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Review

Establishing a relationship between the effect of caffeine and duration of endurance athletic time trial events: A systematic review and meta-analysis

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ABSTRACT

Objectives: Caffeine has well-documented benefits on endurance athletic performance. Because of caffeine's ergogenic effects of reducing perceived fatigue, it is hypothesized that as duration of athletic event increases, so will the effect size of caffeine upon performance. This study aims to examine the relationship between duration of endurance athletic event and the effect size of caffeine compared to placebo for athletic performance.
Design: A systematic review and meta-analysis of placebo-controlled trials assessing the effects of caffeine in adults performing endurance athletic events.
Methods: We searched MedLine, Web of Science, and review article references published through March 2016. We performed meta-analyses on placebo-controlled trials to determine the effect of the duration of an endurance athletic event on the standardized mean difference (Cohen's d) between the caffeine and placebo groups for athletic performance.
Results: Forty articles including 56 unique comparison groups were included. Pooled results showed a Cohen's d of 0.33 (95% CI = 0.21, 0.45; p = 1.00; I^2 = 0%). The effect of the duration of athletic event was significantly associated with Cohen's d (Relative Risk: 0.005; 95% CI = 0.001, 0.009; p = 0.024). For a 30 min increase in duration of the athletic event, Cohen's d will increase by 0.150.
Conclusions: This study is the first to report on the statistical finding that the effect size of caffeine increases along with the increasing duration of the time trial event. Endurance athletes may especially benefit from caffeine for performance enhancement.
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1. Introduction

Caffeine is a chemical naturally found in coffee, tea, and cocoa and is also commonly added to a variety of products marketed for improved sports performance. Caffeine has been touted as an ergogenic aid for over a century and is currently used by over 80% of endurance athletes.[1] Currently permitted in competition at any dose, except limited by the National Collegiate Athletic Association (NCAA), caffeine users generally practice moderate consumption—3–6 mg/kg, generally the equivalent of about 2–3 cups of coffee prior to performance. Extreme endurance athletes, such as ultra-marathoners and IRONMAN triathletes, also tend to consume caffeine during their events, typically in the form of carbohydrate-based gels, sodas, and sports drinks.[1]

Caffeine is readily absorbed by the gastrointestinal tract, with a serum peak of 30–60 min and a long half-life of 4–6 h.[2] Caffeine's active metabolites paraxanthine, theobromine, and theophylline have longer half-lives up to 12 h, prolonging many of the same effects of caffeine[3] and making caffeine potentially a useful aid for endurance events.

Caffeine's various mechanisms of action as an ergogenic aid are primarily rooted in its stimulatory effect on the central nervous system through the antagonistic effect on adenosine receptors.[4] Adenosine is a neurotransmitter that signals a cascade of effects, one of the most profound of which is the promotion of drowsiness, increasing perceived exertion; this fatigue is reversed by caffeine.[5] Adenosine inhibits the release of dopamine, thereby reducing mental alertness and motivation important in athletic competitions; caffeine's antagonism of adenosine prevents these hindrances by

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enhancing dopamine availability.[6] With its slow clearance, caffeine is thus poised as a powerful defense against adenosine's performance-inhibiting effects during endurance events where time to fatigue is a significant predictor of success.

Not only does caffeine work as an indirect stimulant by antagonizing adenosine, it also promotes the release of the powerful stimulant epinephrine from the adrenal glands, which speeds the rate of muscle contraction, increases heart rate, and increases release of free fatty acids for energy.[7] Additionally, metabolites of caffeine, though less understood, show ergogenic potential as receptor antagonists to the calming inhibitory neurotransmitter γ-aminobutyric acid (GABA) and promoters of intracellular calcium release to increase muscular firing speed.[8]

