Review

Dose-Response Effect of Oral Caffeine Use on Aerobic Exercise Performance: A Systematic Review and Meta-Analysis

Gabriel L. Martins [*], Juliana M. Aparecido, Marcelo L. Marquezi, Caroline S. Frientes, Leonardo R. Miedes, Matheus S. Fornel, Tiago Fernandes [†], Antonio H. Lancha-Jr [*,†]

Posted Date: 8 May 2026

doi: 10.20944/preprints202605.0463.v1

Keywords: caffeine; aerobic exercise; moderate caffeine doses; low caffeine doses; ergogenic effect

 doi:10.20944/preprints202605.0463.v1

Review

Dose-Response Effect of Oral Caffeine Use on Aerobic Exercise Performance: A Systematic Review and Meta-Analysis

Gabriel L. Martins [1,2], Juliana M. Aparecido [3], Marcelo L. Marquezi [3], Caroline S. Frientes [3], Leonardo R. Miedes [3], Matheus S. Fornel [4], Tiago Fernandes [5,†] and Antônio H. Lancha Jr [2,6,†]

[1] Plenitude Education Institute, Sao Paulo 01409-000, SP, Brazil.
[2] Laboratory of Applied Nutrition and Metabolism, School of Physical Education and Sport, University of São Paulo, Sao Paulo 05508-030, SP, Brazil.
[3] Laboratory of Physical Education Research (LAPEF), University City of São Paulo (UNICID), Sao Paulo 03071-000, SP, Brazil.
[4] Paulista School of Nursing, Federal University of São Paulo, Sao Paulo 04024-002, SP, Brazil.
[5] Laboratory of Biochemistry and Molecular Biology of Exercise, School of Physical Education and Sport, University of São Paulo, Sao Paulo 05508-030, SP, Brazil.
[6] Laboratory of Clinical Investigation 26: Experimental Surgery, Department of Surgery, Hospital das Clínicas, Medical School, University of São Paulo, Sao Paulo 01246-903, SP, Brazil.
* Correspondence: Dr. Antonio Herbert Lancha Jr; E-mail: lanchajunior@gmail.com
† These authors contributed equally to this work.

Abstract

Background/Objective: Caffeine is one of the most extensively investigated supplements worldwide, with evidence showing improvements in physical performance across ingestion doses commonly used in sports nutrition (2–9 mg·kg^{-1}). However, studies report substantial variability in aerobic performance outcomes following caffeine intake, indicating that acute consumption may produce meaningful ergogenic effects but can also impair performance, with time-trial variation ranging from approximately –3% to +16%. Since higher doses may increase the risk of adverse side effects without offering clear added benefits, this review examined the effects of low (≤3 mg·kg^{-1}), moderate (4–6 mg·kg^{-1}), and high (>6 mg·kg^{-1}) caffeine doses on time-trial performance. Methods: A systematic review and meta-analysis of randomized, placebo-controlled clinical trials evaluating the effects of anhydrous caffeine on aerobic time-trial outcomes was conducted. Random-effects models were applied due to notable heterogeneity across studies, and risk of bias was assessed using the Cochrane Risk of Bias tool. Results: Forty-eight studies (716 participants) met the inclusion criteria. Both low and moderate caffeine doses significantly reduced time-trial completion time relative to placebo. Low doses produced a standardized mean difference of –0.27 (95% CI: –0.44 to –0.11; $p = 0.001$), whereas moderate doses resulted in an SMD of –0.52 (95% CI: –0.77 to –0.28; $p < 0.0001$). Conclusion: This is the first meta-analysis to demonstrate that pre-exercise ingestion of low caffeine doses (1.3–3 mg·kg^{-1}) can enhance generalized aerobic performance. Notably, the use of moderate caffeine doses (4–6 mg·kg^{-1}) appears to produce a more consistent ergogenic effect.

