2024年度　3月修了　修士論文

Acute Effects of Low-Dose Caffeine Intake on Endurance Performance: A Scoping Review and Meta-Analysis

早稲田大学　大学院スポーツ科学研究科

スポーツ科学専攻　スポーツ医科学研究領域

5023A017－8

キン　セイリン

研究指導教員：　宮地　元彦　教授

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1. Introduction

Caffeine (1,3,7-trimethylxanthine) is the most commonly consumed psychoactive substance globally and occurs naturally in numerous plant species, such as tea and cocoa. Caffeine is an odorless white powder that is soluble in water and lipids and has a bitter taste. Due to its structural similarity to adenosine, caffeine binds to adenosine receptors, preventing adenosine from exerting its sedative effects. This blockage enhances central nervous system stimulation, alertness, and reduces fatigue. Many beverages and products contain significant amounts of caffeine, such as coffee, tea, chocolate, cocoa beverages, soft drinks, and energy drinks.

After ingestion, caffeine is quickly absorbed from the gastrointestinal tract into the circulatory system [1]. The maximum plasma concentration is reached after 30-60 minutes from consumption. Caffeine is widely distributed throughout the body. The pre-systemic metabolism takes place in the liver since orally ingested substances are absorbed through the small intestine into the portal circulation before entering the systemic one. Caffeine's pre-systemic metabolism is negligible, and once caffeine is absorbed, it promptly gets into all the body tissues and crosses the blood-brain, blood-placenta, and blood-testis barriers [1]. The hepatic microsomal enzyme system oversees caffeine metabolism in the liver. The main enzyme responsible for caffeine metabolism is cytochrome P4501A2 (CYP1A2), which accounts for about 95% of caffeine clearance. Caffeine's half-life in humans ranges from a minimum of 2 to a maximum of 12 hours [2, 3], mainly due to the interindividual variability in absorption and metabolism.

Caffeine exerts a wide range of effects. For instance, it binds to adenosine receptors in the brain, thereby promoting wakefulness and reducing the perception of fatigue during exercise.

Additionally, pre-exercise caffeine intake has been reported to elevate blood epinephrine levels, activating the sympathetic nervous system. Furthermore, caffeine consumption is associated with an increase in the release of free fatty acids into the bloodstream, thereby enhancing fat utilization as an energy source.

Many studies have shown that caffeine intake enhances sports performance, with its ergogenic effect improving a wide range of physical activities, including endurance, strength, muscular endurance, team sports, repeated high-intensity exercise, and anaerobic performance [4]. Caffeine was previously banned by the International Olympic Committee and the World Anti-Doping Agency but was removed from the list in 2004. Between 2004 and 2008, over 20,000 urine samples collected during doping control at national and international competitions were analyzed. The results showed that approximately 74% of elite athletes used caffeine as an ergogenic aid, with endurance sports showing the highest levels of caffeine excretion after competition [5].

The International Society of Sports Nutrition has stated that moderate doses of caffeine (3-6 mg/kg) taken 60 minutes before exercise can effectively improve sports performance, but high doses (≥9 mg/kg) do not provide additional benefits [4]. In addition, high doses of caffeine are associated with a high incidence of side effects such as dizziness, increased heart rate, anxiety, tremors, and insomnia [6]. Therefore, to optimize athletic performance while minimizing side effects, it is essential to summarize existing evidence on the effects of low-dose caffeine on performance enhancement.

Recent meta-analyses have investigated the effects of caffeine on endurance performance,

but each study has certain limitations, for example, evaluating a single exercise pattern or lack of low-dose evaluation. The meta-analysis by Wang et al. only included studies that focused on endurance running tests [7]. Southward et al.'s analysis only included studies that evaluated time-trial performance and caffeine doses >3 mg/kg [8]. Barreto et al. focused solely on the effects of caffeine in chewing gum on exercise performance [9]. These limitations hinder a clear understanding of how low-dose caffeine influences endurance performance. A review conducted by Pickering and Kiely (2019) examined the effects of low-dose caffeine on exercise performance. Although this review avoided the limitations of the studies mentioned above, it did not conduct a meta-analysis of the data, which limits its ability to draw comprehensive conclusions [10].

Thus, this study aims to investigate the effect of low-dose caffeine on endurance performance. We hypothesize that acute intake of low-dose caffeine will improve endurance performance but to a lesser extent than medium/high-dose caffeine.

2. Materials and Methods

2.1. Search Strategy and Selection of Studies

The current scoping review and meta-analysis were carried out following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [11].

The present review builds upon the review by Pickering and Kiely (2019), which examined the ergogenic effects of low-dose caffeine on exercise performance, and the data included therein spanned studies published from March 1995 to October 2019 [10]. To extend this evidence base

and incorporate recent advancements in the literature, we searched the PubMed database on 1 July 2024, targeting studies published between 1 January 2019 and 1 July 2024. Search terms included the words "caffeine", "exercise", "performance", and "low dose". Titles and abstracts were carefully read and screened for subsequent full-text review and data extraction. The studies for this review and meta-analysis were managed using EndNote (Version 21, Clarivate, Philadelphia, PA, USA).

The search for published studies was independently conducted by two authors (JIN and LI), while disagreements between these authors were settled through discussion, with a third author (DW and MM) consulted for input if consensus could not be reached. To introduce the searched studies in the meta-analysis, the following inclusion criteria had to be fulfilled, with each study involving: (1) randomized controlled trials (RCT); (2) interventions involving caffeine supplementation, with a clear dosage and acute pre-exercise ingestion; (3) studies utilizing a caffeine dose of ≤3 mg/kg; (4) included healthy men and women as participants, aged 18–50 years; (5) outcome measures are a form of exercise performance. The following exclusion criteria were applied to the experimental protocols of the investigation: (1) the absence of a placebo condition; (2) nonoriginal articles (for example, reviews); (3) articles not published in English; (4) nonhuman studies; (5) participants with diagnosed medical conditions, including cardiovascular disease, metabolic disorders, or other chronic illnesses.

From the studies that met the above criteria, those specifically investigating endurance performance were selected for inclusion. The additional selection criteria were as follows: (1) involved endurance activities lasting longer than 5 minutes and primarily relying on aerobic

energy systems. (2) The outcome measures reflected endurance performance, including time to exhaustion (TTE), power, time trial time (TT time), work, or maximal/peak oxygen uptake (VO2max/peak).

2.2. Quality Assessment

Study quality was evaluated using the Physiotherapy Evidence Database (PEDro) scale. The PEDro scale is a widely used tool for evaluating the methodological quality of randomized controlled trials [44]. It comprises 11 items that assess randomization, blinding, attrition, selective reporting, and statistical analysis. Each item is scored based on whether it is satisfied, with a maximum score of 10 (the first item is not included in the total score). The higher the score, the better is the methodological quality and the lower the risk of bias. The quality assessment was independently conducted by two authors (JIN and LI), and input was sought from a third author to resolve any disagreement (DW and MM).