Though caffeine has an array of potential benefits, its ergogenic capacity may be limited by its potential adverse effects. Though its stimulation of epinephrine has the theoretical glycogen-sparing effect of enhancing use of free fatty acids, this benefit has been shown to be nullified likely by epinephrine's other action of speeding the breakdown of glycogen, which in turn reduces these integral energy stores.[9] While temporarily blocking adenosine-triggered fatigue, excess caffeine can cause anxiety and tremors.[10] Its stimulation of the sympathetic nervous system can cause gastrointestinal distress.[11] Furthermore, habitual caffeine use promotes the compensatory mechanism of the central nervous system in which more adenosine receptors are created, causing a tolerance effect whereby more caffeine becomes necessary to receive its desired effects.[12] Likewise, with additional adenosine receptors, a more profound lethargy is experienced when caffeine is withdrawn after habitual use. Headache and irritability are other hallmark symptoms of caffeine withdrawal.[13]

Despite these potential limitations of caffeine as an ergogenic aid, research has well substantiated the benefits of the chemical in athletic performance, both in anaerobic high-intensity events[14] and also more strongly in endurance events where the inhibition of fatigue is an especially profound benefit.[15] Currently, two systematic reviews exist on its benefits in endurance events. In their groundbreaking meta-analysis, Doherty and Smith[15] reviewed 40 articles and 76 effect sizes and showed a mean improvement of 12.3% with a 13.8% standard deviation compared to placebo (95% CI, 9.1–15.4%) with doses 3–13 mg/kg. However, the researchers did not describe how they differentiated the endurance events from the shorter events but only noted that endurance events benefited more from caffeine than the shorter ones. Building upon this review, Ganio et al.[16] published a systematic review that only included endurance performances, which they defined as being 5 min and longer. They also found rather consistent, though more modest, benefits of caffeine ($3.2 \pm 4.3\%$) in their review of 21 articles with 33 effect sizes.

Since this most recent review, research has continued to focus on caffeine's effects in endurance performance, using novel methodologies to examine a variety of caffeinated products, different sports, and additional physiological outcome measures to help elucidate caffeine's biological mechanisms. What has yet to be examined, however, is whether a relationship exists between the duration of the athletic event and the relative ergogenic benefit of caffeine. It is possible that the increasing role of fatigue in diminishing performance over time inhibits performance at a quicker rate than the declining serum concentration of caffeine. Given the long half-life of caffeine and the many athletic events lasting far longer than 5 min, this is an important consideration that could help inform evidence-based sports nutrition practices.

The purpose of this systematic review is to examine the relationship between duration of athletic event and the effect size of caffeine compared to placebo. Because of caffeine's ergogenic effects of reducing perceived fatigue, it is hypothesized that as duration of athletic event increases, so also will the effect size of caffeine upon performance. This review will also discuss research trends and recent novel studies, in addition to proposing areas where more research is warranted.

2. Methods

The electronic databases MedLine and Web of Science were searched for studies evaluating the effects of caffeine on athletic performance, published between August 2007 and March 2016. MeSh search terms included "caffeine", "endurance", "athletic performance", "aerobic", and "sport". Please see Supplemental Appendix I for the full search strategy. Additionally, we reviewed reference lists of the two existing systematic reviews, Ganio et al.[16] and Doherty and Smith[15], for additional references. Doherty and Smith[15] excluded articles before 1975, and Ganio et al.[16] conducted their search on all articles through August 2007. These reviews used similar, yet less stringent search and inclusion criteria than this current review. Thus, this review includes relevant articles published through March 2016. Additional search strategies involved scanning reference lists of review articles identified.

After exclusion of duplicate citations, a first round of article review was completed by JS. Studies were eligible for inclusion if they were from peer-reviewed publications in the English language with laboratory or tightly-controlled, placebo-controlled trials involving adults performing an endurance time trial at maximal effort (that is, measuring time to complete a workload, or measuring a workload completed in a given time) exceeding five minutes in duration and included an oral caffeine condition where the effects of caffeine could be isolated.

During a second round of review, two reviewers (two of JS, MB, JC) independently assessed each publication for further inclusion; the third resolved discrepancies if necessary. Articles were excluded from the next round of data extraction if a Cohen's d was not reported or if data, such as the means and standard deviations of the caffeine and placebo group's performance, were unavailable to calculate the Cohen's d. Authors were contacted for additional information if possible.