Keywords: caffeine; aerobic exercise; moderate caffeine doses; low caffeine doses; ergogenic effect

1. Introduction

The popularity of caffeine as an ergogenic aid is not a recent phenomenon. The stimulant is supported by a substantial scientific foundation demonstrating its benefits on exercise performance, with a relatively favorable safety profile in studies conducted prior to the 2000s CE—a body of evidence that prompted the World Anti-Doping Agency (WADA) to remove caffeine from its list of

 doi:10.20944/preprints202605.0463.v1

"prohibited substances" as of January 1st, 2004[1]. [number]. By the early 2000s, caffeine supplementation had already gained prominence in position stands, consensus statements, and conferences organized by leading authorities in the field, such as the International Society of Sports Nutrition (ISSN) and the International Olympic Committee (IOC)[2,3]. At that time, both organizations classified caffeine within a select group of substances capable of enhancing aerobic sports performance, primarily due to its effects on adenosine receptors in the central nervous system (CNS), which are strongly associated with reduced perception of exertion (i.e., physical discomfort) and parallel increases in alertness and vigor when doses ranging from 3–6 mg of caffeine per kilogram of body mass were ingested prior to aerobic exercise.

Incorporating nearly a decade of new research, updated ISSN and IOC position stands reinforced previous statements. Although there is substantial variability in performance responses following caffeine ingestion, the updated guidelines consolidated that lower caffeine doses (~2 $mg \cdot kg^{-1}$) may positively influence aerobic exercise performance, with no apparent additional benefits from ingesting ≥9 $mg \cdot kg^{-1}$ [4,5]. In part, these developments motivated researchers to investigate whether caffeine could exert ergogenic effects across a broader dosage range (2–9 $mg \cdot kg^{-1}$) [6–8]. This line of inquiry is based on the hypothesis that caffeine may produce optimized CNS-mediated effects at low doses (2–3 $mg \cdot kg^{-1}$), while increases in dosage may or may not be accompanied by additional peripheral physiological effects—such as elevated ionic calcium concentrations and enhanced muscle fiber contractile force via actin–calcium–myosin interactions [8,9].

Additionally, a comprehensive review of 21 meta-analyses conducted by Grgic et al. (2020) [10] identified substantial variability in the magnitude of caffeine's ergogenic effects across investigations focusing on time trial and time to exhaustion performance. The authors reported that caffeine could yield small to moderate improvements in motor performance (Cohen's d ranging from 0.22 to 0.68). Given the methodological differences among meta-analyses evaluating caffeine's impact on aerobic performance, including exercise protocol type, performance metrics, timing of caffeine administration, supplementation vehicle or form, and even the year the meta-analysis was conducted, these findings should be interpreted cautiously. Within this context, few meta-analyses have explicitly examined the dose–response relationship between caffeine and aerobic performance [11,12]. Interestingly, both contradict current position stands from major international organizations by reporting a lack of ergogenic effects from low caffeine doses (1–3 $mg \cdot kg^{-1}$). Notably, both studies analyzed athletic performance primarily through event completion time (seconds or minutes) and mean power output (or physical work performed, expressed in watts) based on data extracted from eligible trials. Moreover, the two meta-analyses reported different "average effect sizes" for performance improvements associated with moderate caffeine doses, ranging from small to moderate [11,12]. These discrepancies limit interpretability and hinder a clear understanding of caffeine's dose–response effects in endurance-based sports (e.g., running, cycling, swimming, Ironman events), where final rankings are closely determined by precise temporal outcomes.

Based on this context, the present meta-analysis aims to comparatively investigate the effects of low (≤3 $mg \cdot kg^{-1}$), moderate (3.1–6 $mg \cdot kg^{-1}$), and high (>6 $mg \cdot kg^{-1}$) caffeine doses on performance outcomes exclusively related to time-trial completion across various exercise protocols. Given that caffeine consumption among competitive cyclists occurs primarily through caffeinated coffee and pharmaceutical preparations [13], and considering that caffeinated beverages may vary in caffeine content by more than 50% depending on factors such as cultivation conditions, bean type, and preparation method [14–16], the present investigation restricted inclusion criteria to studies administering pharmacological doses of anhydrous caffeine via oral ingestion (capsules or aqueous solutions).