PEDro scale items: (1) eligibility criteria were specified; (2) subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); (3) allocation was concealed; (4) the groups were similar at baseline regarding the most important prognostic indicators; (5) there was blinding of all subjects; (6) there was blinding of all therapists who administered the therapy; (7) there was blinding of all assessors who measured at least one key outcome; (8) measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; (9) all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by “intention to

treat" ; (10) the results of between-group statistical comparisons are reported for at least one key outcome; (11) the study provides both point measures and measures of variability for at least one key outcome.

2.3. Data Extraction

Data extraction was carried out by one author (JIN) and verified by another (LI). The extracted data were organized and managed using spreadsheet software (Microsoft Excel 365, Microsoft Corporation, Redmond, WA, USA).

Information collected from each study included sample size, characteristics, age, weight, height, VO2max/peak, habitual caffeine consumption, caffeine dose, time of caffeine ingestion, mode of exercise, exercise protocol, endurance performance outcomes for placebo and caffeine trials. Endurance performance was assessed using TTE, power, TT time, work, VO2max/peak as the primary indicators. These values were extracted and recorded as mean ± standard deviation/standard error (mean ± SD/SE). If caffeine was reported as an absolute dose in the study, the relative dose per kilogram of body weight was calculated using the average body weight.

When data required for the creation of a forest plot could not be collected, the article's corresponding author was contacted. In cases in which numerical data were not available and a response could not be obtained from the corresponding author but the data were available as graphs, numerical values were obtained using the web-based tool WebPlotDigitizer, version 4.1 (Ankit Rohatgi; Pacifica, CA).

2.4. Statistical Analyses

The statistical analysis was performed using STATA software (StataSE 18.0, StataCorp LLC,

College Station, TX, USA).

Change over placebo and relative standard error were calculated based on the means and standard deviations of the placebo and caffeine trials, the correlations between trials, and the number of participants. Since none of the studies reported a correlation, a 0.5 correlation was assumed for all trials [45]. A random-effects model was used for the analysis, with the statistical significance threshold set a priori at $p < 0.05$.

$$change\ over\ placebo\ (\%) = 100 \times \frac{mean_{caffeine} - mean_{placebo}}{mean_{placebo}}$$

$$SE\ (\%) = 100 \times \frac{\sqrt{SD_{caffeine}{}^2 + SD_{placebo}{}^2 - 2 \times r \times SD_{caffeine} \times SD_{placebo}}}{\sqrt{N} \times mean_{placebo}}$$

SE (%), relative standard error; SD, standard deviation; r, correlation; N, sample size.

The I^2 statistic was used to assess the degree of heterogeneity, with values of ≤50% indicating low heterogeneity, 50–75% indicating moderate heterogeneity, and >75% indicating a high level of heterogeneity [46]. Publication bias was assessed using the Begg and Egger test by plotting change over placebo against the standard error with 95% CI using a funnel plot [12].

Subgroup analyses for the effects of caffeine on endurance performance were performed for the following indicators: (a) TTE, (b) power, (c) TT time, (d) work, (e) VO2max/peak, (f) habitual caffeine intake and (g) caffeine intake dosage.

3. Results

3.1. Selection of Studies

A total of 241 articles were initially identified. We evaluated 109 full-text articles, and after

applying inclusion and exclusion criteria, we included 22 articles [13-34] in qualitative synthesis (Figure 1).

3.2. Study Methodological Quality

Among the studies that evaluated endurance performance, the mean PEDro methodological quality score was 9.77, with the values for individual studies ranging from 6 to 10 (Table 1).

Except for Schubert et al. (2013), which used a single-blind design, all other studies employed a double-blind or triple-blind design, so Schubert's study did not receive a score for the blinding items (items 3, 6, 7) [28]. Schubert et al. (2013) also had 3 out of 9 participants withdraw due to injury or illness, resulting in a deduction for the Adequate Follow-Up item (item 8). Moesgaard et al. (2024) included data from two participants who missed one day of creatine supplementation, thus failing to meet the Intention-to-Treat analysis criteria (item 9) [14].

3.3. Study Characteristics

Among the 22 selected studies, a total of 419 participants were included, consisting of 351 males and 68 females (Table 2). Cycling was the most common form of exercise used by 15 of the 22 studies [13, 14, 16-18, 21-25, 27, 29, 30, 32, 34], while 5 studies used running protocols [15, 19, 20, 28, 33] and 2 studies used rowing protocols [26, 31].

6 studies used a fixed caffeine dose [13, 15, 16, 19, 28, 29], while 16 studies used a body weight-relative caffeine dose [14, 17, 18, 20-27, 30-34]. 14 studies used a single caffeine dose [14, 15, 17-23, 25, 26, 29, 30, 34], while 8 studies used multiple caffeine doses [13, 16, 24, 27, 28, 31-33]. Among these, the most commonly used dose was 3 mg/kg, which was used in 14 studies [14, 17, 18, 20-23, 25-27, 30, 32-34], with caffeine doses ranging from 1 to 9 mg/kg across

the included studies. According to international guidelines, a dose of <3 mg/kg is considered low, 3 to 6 mg/kg is medium, and >6 mg/kg is high. Among the included studies, 6 studies used only low doses [13, 15, 16, 19, 28, 29], 16 studies used medium doses [14, 17, 18, 20-27, 30-34], and 1 study used high doses [33].

3.4. Meta-Analysis

Results of the meta-analysis indicated a significant difference ($p < 0.001$) between the placebo and caffeine trials on endurance performance (Figure 2). The pooled improvement rate of endurance performance with caffeine intake was 1.61% (95% CI: 0.90, 2.33). The I^2 statistic indicated low heterogeneity for the studies assessing endurance performance ($I^2 = 0.00\%$; $p = 0.99$). The funnel plot was visually inspected to assess potential publication bias and appeared symmetric. Neither Begg's test ($p = 0.064$) nor Egger's test ($p = 0.051$) indicated significant publication bias (Figure 3).

A subgroup analysis indicated that caffeine significantly improves TTE (improvement rate = 4.08%; 95% CI: 1.54, 6.63; $p < 0.001$; Figure 4) and power (improvement rate = 2.36%; 95% CI: 0.30, 4.42; $p = 0.02$; Figure 5) and TT time (improvement rate = 1.24%; 95% CI: 0.37, 2.12; $p = 0.01$; Figure 6). However, no significant effects were found on work (improvement rate = 2.48%; 95% CI: -2.12, 7.07; $p = 0.29$; Figure7) and VO2max/peak (improvement rate = 1.42%; 95% CI: -1.85, 4.69; $p = 0.40$; Figure 8).

A subgroup analysis was conducted based on habitual caffeine intake, comparing individuals with low habitual caffeine intake (< 1mg/kg/day) to those with high habitual caffeine intake (> 3mg/kg/day). The results indicated that caffeine improved endurance performance in both groups:

in the low habitual caffeine intake group (improvement rate = 2.39%; 95% CI: 0.05, 4.73; p = 0.045; Figure 9) and in the high habitual caffeine intake group (improvement rate = 2.29%; 95% CI: 0.03, 4.56; p = 0.047; Figure 10).

A subgroup analysis was conducted based on acute caffeine intake dosage, comparing the low-dose group (< 3mg/kg) to the medium/high-dose group (≥ 3mg/kg). The results indicated that caffeine did not significantly improve endurance performance in the low-dose group (improvement rate = 1.01%; 95% CI: -0.21, 2.23; p = 0.11; Figure 11). However, a significant improvement was observed in the medium/high-dose group (improvement rate = 1.97%; 95% CI: 1.05, 2.89; p < 0.001; Figure 11).