Two reviewers (two of JS, MB, JC) independently extracted all study data; the third resolved discrepancies if necessary. Data were entered into separate Excel spreadsheets and then imported into SAS V9.4 where they were compared for differences. Once all discrepancies were resolved, a single dataset was produced. For each included study, we extracted author's name, year of publication, study design, mean and standard deviations (or standard errors, depending on which was reported) of performance for the caffeine and placebo groups, duration of the athletic event in minutes, VO_2 max (in ml/kg/min if possible), sample size of each group, sex, mean age, caffeine dose in mg/kg, amount of time caffeine was given prior to the athletic event, and type of athletic event.

The main study outcome was Cohen's d, a measure of effect size that indicates a standardized difference between two group means. Cohen's d was either reported directly or calculated using the means and standard deviations of the performance measure for the caffeine and placebo groups. The main independent variable of interest was performance duration, defined as the length of time of the athletic event. The inclusion criterion for endurance was greater than or equal to five minutes and was the selected cut-off for performances to be considered "endurance". This allowed all events to rely primarily upon the same aerobic mechanisms of energy production, as there is a shift in relative contribution towards aerobic pathways of energy production versus anaerobic pathways that occurs near 2 min of athletic event.[17] Performance could be measured in two ways, as the amount of work that was performed in a set duration of time or as the amount of time taken to com-

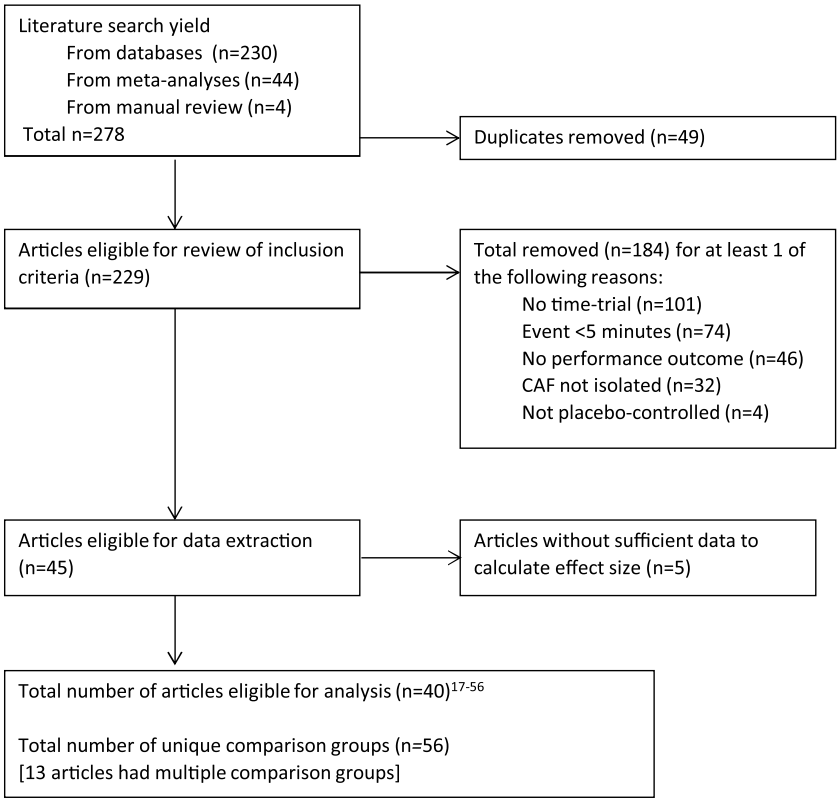


Fig. 1. Flow diagram of the article selection process.

plete a set athletic event. Cohen's d standardized the differences in means between the two placebo and caffeine groups so differences in units used to measure performance in each study did not affect the outcome. We took care to capture the appropriate direction of the effect. If the time to complete a set performance decreased with caffeine as compared to placebo, it was considered a positive effect, whereas if the work completed in a set time trial increased with caffeine as compared to placebo, it was considered a positive effect. Sex was captured as the proportion of males. The time before caffeine was administered is measured in minutes. Type of athletic event was classified in a binary response of cycling or not cycling.