2. Materials and Methods

2.1. Search Strategy

The search was restricted to a pre-established cutoff date of July 2022 (articles published up to July 1st, 2022) and conducted in accordance with the Preferred Reporting Items for Systematic

 doi:10.20944/preprints202605.0463.v1

Reviews and Meta-Analyses (PRISMA) guidelines—Prospero: CRD42022384198 [17]. Academic articles were identified through searches in the following electronic databases and libraries: the US National Library of Medicine (PubMed), the Virtual Health Library (VHL), and Embase.

The "PICo" framework (P = Population; I = Intervention; Co = Context) guided the development of the search strategy, which incorporated a combination of keywords and descriptors connected using the Boolean operators "OR" and "AND." An integrated title-based search was conducted using the following terms: "caffeine effect" AND "aerobic performance," OR "cross country performance," OR "time trial performance," OR "running performance," OR "endurance performance," AND "high dose," AND "low dose," AND "different doses." All reference selection and organizational procedures were managed using the mobile application designed for systematic reviews (Rayyan)[18], which facilitated real-time information sharing and workflow coordination among all authors involved in the present study.

2.2. Study Selection and Exclusion Criteria

Five independent reviewers (G.M., J.A., C.F., L.M., and M.F.) participated in the selection and screening process based on an initial evaluation of the titles and abstracts imported into the mobile application for systematic reviews. Each clinical article identified during the search was randomly assigned to one of the reviewers for assessment. For studies classified as "eligible" by a reviewer, a second evaluation was performed by another independent reviewer. In cases of disagreement regarding eligibility between the first two reviewers, the article was subsequently evaluated by a third reviewer (physiologist, DSc. M.M.) to determine the final decision. After the initial screening, full-text articles were examined by all five independent reviewers to verify whether the selected studies indeed met the eligibility criteria based on their methodological design and reported outcomes. When a study fulfilled all inclusion criteria but did not provide complete time-based performance measures (e.g., group means and standard deviations), the corresponding authors were contacted via email or ResearchGate to request the missing data. If the required information could not be obtained, the study was excluded due to the impossibility of performing proper analyses.

The inclusion criteria for the studies in our analyses were as follows: (1) Subjects—healthy adult individuals (ages 18-59 years); (2) Intervention—studies that examined only the effects of prior oral supplementation with pharmacological dosages of caffeine (via capsules or through an aqueous solution) in time trial aerobic tests lasting at least 3 minutes—thus characterizing a major use of aerobic energy metabolism in the exercise performed[19]; (3) Comparators—included a placebo group as a control; (4) Outcome—the intervention measured the improvement in time trial aerobic performance only through units of time measurement (such as seconds and/or minutes); (5) Publication period — original articles published until July 2022.

The exclusion criteria were: (A) The published clinical trial was not written entirely in English; (B) The pharmacological dosage of caffeine was not adjusted for the total weight of the participants; (C) Caffeine treatment involved dose fractionation during and before the start of performance tests; (D) Pharmacological use of caffeine was employed in combination with other known or potential ergogenic compounds (such as: creatine, beta-alanine, sodium bicarbonate, L-citrulline, or nitrates); (E) Caffeine administration was performed via dietary sources (e.g., filtered coffee and energy drinks) or through alternative forms of supplementation (such as: chewing gum, mouthwash, or sprays); (F) High-intensity interval training protocols and/or graded tests to exhaustion were performed; (G) Caffeine use was performed in the context of prior (partial or total) sleep deprivation; (H) Improvement in aerobic performance was measured through total work performed and/or total distance covered; (I) Data that could be used in this meta-analysis could not be obtained (absence of mean and standard deviation in performance tests).

2.3. Risk of Bias Assessment

After the randomized studies were selected through the search strategy, the risk of bias for each included study was evaluated using the "Risk of Bias" tool, version 2.0 (RoB2) [20,21], following the

 doi:10.20944/preprints202605.0463.v1

guidelines of the Cochrane Collaboration. The Cochrane tool for randomized controlled trials assesses risk of bias across the following domains: selection bias, performance bias, attrition bias, reporting bias, detection bias, and other potential sources of bias. For each domain, the risk of bias was classified as (1) low risk of bias, (2) unclear risk of bias, or (3) high risk of bias. It is important to note that the scale was used as an indicator of scientific evidence rather than as an exclusionary criterion.