4. Discussion

The purpose of this scoping review and meta-analysis was to critically evaluate the acute effects of low-dose caffeine intake on endurance performance. The main finding was that caffeine intake has a small but significant effect on endurance performance (improvement rate = 1.61%; 95% CI: 1.54, 6.63; p < 0.001). Subgroup analyses revealed that caffeine consistently improves TTE, power, and TT time, with respective improvement rates of 4.08%, 2.36%, and 1.24%. However, no significant effect was observed on work or VO2 max/peak. The data also highlight that medium/high caffeine doses (≥ 3 mg/kg) are more effective than low doses (< 3 mg/kg), as the latter did not achieve significant improvements. Interestingly, habitual caffeine intake had no notable influence on endurance performance enhancement, with both low and high-habitual intake groups benefiting similarly from caffeine ingestion.

Caffeine can enhance endurance performance by increasing central nervous system stimulation and reducing the perception of effort [35], which can lead to improvements in TTE, power, and TT time performance. These outcomes are more likely influenced by caffeine's ability to delay fatigue and improve pacing strategies rather than by alterations in maximal aerobic capacity. In contrast, VO2 max/peak reflects the maximal/peak volume of oxygen the body can consume during intense exercise, and work. It is a measure of the total energy expended during exercise. These variables may not show significant improvements from caffeine because they are more dependent on the cardiovascular and respiratory systems' maximal capabilities [36].

The systematic review and meta-analysis conducted by Chen et al. (2024) [37] on the effects of caffeine on TT performance in cyclists demonstrated that moderate doses (4-6 mg/kg) significantly improved TT time (SMD = -0.55, 95% CI: -0.84, -0.26; $p < 0.01$) and mean power output (SMD = 0.44, 95% CI: 0.09, 0.79, $p < 0.05$), whereas low doses (1-3 mg/kg) failed to show significant improvements. This finding aligns with our results regarding the limited effects of low-dose caffeine. Caffeine is commonly believed to enhance performance primarily through its action on the central nervous system [38], reducing perceived exertion and pain. Other proposed mechanisms include increased myofibrillar calcium availability [39] and optimized exercise metabolism[40]. However these mechanisms may not be activated at low caffeine doses, limiting its ergogenic effects. Additionally, because individuals' sensitivity to caffeine varies due to genetic factors, such as ADORA2A and CYP1A2 genes, low doses may be effective for some people while having little effect on others [41].

To further study the dose-response relationship between acute caffeine intake and endurance

exercise performance, a weighted scatter plot was made with the intake amount as the horizontal axis and the improvement rate as the vertical axis, and a trend line was added (Figure 12). This figure suggests that not all caffeine doses <3 mg/kg fail to enhance endurance performance. In the low-to-medium dose range, although the linear relationship is weak (R^2=0.01062), a positive correlation (y=0.1922x+1.0214) between dose and improvement rate is evident. Taking individual differences into account, different people may require different doses to achieve optimal effects.

Carvalho et al. (2022) [42] conducted meta-analyses for different exercise types (endurance, power, strength) and found that caffeine was effective across all exercise types. Their subgroup and meta-regression analyses indicated that habitual caffeine consumption had no influence on the ergogenic effect of caffeine on endurance (R^2 = 0%, estimate = 0.03, 95% CI: -0.03, 0.08), which is consistent with our findings that individuals with different levels of daily caffeine consumption experience similar benefits from acute caffeine intake, regardless of their daily level of caffeine intake. This information is important for athletes who regularly consume caffeine, as it suggests they may continue to do so without significant impact to the acute ergogenic effects of their pre-training or pre-competition caffeine dose. From the perspective of metabolic adaptation, with chronic high caffeine intake, the liver becomes more efficient at metabolizing caffeine, allowing the body to process it more rapidly [43]. However, acute ingestion leads to a temporary elevation in caffeine levels in the body, and its effects manifest quickly. Therefore, metabolic changes induced by habitual consumption are unlikely to have a significant impact on the acute effects of caffeine.

Unlike previous reviews that included only one type of exercise mode or restricted caffeine dosage, this study included various endurance exercise modes, such as cycling, running, and rowing, and conducted subgroup analyses of measurement indicators, including TTE, power, TT time, work, and VO2max/peak, across low, medium, and high caffeine doses. These diverse exercise modes enhance the broader applicability of the findings, while the subgroup analyses provide detailed insights into caffeine's effects on different aspects of endurance.

On the other hand, several limitations should be acknowledged. As the literature search was limited to PubMed, this may have resulted in not all articles being retrieved. Only one included study used a high dose (>6mg/kg) of caffeine, potentially reducing the statistical power of the subgroup analyses. Second, we did not extract or analyze physiological indicators and subjective indicators (e.g., respiratory exchange ratio, blood lactate concentration, blood glucose, and rating of perceived exertion). Finally, potential confounding factors, such as training status, sleep quality, and genotypes associated with caffeine metabolism (ADORA2A and CYP1A2), were not accounted for, which could influence the observed effects [47-49].

The findings of this study have important practical implications for enhancing endurance performance in athletes. Specifically, caffeine intake, particularly at medium/high doses, has been shown to improve performance in endurance sports such as running, cycling, and rowing. Therefore, athletes can benefit from caffeine supplementation before competitions to optimize their performance. Sports nutritionists and trainers can use these insights to design tailored caffeine intake plans that maximize the ergogenic effects for individual athletes. Moreover, the results can guide the development of sports supplements, such as energy drinks and gels, to

enhance endurance performance. This research also underscores the need for future studies to explore the underlying physiological mechanisms and to account for factors like training status, sleep quality, and genetic variations to further refine caffeine supplementation strategies.

5. Conclusion

Acute caffeine intake before exercise can improve endurance performance. Caffeine consistently enhances TTE, power, and TT time performance, but shows no significant effect on work and VO2max/peak. These effects are insufficient with acute intake of low-dose (<3mg/kg) caffeine. Habitual caffeine intake has no effect on the acute ergogenic effects of caffeine.

References

1. Arnaud, M. J. (1993). Components of coffee. Caffeine, coffee, and health, 43.
2. Daly, J. W. (1993). Mechanism of action of caffeine. Caffeine, coffee, and health, 97-150.
3. Benowitz, N. L. (1990). Clinical pharmacology of caffeine. Annual review of medicine, 41,277-288.
4. Guest, N. S., VanDusseldorp, T. A., Nelson, M. T., Grgic, J., Schoenfeld, B. J., Jenkins, N. D., ... & Campbell, B. I. (2021). International society of sports nutrition position stand: caffeine and exercise performance. Journal of the International Society of Sports Nutrition, 18(1), 1.
5. Van Thuyne, W., & Delbeke, F. T. (2006). Distribution of caffeine levels in urine in different sports in relation to doping control before and after the removal of caffeine from the WADA

doping list. International journal of sports medicine, 27(09), 745-750.