Continuous study characteristics were reported as mean ± standard deviation (SD) unless otherwise noted. The frequency of categorical variables was also reported. We assessed heterogeneity using Cochran's Q to measure the inconsistency of individual study results and the I^2 statistic to identify the percentage of variation across individual studies that is due to true heterogeneity rather than chance. If the Cochran's Q test was statistically significant or the higher the I^2 statistic, there was evidence to suggest the presence of heterogeneity and a random effects model was used. Else, a fixed effects model can be used. A forest plot was constructed to illustrate this heterogeneity of individual study effect sizes compared to the pooled effect size. We assessed potential publication bias by examining a funnel plot, a simple scatter plot with Cohen's d on the x-axis and standard error on the y-axis. The Physiotherapy Evidence Database (PEDro) scale[18] was used to critically analyze each study's internal validity.

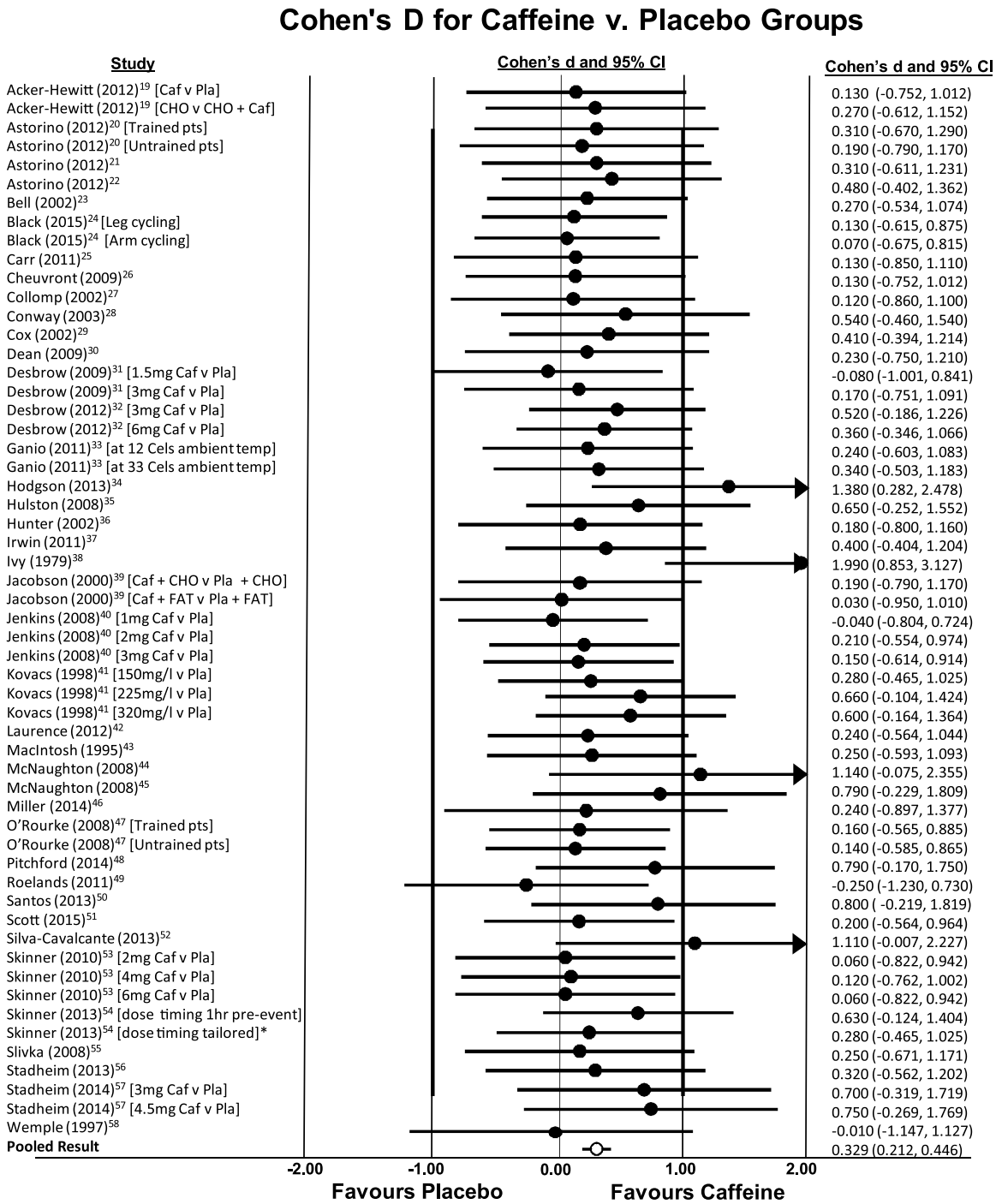
Meta-regression was conducted using linear regression to assess the association of athletic event duration and difference in performance between the caffeine groups and placebo groups. Independent associations with Cohen's d were explored for all potential covariates, including the duration of the athletic event, VO_2 max, sex, age, caffeine dose, amount of time prior to the athletic event that caffeine was administered, and type of athletic event. Interaction terms were also explored to assess the possible modification of the effect of duration by both VO_2 max and caffeine dose. To select a final model, we used a stepwise selection procedure, including only those covariates significantly associated with Cohen's d. Covariates were included in the models as study averages, and each study was weighted based on sample size. All hypothesis tests were two-sided and conducted at the $\alpha = 0.05$ level.