2.4. Statistical Analysis

Aerobic performance measures from eligible studies (means and standard deviations) were used to construct forest plots in Review Manager software (version 5.4.1). A continuous random-effects model, based on the inverse variance method, was applied to efficiently calculate the effect size associated with the administration of low (≤3 mg·kg^{-1}), moderate (3.1–6 mg·kg^{-1}), or high (≥6.1 mg·kg^{-1}) caffeine doses (treatment group) compared with the effect generated under placebo conditions (control group). Effect size (ES) distribution was considered heterogeneous if the chi-square test (I^2) reached statistical significance at $p < 0.05$, with a 95% confidence interval (95% CI). Heterogeneity was evaluated using the I^2 statistic, with values of <25%, ≥50%, and ≥75% interpreted as low, moderate, and high heterogeneity, respectively [21].

Qualitative publication bias was also assessed for each forest plot through the construction of funnel plots and Kendall's tau, which examined the dispersion of the standardized mean difference of each study relative to its standard error and the 95% CI of the pooled sample. If any study appeared outside the 95% CI limits of the overall analysis, an additional complementary forest plot was generated without the respective study to confirm the presence of any detected effect (supplementary figures available).

3. Results

3.1. Study Selection

Our initial search identified 6,948 article titles, which were reduced to 3,010 after the removal of duplicate records using automation tools (Rayyan) followed by a secondary manual verification. After screening titles and abstracts—and excluding studies that were letters, reviews, meta-analyses, or original articles that did not assess exercise performance and/or did not administer pharmacological doses of caffeine specifically adjusted to participant body mass (mg·kg^{-1})—a total of 212 studies were selected for full-text reading and methodological assessment. Articles with abstracts in English but full texts available only in other languages, as well as studies not accessible in full (by databases or ResearchGate), were excluded, resulting in 203 articles eligible for full-text evaluation by the reviewers. Of the 203 studies initially selected for full-text review, we excluded 38 studies in which aerobic performance was assessed to exhaustion (rather than through time-trial performance tests); 37 studies due to the use of divergent performance outcome metrics (distance, watts, power output, etc.); 28 studies because caffeine administration was combined with other known or potential ergogenic substances; 21 studies in which caffeine was delivered through alternative forms (aerosols, chewing gum, or mouth rinses); 18 studies because caffeine dosage was fractionated at different moments (before and during time-trial tests); 9 studies because the total duration of the time-trial tests was under 180 seconds; and 4 studies due to the absence of complete performance-time data (means and standard deviations), which remained unobtainable after attempts to contact the authors (by e-mail or ResearchGate). Finally, 1 study was excluded after full-text assessment because caffeine was tested under conditions of prior sleep restriction.

After all exclusions, 47 articles remained. These studies were then subjected to a more detailed examination of their data, as well as to a verification of additional potentially eligible clinical trials cited within their reference lists (gray literature). During this process, it was identified that two of the selected articles [22,23] originated from the same cohort (registered under NCT 02109783), and therefore one of them [22] was excluded to avoid duplicate analysis of the same group of individuals. Moreover, two additional eligible studies identified through gray literature sources were

 doi:10.20944/preprints202605.0463.v1

incorporated into this meta-analysis. In total, 48 studies were included in the present meta-analysis (FIGURE 1).