6. de Souza, J. G., Del Coso, J., Fonseca, F. D. S., Silva, B. V. C., de Souza, D. B., da Silva Gianoni, R. L., ... & Claudino, J. G. (2022). Risk or benefit? Side effects of caffeine supplementation in sport: a systematic review. European journal of nutrition, 61(8), 3823-3834.
7. Wang, Z., Qiu, B., Gao, J., & Del Coso, J. (2022). Effects of caffeine intake on endurance running performance and time to exhaustion: A systematic review and meta-analysis. Nutrients, 15(1), 148.
8. Southward, K., Rutherfurd-Markwick, K. J., & Ali, A. (2018). The effect of acute caffeine ingestion on endurance performance: a systematic review and meta-analysis (vol 48, pg 1913, 2018). SPORTS MEDICINE, 48(10), 2425-2441.
9. Barreto, G., Loureiro, L. M. R., Reis, C. E. G., & Saunders, B. (2023). Effects of caffeine chewing gum supplementation on exercise performance: A systematic review and meta-analysis. European Journal of Sport Science, 23(5), 714-725.
10. Pickering, C., & Kiely, J. (2019). Are low doses of caffeine as ergogenic as higher doses? A critical review highlighting the need for comparison with current best practice in caffeine research. Nutrition, 67, 110535.
11. Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., ... & Prisma-P Group. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews, 4, 1-9.
12. Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis

detected by a simple, graphical test. bmj, 315(7109), 629-634.

13. Banks, N. F., Rogers, E. M., Helwig, N. J., Schwager, L. E., Alpers, J. P., Schulte, S. L., ... & Jenkins, N. D. (2024). Acute effects of commercial energy drink consumption on exercise performance and cardiovascular safety: a randomized, double-blind, placebo-controlled, crossover trial. Journal of the International Society of Sports Nutrition, 21(1), 2297988.
14. Moesgaard, L., Jessen, S., Christensen, P. M., Bangsbo, J., & Hostrup, M. (2024). No additive effect of creatine, caffeine, and sodium bicarbonate on intense exercise performance in endurance-trained individuals. Scandinavian Journal of Medicine & Science in Sports, 34(4), e14629.
15. Yoo, C., Xing, D., Gonzalez, D. E., Jenkins, V., Nottingham, K., Dickerson, B., ... & Kreider, R. B. (2024). Paraxanthine provides greater improvement in cognitive function than caffeine after performing a 10-km run. Journal of the International Society of Sports Nutrition, 21(1), 2352779.
16. Penna, E. M., Harp, A., Hack, B., Talik, T. N., & Millard-Stafford, M. (2023). Guarana (Paullinia cupana) but not low-dose caffeine improves cycling time-trial performance versus placebo. International journal of sport nutrition and exercise metabolism, 34(1), 30-37.
17. Ruiz-Moreno, C., Amaro-Gahete, F. J., González-García, J., Giráldez-Costas, V., Mañas, A., Gutiérrez-Hellín, J., & Del Coso, J. (2022). Caffeine increases exercise intensity and energy expenditure but does not modify substrate oxidation during 1 h of self-paced cycling. European Journal of Nutrition, 61(6), 3285-3292.
18. Clarke, N. D., & Richardson, D. L. (2020). Habitual caffeine consumption does not affect

the ergogenicity of coffee ingestion during a 5 km cycling time trial. International journal of sport nutrition and exercise metabolism, 31(1), 13-20.

19. Fye, H., Pass, C., Dickman, K., Bredahl, E., Eckerson, J., & Siedlik, J. (2021). The effect of a multi-ingredient pre-workout supplement on time to fatigue in NCAA division I cross-country athletes. Nutrients, 13(6), 1823.

20. Khcharem, A., Souissi, M., Atheymen, R., Souissi, W., & Sahnoun, Z. (2021). Acute caffeine ingestion improves 3-km run performance, cognitive function, and psychological state of young recreational runners. Pharmacology Biochemistry and Behavior, 207, 173219.

21. Lara, B., Gutiérrez-Hellín, J., García-Bataller, A., Rodríguez-Fernández, P., Romero-Moraleda, B., & Del Coso, J. (2020). Ergogenic effects of caffeine on peak aerobic cycling power during the menstrual cycle. European journal of nutrition, 59, 2525-2534.

22. Ruíz-Moreno, C., Lara, B., Brito de Souza, D., Gutiérrez-Hellín, J., Romero-Moraleda, B., Cuéllar-Rayo, Á., & Del Coso, J. (2020). Acute caffeine intake increases muscle oxygen saturation during a maximal incremental exercise test. British journal of clinical pharmacology, 86(5), 861-867.

23. Skinner, T. L., Desbrow, B. E. N., Arapova, J., Schaumberg, M. A., Osborne, J., Grant, G. D., ... & Leveritt, M. D. (2019). Women experience the same ergogenic response to caffeine as men. Medicine and science in sports and exercise, 51(6), 1-1202.

24. Guest, N., Corey, P., Vescovi, J., & El-Sohemy, A. (2018). Caffeine, CYP1A2 genotype, and endurance performance in athletes. Medicine & Science in Sports & Exercise, 50(8), 1570-1578.

25. Quinlivan, A., Irwin, C., Grant, G. D., Anoopkumar-Dukie, S., Skinner, T., Leveritt, M., & Desbrow, B. (2015). The effects of Red Bull energy drink compared with caffeine on cycling time-trial performance. International journal of sports physiology and performance, 10(7), 897-901.

26. Christensen, P. M., Petersen, M. H., Friis, S. N., & Bangsbo, J. (2014). Caffeine, but not bicarbonate, improves 6 min maximal performance in elite rowers. Applied Physiology, Nutrition, and Metabolism, 39(9), 1058-1063.

27. Desbrow, B., Biddulph, C., Devlin, B., Grant, G. D., Anoopkumar-Dukie, S., & Leveritt, M. D. (2012). The effects of different doses of caffeine on endurance cycling time trial performance. Journal of sports sciences, 30(2), 115-120.

28. Schubert, M. M., Astorino, T. A., & Azevedo Jr, J. L. (2013). The effects of caffeinated "energy shots" on time trial performance. Nutrients, 5(6), 2062-2075.

29. Spence, A. L., Sim, M., Landers, G., & Peeling, P. (2013). A comparison of caffeine versus pseudoephedrine on cycling time-trial performance. International journal of sport nutrition and exercise metabolism, 23(5), 507-512.

30. Irwin, C., Desbrow, B., Ellis, A., O'Keeffe, B., Grant, G., & Leveritt, M. (2011). Caffeine withdrawal and high-intensity endurance cycling performance. Journal of sports sciences, 29(5), 509-515.

31. Skinner, T. L., Jenkins, D. G., Coombes, J. S., Taaffe, D. R., & Leveritt, M. D. (2010). Dose response of caffeine on 2000-m rowing performance. Medicine and science in sports and exercise, 42(3), 571-576.

32. Jenkins, N. T., Trilk, J. L., Singhal, A., O'Connor, P. J., & Cureton, K. J. (2008). Ergogenic effects of low doses of caffeine on cycling performance. International journal of sport nutrition and exercise metabolism, 18(3), 328-342.