We used SAS V9.4 for descriptive statistics and Comprehensive Meta-Analysis V3.0 for all other tests.

The Harvard University Institutional Review Board declared this study exempt with a not human subjects research determination.

3. Results

A total of 278 citations were identified: 230 through the database searches, 44 through the existing meta-analyses, and 4 through reference lists of review articles. Of those identified, 229 were unique and were assessed for eligibility. A total of 184 were excluded for at least 1 of the following reasons: 101 did not include a time-trial, 74 included athletic events of duration less than five minutes, 46 had no performance outcome, 32 were not able to isolate the effects of caffeine, and 4 were not placebo-controlled. This left 45 studies eligible for data extraction. During the extraction process, five articles were further excluded due to a lack of sufficient data to calculate the effect size (Cohen's d), and we were unable to receive the necessary data from authors. Overall, this led to 40 articles included for analysis.[19–58] Within these 40 studies, we identified 56 unique comparison groups, as 13 articles reported on multiple groups. For example, if a study looked at three groups, such as placebo, 3 mg/kg caffeine, and 6 mg/kg caffeine, and we were able to compare both of the caffeine groups individually to the placebo group, then we disaggregated the results and reported on the multiple comparison groups. See Fig. 1 for full flow of article selection.



Abbreviations: Caf= caffeine; CHO= carbohydrate; Pla= placebo; Pts= participants; Cels= Celsius
*These trials examined Caf v Pla taken at a time before the event that would cause the participant's Caf serum to be highest at the start of the event, as opposed to the other trials in the study[55] where Caf or Pla were taken 1hr prior to the event.

Fig. 2. Forest plot of individual and pooled effect sizes.

All studies identified were blinded, placebo-controlled crossover design. This analysis represents 582 adults, each receiving a caffeine dose and a placebo dose prior to exercise. Across the 56 comparison groups, there were an average of 10.4 (SD: 2.7) participants, 92.8% of which were male and the mean age was 26.3 (SD: 4.7) years old. Cycling was the athletic event in 44 (78.6%) of studies, and the overall mean duration of the athletic event was 34.3 (SD: 28.7) min. The mean dose of caffeine administered was 5.0 (SD: 2.0) mg/kg and it was, on average, administered 65.5 (SD: 25.0) min prior to the athletic event. See Supplemental Table 1 for more details on included studies. The studies had a mean PEDro score of 9.5 out of 10 (SD = 1.0), indicating strong internal validity.

Overall for the 56 study groups, 4 had negative results (placebo group performed better than caffeine group) and 52 had positive results. The range of the percent difference between the caffeine and placebo group was −3.0% to 15.9%. The average percent difference for all 56 studies was 2.9% (SD: 2.7).