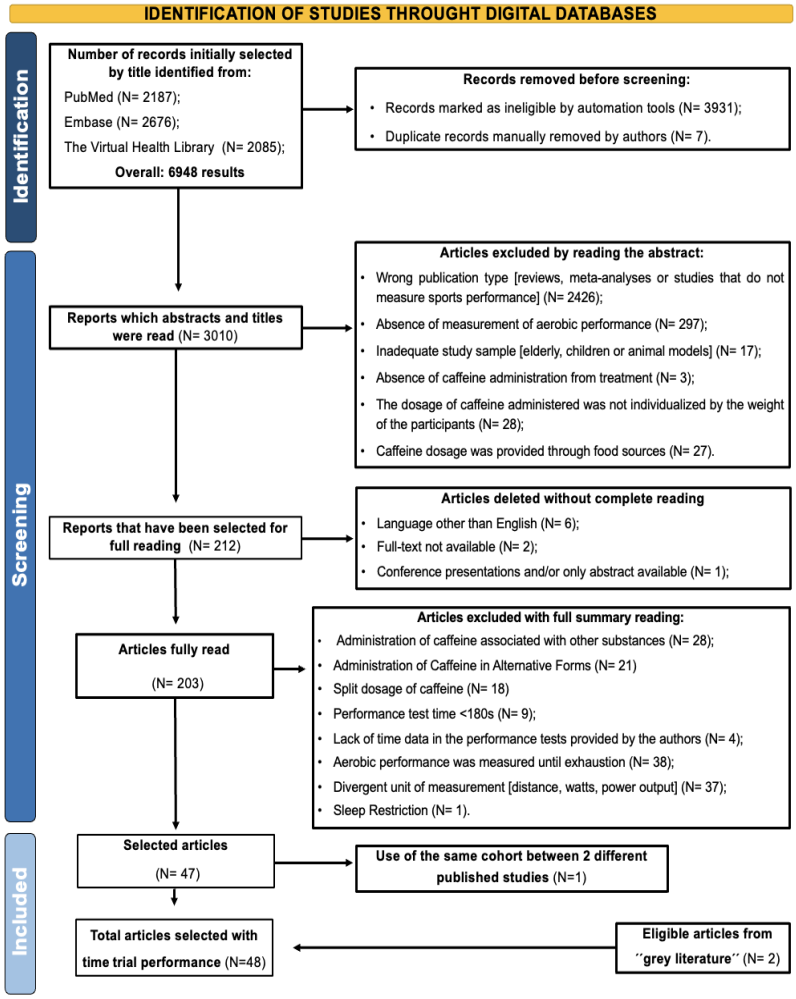

Figure 1. PRISMA flow diagram of research processes and excluded studies. Prepared from the PRISMA 2020 flow diagram [24].

3.2. Study Characteristics

The characteristics of the eligible studies (N = 48) are summarized in a table (TABLE 1). Variables such as publication year, sex and number of participants, aerobic capacity (VO_2max), acutely administered caffeine dose, timing of pre-exercise caffeine ingestion, the aerobic exercise protocol employed, as well as the mean change in performance observed in the caffeine-treated groups across the different pharmacological dosages (vs. placebo performance) were highlighted. The total sample consisted of 689 individuals (47 females [6.82%] and 642 males [93.18%]; mean participant age across studies ranged from 20 to 41.9 years). Ten studies (20.8%) did not report the cardiorespiratory fitness of their participants via VO_2max or VO_2peak. The pharmacological caffeine doses administered ranged from approximately 1.3 to 6 $mg \cdot kg^{-1}$ of body mass. Notably, no eligible studies employing high caffeine doses (>6 $mg \cdot kg^{-1}$) with performance outcomes quantified strictly by time (mean ± SD) were identified in the present assessment.

Regarding the characteristics of the time-trial performance tests included in the studies, 33 involved cycling (68.75%), 10 involved running (20.84%), 2 were rowing competitions (4.17%), 1 involved skiing (2.08%), 1 swimming competition (2.08%), and 1 was a triathlon event (2.08%). Finally, four studies [25–28] reported an ergolytic effect in the caffeine-treated groups relative to

 doi:10.20944/preprints202605.0463.v1

control (maximum performance decrement of −3%), whereas the greatest mean improvement in performance observed across the included studies was +15.9% compared with the placebo group.

Table 1. General characteristics of the studies included (N = 48). CAF=caffeine group; PLA=placebo group; DM= Minimum duration of exercise performed among participants; NR=Not Reported.