33. Graham, T. E., & Spriet, L. L. (1995). Metabolic, catecholamine, and exercise performance responses to various doses of caffeine. Journal of applied physiology, 78(3), 867-874.

34. Dodd, S. L., Brooks, E., Powers, S. K., & Tulley, R. (1991). The effects of caffeine on graded exercise performance in caffeine naive versus habituated subjects. European journal of applied physiology and occupational physiology, 62, 424-429.

35. Tarnopolsky, M. A. (2008). Effect of caffeine on the neuromuscular system—potential as an ergogenic aid. Applied physiology, nutrition, and metabolism, 33(6), 1284-1289.

36. Transactions of the Royal Society of Tropical Medicine and Hygiene, 2018; 112 (10): 423–35; https://doi. org/10.1093/trstmh/try078. (2019). Corrigendum to: Neglected tropical diseases and vitamin B12: a review of the current evidence. Transactions of The Royal Society of Tropical Medicine and Hygiene, 113(5), 292-292.

37. Chen, B., Ding, L., Qin, Q., Lei, T. H., Girard, O., & Cao, Y. (2024). Effect of caffeine ingestion on time trial performance in cyclists: a systematic review and meta-analysis. Journal of the International Society of Sports Nutrition, 21(1), 2363789.

38. Daly, J. W., Butts-Lamb, P., & Padgett, W. (1983). Subclasses of adenosine receptors in the central nervous system: interaction with caffeine and related methylxanthines. Cellular and molecular neurobiology, 3, 69-80.

39. Klein, M. G., Simon, B. J., & Schneider, M. F. (1990). Effects of caffeine on calcium

release from the sarcoplasmic reticulum in frog skeletal muscle fibres. The Journal of physiology, 425(1), 599-626.

40. Graham, T. E., & Spriet, L. L. (1991). Performance and metabolic responses to a high caffeine dose during prolonged exercise. Journal of applied physiology, 71(6), 2292-2298.

41. Yang, A., Palmer, A. A., & De Wit, H. (2010). Genetics of caffeine consumption and responses to caffeine. Psychopharmacology, 211, 245-257.

42. Carvalho, A., Marticorena, F. M., Grecco, B. H., Barreto, G., & Saunders, B. (2022). Can I have my coffee and drink it? A systematic review and meta-analysis to determine whether habitual caffeine consumption affects the ergogenic effect of caffeine. Sports Medicine, 52(9), 2209-2220.

43. Barcelos, R. P., Souza, M. A., Amaral, G. P., Stefanello, S. T., Bresciani, G., Fighera, M. R., ... & Barbosa, N. V. (2014). Caffeine supplementation modulates oxidative stress markers in the liver of trained rats. Life sciences, 96(1-2), 40-45.

44. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. (2003). Reliability of the PEDro scale for rating quality of randomized controlled trials. Physical Therapy, 83(8), 713-721.

45. Follmann, D., Elliott, P., Suh, I. L., & Cutler, J. (1992). Variance imputation for overviews of clinical trials with continuous response. Journal of clinical epidemiology, 45(7), 769-773.

46. Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. Bmj, 327(7414), 557-560.

47. Berjisian, E., Naderi, A., Mojtahedi, S., Grgic, J., Ghahramani, M. H., Karayigit, R., ... &

Forbes, S. C. (2022). Are caffeine's effects on resistance exercise and jumping performance moderated by training status?. Nutrients, 14(22), 4840.

48. Bodenmann, S., Hohoff, C., Freitag, C., Deckert, J., Rétey, J. V., Bachmann, V., & Landolt, H. P. (2012). Polymorphisms of ADORA2A modulate psychomotor vigilance and the effects of caffeine on neurobehavioural performance and sleep EEG after sleep deprivation. British journal of pharmacology, 165(6), 1904-1913.

49. Yang, A., Palmer, A. A., & De Wit, H. (2010). Genetics of caffeine consumption and responses to caffeine. Psychopharmacology, 211, 245-257.

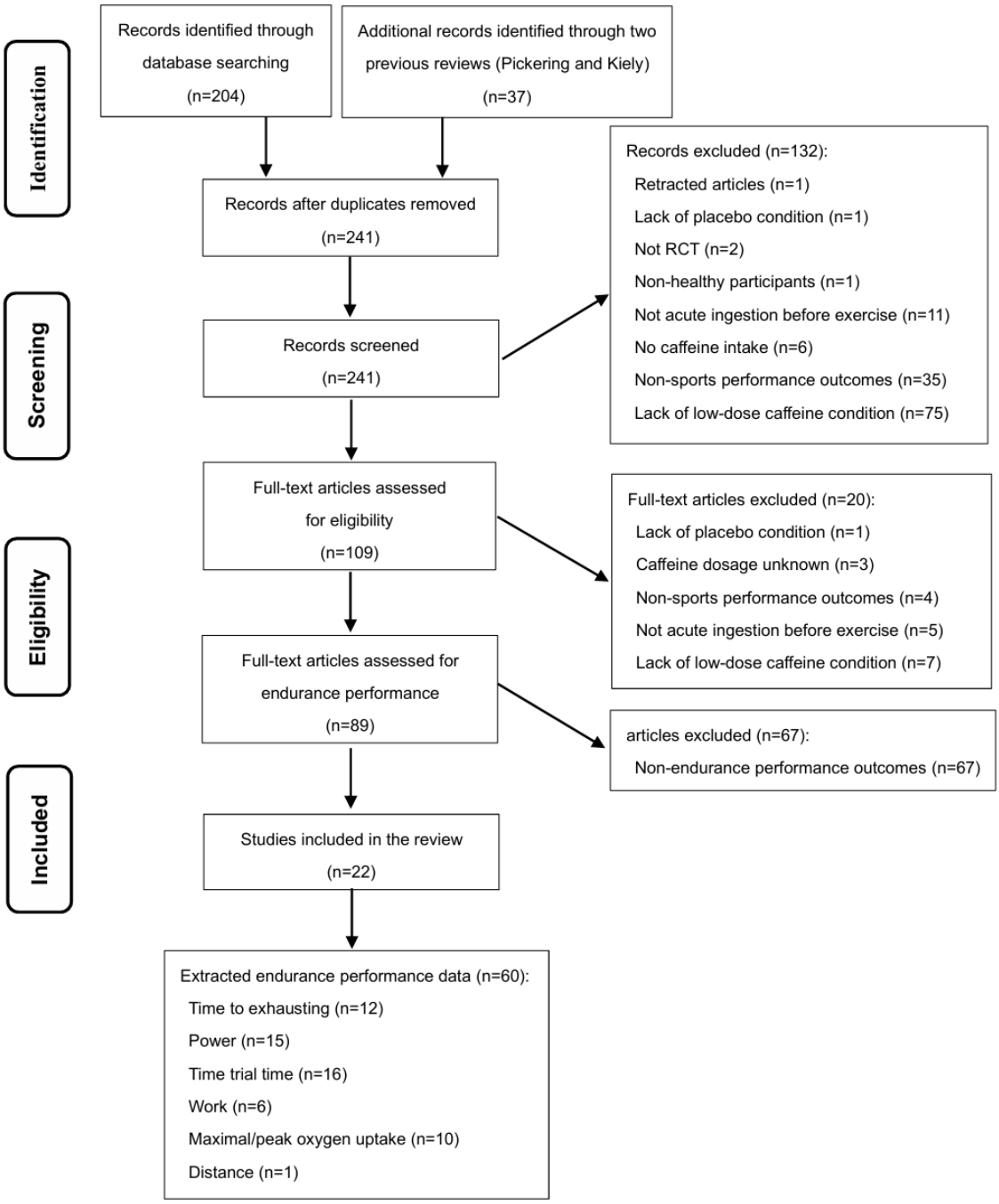

Figure 1. Flowchart of search strategy and selection of studies.