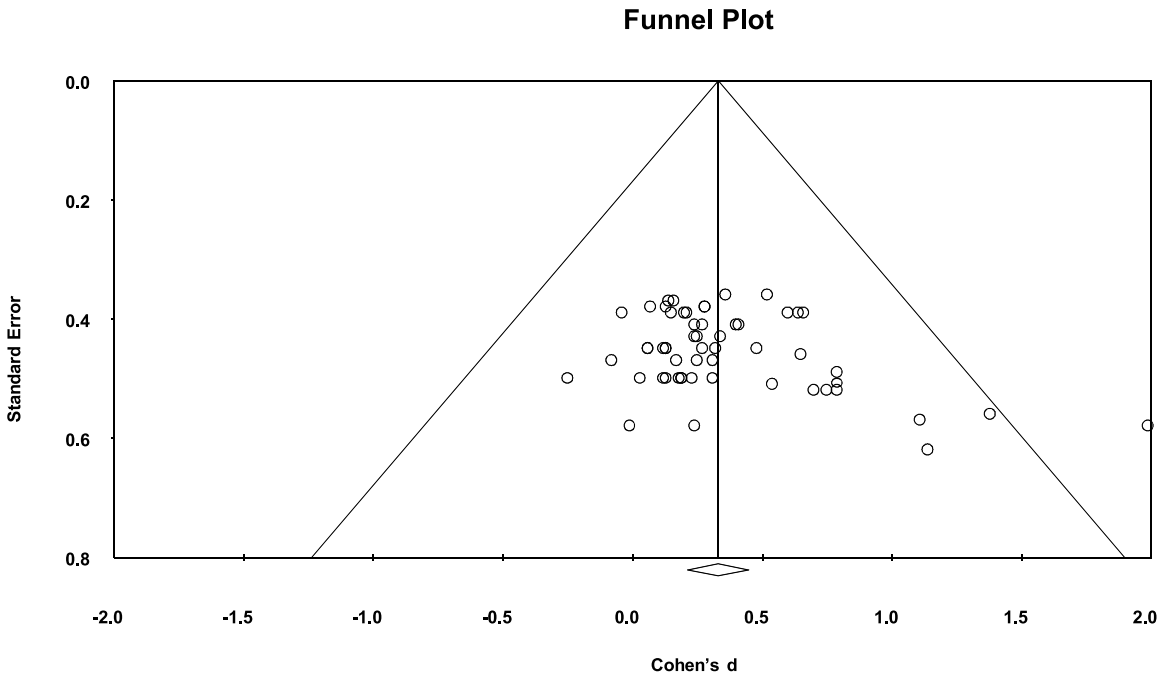


Fig. 3. Funnel plot to detect publication bias.

Heterogeneity among the studies was low, as indicated by a Q-value of 28.7 (p-value = 1.000) and an I^2 statistic of 0.0. Because there was no significant heterogeneity, a fixed effects model was used to identify a pooled Cohen's d of 0.33 (95% CI: 0.21, 0.45; standard error: 0.06). The forest plot showed the individual effect sizes per study and 95% CIs, in relation to the pooled effect size (Fig. 2). We noted that 52 out of the 56 comparison groups showed increased performance in the caffeine group compared to the placebo group.

Funnel plots gave no indication of bias, although one study was plotted outside of the funnel due to a larger observed effect size (Fig. 3). Studies were spread fairly evenly around the pooled effect size. It is important to note that the standard errors were consistent across all studies due to low sample sizes.

Duration of the athletic event was the only covariate found to be independently significantly associated with Cohen's d. Interaction terms between duration and sex, age, VO_2 max, and event were considered, but did not meet the nominal 0.05 level of significance to be included. The final model yielded a single variable, duration of event, which produced an effect estimate of 0.005 (95% CI: 0.001, 0.009; p-value: 0.024). Our final model is:

$$\text{Cohen'sd} = 0.147 + 0.005(\text{duration})$$

Thus, we observed a linear relationship between duration of event and the standardized difference between the caffeine and placebo group's performance. For a one minute increase in duration of the event, we anticipate the Cohen's d to increase by 0.005, whereas for a 30 min increase in duration, we anticipate the Cohen's d to increase by 0.150.

4. Discussion

This meta-analysis is the first to statistically examine the relationship between the ergogenic effects of caffeine and the duration of the athletic event. As hypothesized, there was a linear relationship, which suggests caffeine may better inhibit deleterious adenosine for improved athletic performance as the event's duration increases.