Author/Year	Sample size and Age (years)	VO2max (ml/min/ kg-1)	Caffeine does (mg/ kg-1)	Timing (min)	Exercise protocol; DM	Change in average performance (caffeine vs. Placebo)
ACKER-HEWITT et al. (2012) [36]	10 ♂; 28 ± 9 years	66 ± 9	6	60	20km cyclin time trial; DM: 38.7 min	+1,35%
AL-NAWAISEH et al. (2020) [25]	11 (9♂ + 2♀); 24,5 ± 6,3 years	61 ± 6,1	5	60	5 km run; DM: ≈16.1 min	-2%
ASTORINO et al. (2011) [29]	16 ♂; 20,8-34 years	**Physically active Group:** 46,5 ± 6,3 **Physically Trained Group:** 57,5 ± 3,9	5	60	10km Cycling time trial; DM: ≈16,1 min.	**Physically active Group:** + 0,96% **Physically Trained Group:** + 1,61%
ASTORINO et al. (2012) [37]	10♀; 22,1 ± 1,9 years	*NR	6	60	8.2 km cycling time trial; DM:16,7 min.	+2,75%
ASTORINO et al. (2012) [30]	9 (8♂ + 1♀); 27,4 ± 5,9 years	57,5 ± 3,9	5	60	10km Cycling time trial; DM: ≈16 min.	+1,6%
BELL et al. (2002) [38]	12 (10♂ + 2♀); 33 ± 7 years	VO_2peak: 57,5 ± 3,4	4	60	10 km run with an extra 11 kg load; DM: 43.2 min.	+1,7%
BLOOMER et al. (2011) [39]	12 (6♂ + 6♀); 21,9 ± 2,9 years	*NR	4	60	10 km run; DM: ≈50,1 min.	+1%
BORBA et al. (2019) [40]	13 (8♂ + 5♀); 18–40 years	*NR.	6	60	1,6 km run; DM: 8,45 min.	+0,39%
BRIDGE et al. (2006) [41]	8 ♂; 21,3 ± 1,2 years	*NR.	3	60	8 km run; DM: ≈31min.	+1,2%
CONWAY et al. (2003) [42]	8 ♂; 25,5 ± 5 years	71,98 ± 3,9	6	60	Cycling time trial (work equivalent to 80% VO2max for 30 min.); DM: 21 min.	+15,9%
COUTO et al. (2022)[43]	9 ♂; 32,3 ± 6 years	55,2 ± 5,7	5	60	4 km run; DM: ≈5,9 min	+3,17%

 doi:10.20944/preprints202605.0463.v1

COX et al. (2002)[4]	12 ♂; 27,1 ± 1,3 years	VO_2peak: 66,4 ±1,3	6	60	Cycling time trial (Equivalent to 80% VO2max for 30 min.); DM: ≈27,5 min.	+ 3,4%
DEAN et al. (2009) [45]	8 ♂; 36,4 ± 6,1 years	52,5 ± 6,1	3	60	40 km cycling time trial; DM: ≈58 min.	+1,4%
DESBROW et al. (2009) [26]	9 ♂; 29,4 ± 4,5 years	VO_2 peak: 61,7 ± 4,8	1,5 and 3	60	Cycling time trial (Equivalent to approximately 82% PP for 30 min); DM: ≈26.3 min.	**1.5 mg.kg^{-1}:** -0,93% **3 mg.kg^{-1}:** +1,86%
DESBROW et al. (2012) [46]	16 ♂; 32,6 ± 8,3 years	VO2peak: 60,4 ± 4,1	3 and 6	90	Cycling time trial (Equivalent to approximately 75% PP for 1h); DM: 57,53 min.	**3 mg.kg^{-1}:** +4,2% **6 mg.kg^{-1}:** +2,9%
DUNCAN et al. (2016) [47]	12 ♂; 24,6 ± 6 years	*NR.	3	60	5 km run; DM: ≈21,5min.	+5,5%
FELIPPE et al. (2018) [48]	11 ♂; 34 ± 4 years	55 ± 4	5	60	4 km cycling time trial; DM: 6.5 min.	+1,8%
FERREIRA VIANA et al. (2020) [49]	9 ♂; 32 ± 7,5 years	55 ± 6,1	6	60	4 km cycling time trial; DM: 5.6 min.	+1.8%
FRANCO-ALVARENGA et al. (2019) [50]	12 ♂; 34,3 ± 6,2 years	58,9 ± 6,2	5	50	20 km cycling time trial; DM: 31.2 min.	+1.7%
GLAISTER et al. (2015) [51]	14♀; 31 ± 7 years	52,3 ± 4,9	5	60	20 km cycling time trial; DM: ≈33,4 min.	+ 2,12%
GLAISTER et al. (2021) [52]	40 ♂; 41,9 ± 8,6 years	47,05-61,5	5	60	Cycling time trial (work equivalent to 85% Wmax for 25 min); DM: 27.9 min.	+3,57%
GONÇALVES et al. (2017) [53]	40 ♂; 37 ± 8 years	50,10 ± 8,45	6	60	Cycling time trial (work equivalent to 85% Wmax for 30 min); DM: ≈27.8 min.	+2,89%
GRAHAM-PAULSON et al. (2016)[54]	11 ♂; 24 ± 4 years	VO_2peak: 42,9 ±7,3	4	45	10km cycling time trial; DM: ≈22.8min.	+1,8%
	100♂;		2			**2 mg.kg^{-1}:** +1,65%