Study	Item1	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Total
Banks et al. (2024) [13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Moesgaard et al. (2024) [14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9
Yoo et al. (2024) [15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Penna et al. (2023) [16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Ruiz-Moreno et al. (2022) [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Clarke et al. (2021) [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Fye et al. (2021) [19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Khcharem et al. (2021) [20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Lara et al. (2020) [21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Ruiz-Moreno et al. (2020) [22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Skinner et al. (2019) [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Guest et al. (2018) [24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Quinlivan et al. (2015) [25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Christensen et al. (2014) [26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Desbrow et al. (2011) [27]	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	6
Schubert et al. (2013) [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Spence et al. (2013) [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Irwin et al. (2011) [30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Skinner et al. (2010) [31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Jenkins et al. (2008) [32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Graham & Spriet (1995) [33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Dodd et al. (1991) [34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10

Table 1. Quality score for eligible studies.

Study	Sample	Age(mean ± SD)	VO2max/peak(mean ± SD, ml/kg/min)	Ingestion method	Caffeine dose(mg/kg)	Caffeine timing (min pre-exercise)	Mode of exercise	Exerciseprotocol
Banks et al. (2024) [13]	30M	24.8 ± 4.4	-	capsule	0, 1.91, 2.38	62	cycling	graded, maximal aerobic exercise test
Moesgaard et al. (2024) [14]	6M6F	23 ± 3 (M), 23 ± 2 (F)	57.9 ± 4.4(M), 50.6 ± 3.1(F)	drink	0, 3	60	cycling	maximal voluntary contraction, 15s sprint, 6min TT
Yoo et al. (2024) [15]	11M1F	26.4 ± 5.1	52.4 ± 10.6	capsule	0, 2.92	60	running	10km TT
Penna et al. (2023) [16]	10M1F	24.5 ± 4.7	55.5 ± 7.5	capsule	0, 1.32, 1.73	60	cycling	60min fixed cycling workload, 15min TT
Ruiz-Moreno et al. (2022) [17]	11M4F	29 ± 6	49.3 ± 10.4	capsule	0, 3	60	cycling	1h pedaling with a self-selected wattage
Clarke et al. (2021) [18]	27M19F	29 ± 6 (M), 28 ± 6 (F)	55 ± 11 (M), 41 ± 9 (F)	drink	0, 3	60	cycling	5km TT
Fye et al. (2021) [19]	6M5F	20 ± 2	-	capsule	0, 2.36	30	running	20min warm-up, 5min transition
Khcharem et al. (2021) [20]	13M	21.3 ± 0.8	51.3 ± 6.1	capsule	0, 3	120	running	3km TT
Lara et al. (2020) [21]	13F	31 ± 6	48.1 ± 7.3	capsule	0, 3	60	cycling	graded exercise test
Ruiz-Moreno et al. (2020) [22]	6M7F	32.5 ± 6.5	49.7 ± 8.5	capsule	0, 3	60	cycling	graded exercise test
Skinner et al. (2019) [23]	16M11F	32.6 ± 8.3 (M), 29.7 ± 5.3 (F)	60.4 ± 4.1 (M), 51.9 ± 7.2 (F)	capsule	0, 3	90	cycling	TT
Guest et al. (2018) [24]	101M	25 ± 4	49 ± 8 (AA), 47 ± 12 (AC), 44 ± 12 (CC)	capsule	0, 2, 4	45	cycling	10km cycle ergometer TT
Quinlivan et al. (2015) [25]	11M	31.6 ± 6.1	60.7 ± 8.1	capsule,drink	0, 3, 3	90	cycling	TT equivalent to 1h cycling at 76% peak power output
Christensen et al. (2014) [26]	11M1F	25 ± 1 (M, open-weight), 24 ± 3 (M, light-weight), 27 (F, light-weight)	-	pill	0, 3	45	rowing	four 6 min maximal rowing tests
Desbrow et al. (2011) [27]	16M	32.6 ± 8.3	60.4 ± 4.1	capsule	0, 3, 6	90	cycling	60min cycle at 75% peak sustainable power
Schubert et al. (2013) [28]	6M	22.5 ± 1.8	69.1 ± 5.7	drink	0, 1.22, 2.14	65	running	5km TT
Spence et al. (2013) [29]	10M	30 ± 2	58.9 ± 2.0	capsule	0, 2.53	60	cycling	40km TT
Irwin et al. (2011) [30]	12M	28.3 ± 5.8	63.7 ± 7.4	capsule	0, 3	90	cycling	1h cycle at 75% peak power output
Skinner et al. (2010) [31]	10M	20.6 ± 1.4	58.2 ± 6.8	capsule	0, 2, 4, 6	60	rowing	2km TT
Jenkins et al. (2008) [32]	13M	26.3 ± 6.8	55.2 ± 7.2	capsule	0, 1, 2, 3	60	cycling	15 min VO2peak performance cycle
Graham & Spriet (1995) [33]	8M	19 - 34	65 - 76.4	capsule	0, 3, 6, 9	60	running	TTE run at 85% VO2max
Dodd et al. (1991) [34]	17M	21.1 ± 3.4 (CN), 26.6 ± 2.6 (CH)	40.85 ± 4.23 (CN), 41.69 ± 2.60 (CH)	capsule	0, 3	60	cycling	graded, incremental cycle ergometer test

Table 2. Summary of studies measuring caffeine effects on endurance performance.

SD, standard deviation; M, Males; F, Females; CN, caffeine consumption 25 mg/day or less; CH, caffeine consumption above 300 mg/day; AA/AC/CC, CYP1A2 genotype; VO2max/peak, maximal/peak oxygen uptake; TT, time trial; TTE, time to exhaustion.

