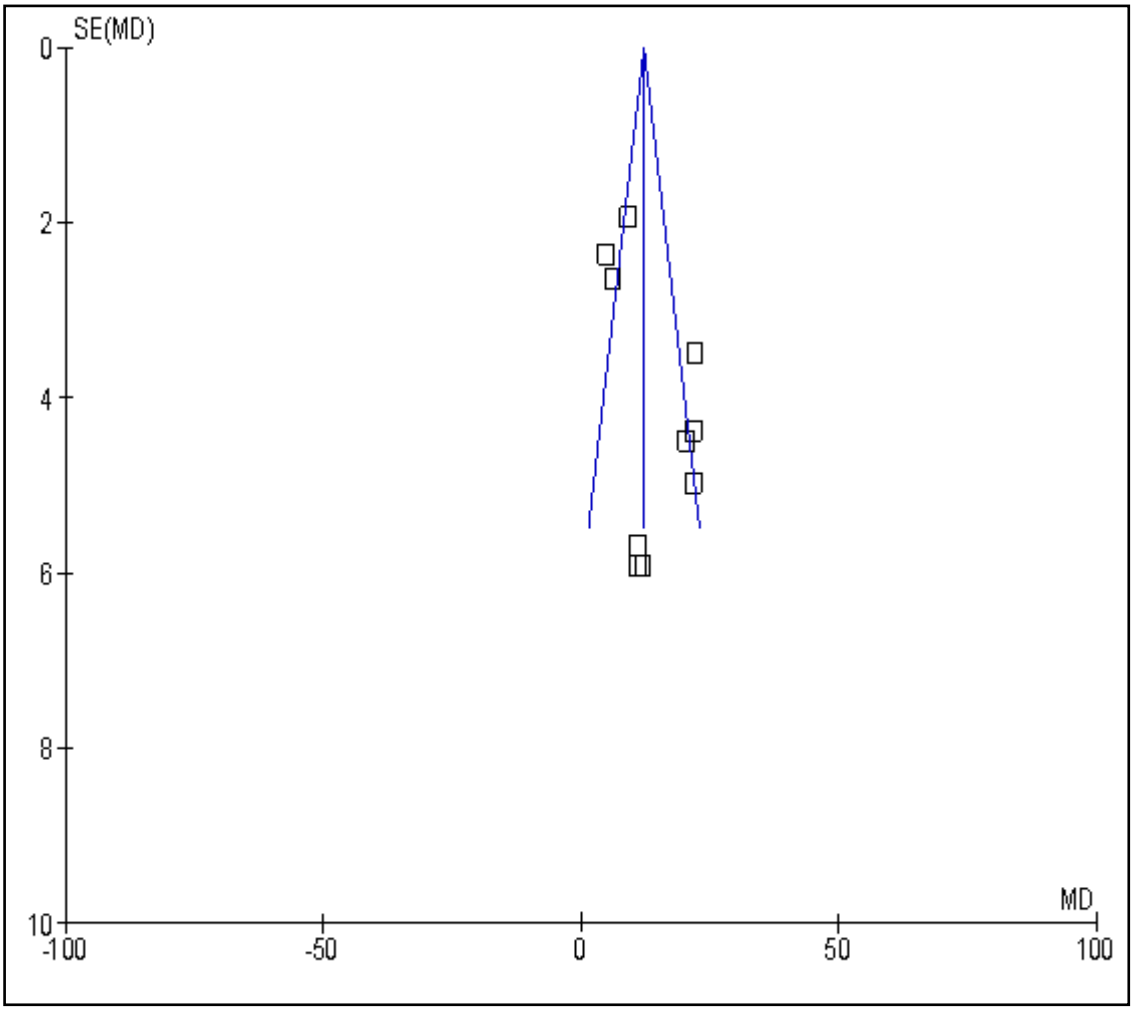


Figure 5- Funnel plot of comparison 1: All doses of Caffeine vs. Placebo, outcome: time to exhaustion.