The average improvement of caffeine in this study was similar to that found by Ganio et al.[16] in their review on endurance events—2.9 ± 2.7% to their 3.2 ± 4.3%; Doherty and Smith[15] found a much higher mean of 12.3 ± 13.8%, but 18 of the 24 studies analyzed examined the outcome of time to exhaustion. In trials of time to exhaustion, a small increase in power output yields a much greater percent improvement, necessitating conversions for these results to be comparable with time trials[59]; thus, separate analyses on the effects of caffeine with time to exhaustion trials is needed.

Ganio et al.[16] and Doherty and Smith[15] found no statistically significant moderating variables, just as this review the dose of caffeine and the timing did not influence its benefit. Likewise as with ours, neither review found an effect of VO_2 max, sporting event, and age on the ergogenic potential of caffeine. However, the ranges of these variables are limited (see Supplemental Table 1), and future research outside these limits may help clarify any potential relationships.

While this analysis found the positive relationship between duration and ergogenicity, a limitation of this study is the possibility that there are non-linear associations between caffeine intake and endurance performance. However, we justify the use of a linear model in our analysis for two reasons: First, the durations of the included studies were well within the half-life of caffeine. And, second, the length of time prior to the event that caffeine was administered had no significant association with performance and did not confound the effect of duration. More research is needed on the effects of caffeine with events outlasting its metabolism to determine when caffeine yields diminishing effects.

There are no standard criteria to classify athletic events as endurance events. This study based our minimum duration on the time where theoretically aerobic energy pathways predominate over anaerobic metabolism. Because anaerobic metabolic pathways do not predominate in events past approximately 2–3 min, in an event of 5 min aerobic metabolic pathways predominate for most of the event. However, other studies include events shorter than 5 min yet classify them as endurance events. A consensus on an operational definition is needed for future research.

Several forms of caffeine delivery have been studied, including capsules, gum, and as a mouth rinse. This review also yielded stud-

ies with caffeine in combination with other active ingredients as commercial products, such as carbohydrate–electrolyte solutions, coffee, energy drinks, energy shots, and supplement powders. As athletes have a growing variety of caffeinated products available for use, for practical application more research is needed on the effects of the products' other chemicals on caffeine.

This review yielded studies that considered participants' habituation to caffeine, with some studies excluding participants who consumed more than a given minimum of daily caffeine, while other studies examined whether habituation moderates the benefits of caffeine prior to performance, with conflicting results. More research is needed on the effects of varying degrees and quantities of habituation.

This study's generalizability is limited by the exclusion of sporting events that are not laboratory controlled time trials and also events and competitions not of a time trial nature. Though these were excluded due to methodological dilemmas of statistical comparison, it omits the large group of field events that share aerobic energy pathways that may also benefit from caffeine. Additionally, only studies with adult participants aged 18 years and older were included, and only 9% of the participants were females; the ergogenicity of caffeine in younger participants and in women needs more research.

Of the 62 trials, 12 had administration of caffeine at different time points prior to the event, and only 4 included caffeine during the event. However, it may be general practice for athletes to consume caffeine at multiple time points prior to competition. In longer events, such as marathons, long-distance cycling, and ultra-distance triathlons, which were not found in this study, athletes often consume caffeinated products during competition. More research is needed on potential benefits of caffeine during such endurance competitions.

In conclusion, caffeine is a permitted substance with much evidence of ergogenic aid in sports. Though much previous research has demonstrated its benefits in endurance athletic events particularly, this study is the first to report on the statistical finding that the effect size of caffeine increases along with the increasing duration of the event.

Practical implications

The findings from this study can help inform evidence-based sports nutrition practices.

- Caffeine is a significantly strong ergogenic aid for endurance events of a time-trial nature, which may improve performance by approximately 3% compared to placebo.
- The benefits of caffeine in endurance time-trial performance do not appear to be influenced by sex, age, athlete's VO_2 max, sporting event, the dose of caffeine, or the timing of ingesting caffeine before the competition.
- Results indicate that the longer the endurance time-trial competition is, the greater the performance enhancement from caffeine.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jsams.2018.07.022.

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