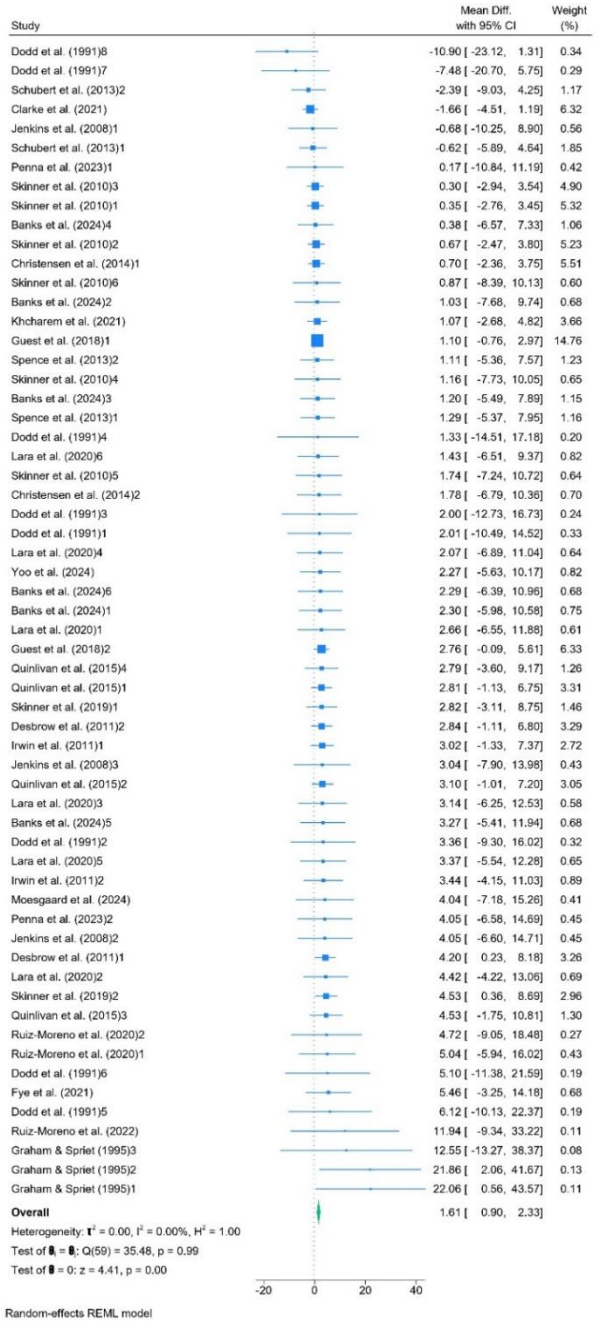

Figure 2. Forest plot of caffeine effects on endurance performance.

Forest plot shows differences between the effects of placebo and caffeine trials on endurance performance. The size of the plotted squares reflects the relative statistical weight of each study. The numbers on the x-axis denote the improvement over placebo (%). The horizontal lines denote the respective 95% confidence intervals (CI).

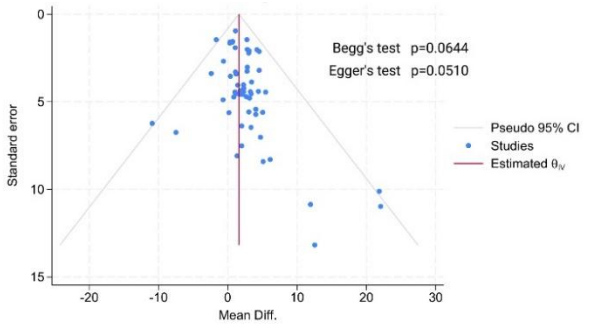

Figure 3. Funnel plot of caffeine effects on endurance performance with Begg and Egger bias tests.

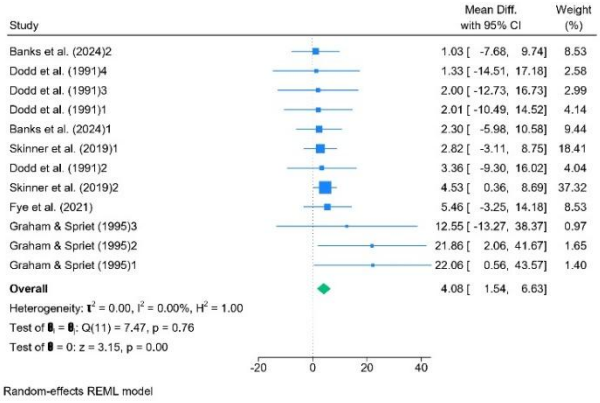

Figure 4. Forest plot of caffeine effects on TTE.

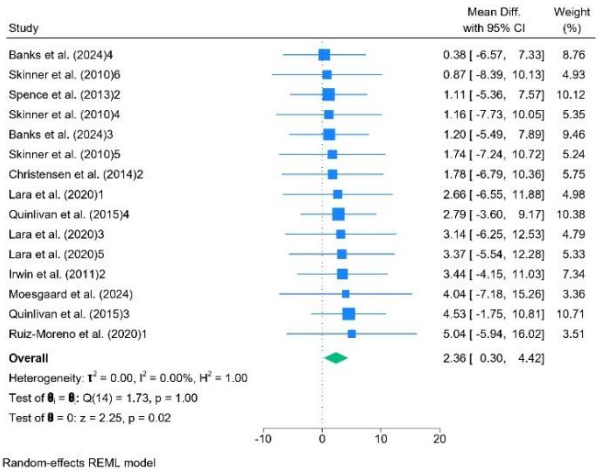

Figure 5. Forest plot of caffeine effects on power.

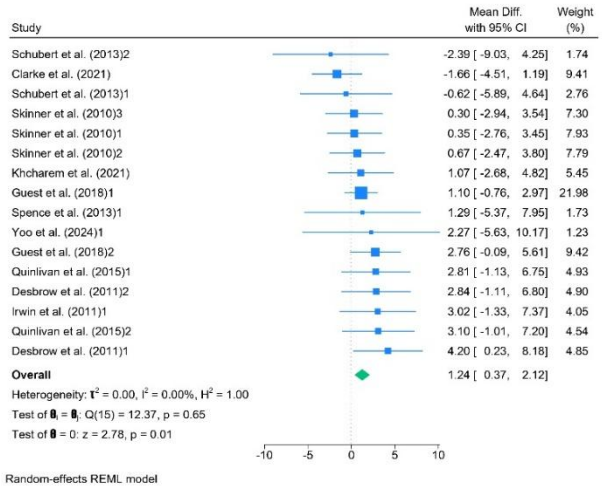

Figure 6. Forest plot of caffeine effects on TT time.

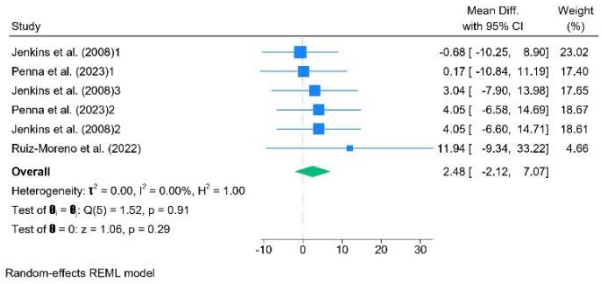

Figure 7. Forest plot of caffeine effects on work.

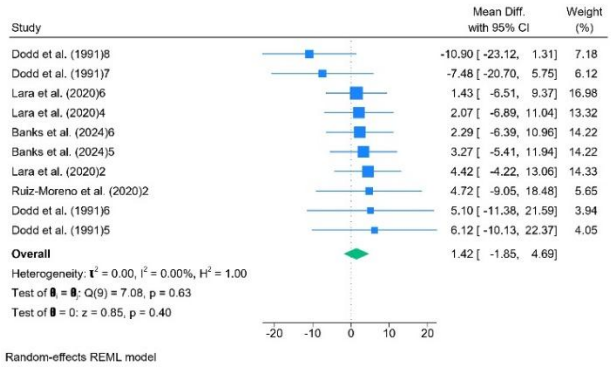

Figure 8. Forest plot of caffeine effects on VO2max/peak.

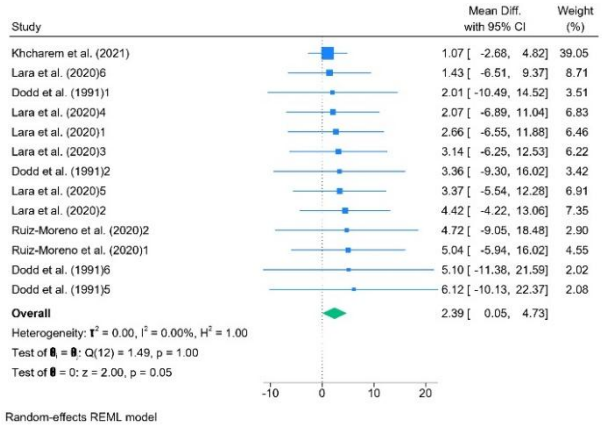

Figure 9. Forest plot of caffeine effects on endurance performance in the low habitual caffeine intake group.

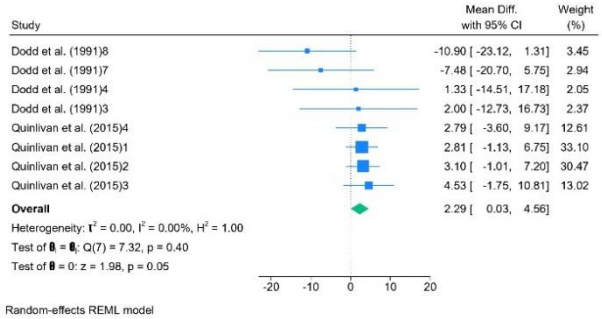

Figure 10. Forest plot of caffeine effects on endurance performance in the high habitual caffeine intake group.

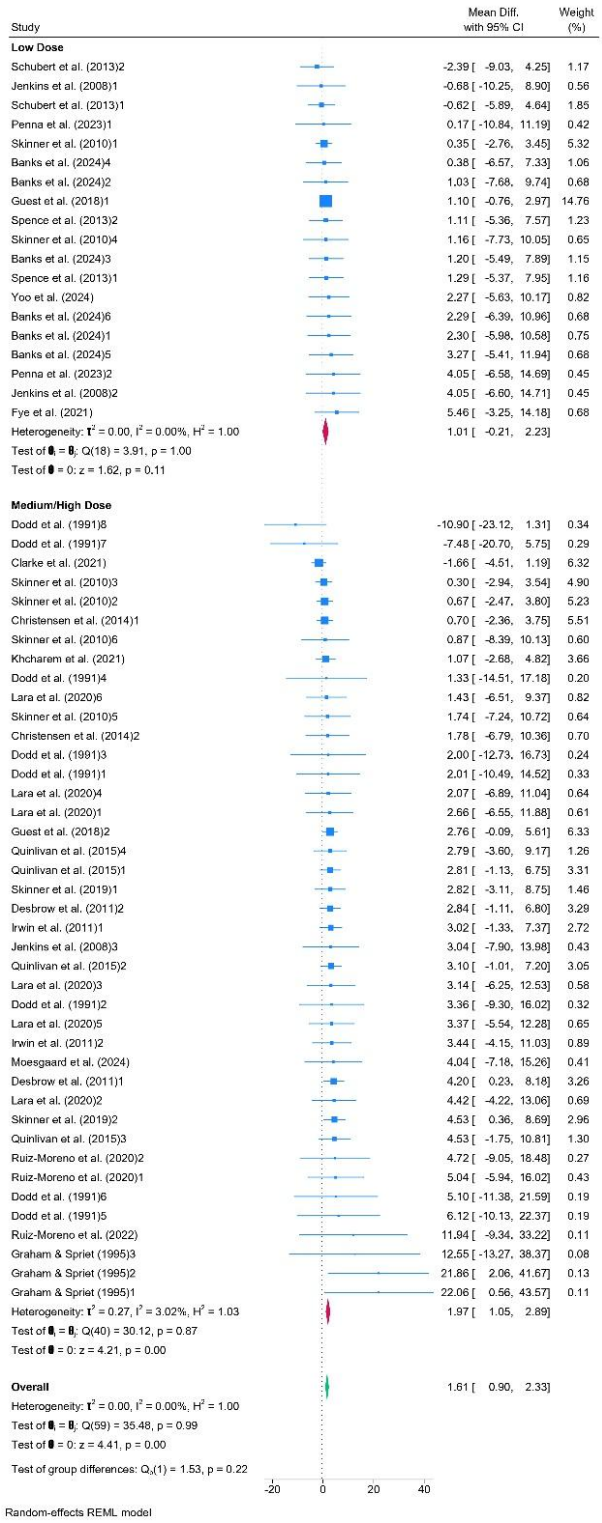

Figure 11. Forest plot of caffeine effects on endurance performance in the low-dose group and medium/high-dose group.

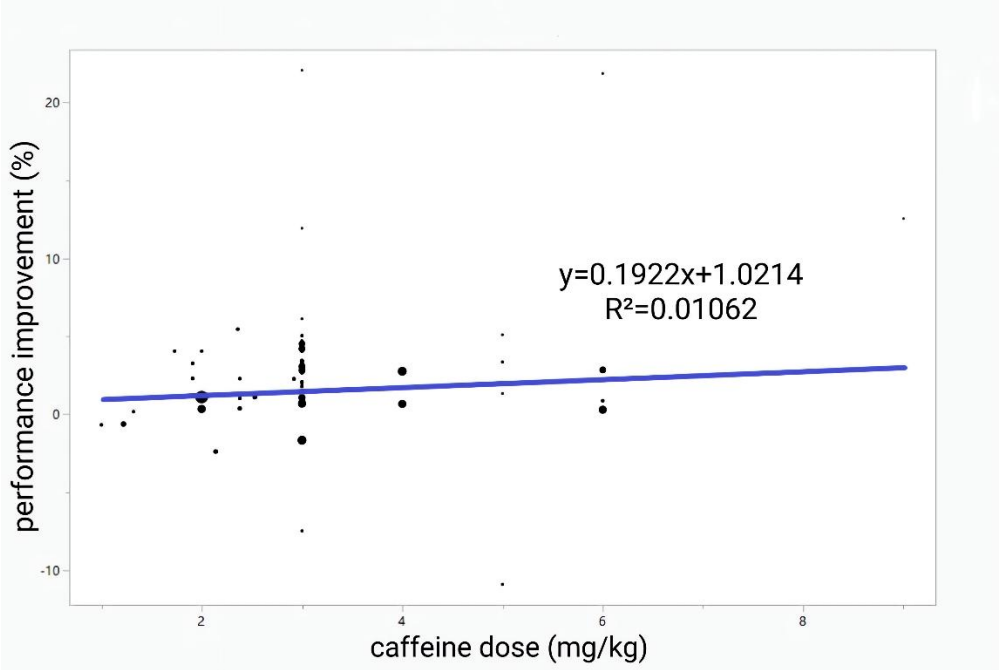

Figure 12. Relationship between caffeine dose and performance improvement.