 doi:10.20944/preprints202605.0463.v1

GUEST et al. (2020) [23]	25 ± 4 years	VO_2peak: 32-59	and 4	60	10-km cycling time trial; DM:17,4 min.	**4 mg.kg^{-1} :** +3%
HANSON et al. (2019) [27]	10 (6♂ + 4♀); 26 ± 9 years	46.9-71.6	3 and 6	60	10 km run; DM:45,2 min.	**3 mg.kg^{-1} :**-0,38% **6 mg.kg^{-1}:**+0,94%
HODGSON et al. (2013) [31]	8♂; 25 ± 4 years	58 ± 3	5	60	Cycling time trial (Equivalent to 70% Wmax for 45 min); DM: ≈37.9 min.	+4,27%
IRWIN et al. (2011) [55]	12♂; 28,3 ± 5,8 years	VO_2peak: 63,7 ± 7,4	3	90	Cycling time trial (work equivalent to 75% PP for 1 hour); DM: 53.85 min	+2,5%
KHCHAREM et al. (2021) [56]	13♂; 21,3 ± 0,8 years	51,3 ± 6.1	3	60	3 km run; DM: 9,5 min.	+1,1%
KILDING et al. (2012) [57]	10♂; 24,2 ± 5,4 years	*NR.	3	60	3km cycling time trial; DM: ≈3.62 min.	+ 0,96%
MACINTOSH et al. (1995) [58]	11 (7♂ + 4♀); 22,9 ± 1,1 years	*NR.	6	120-30	1.5 km swim test; DM: ≈20.4 min.	+2,97%
MORALES et al. (2020) [59]	14♂; 34,1 ± 4,4 years	51,5 ± 6,3	6	60	16km cycling time trial; DM: ≈26.7 min	+ 2,55%
O'ROURKE et al., (2008) [60]	30♂;23,3-41 years	*NR.	5	60	5 km run;DM: 16,3 min	**Physically active Group:** +1%; **Physically Trained Group:** +1,1%
PITCHFORD et al. (2014) [61]	9♂; 22–42 years	64,4 ± 6,8	3	90	Cycling time trial (Equivalent to 75% Wmax for 1 hour); DM: 57.5 min.	+6,7%
POLLOW et al. (2016) [34]	7♂; 26,9 ± 3,9 years	VO_2peak: 67,7 ±10,3	6	60	50km cycling time trial; DM: 80.9 min.	+ 0,6%
POTGIETER et al. (2018) [62]	26 (14♂ + 12♀); 37,8 ± 10,6 years	*NR.	6	60	Triathlon (1.5 km swim, 40 km bike, 10 km run); DM: 129.8 min.	+ 1,3%
QUINLIVAN et al. (2015) [63]	11♂; 31,7 ± 5,9 years	60,3 ±7,8	3	90	40km cycling time trial; DM: 58.50 min.	+ 3,1%
ROELANDS et al. (2011) [28]	8♂; 23 ± 5 years	*NR.	6	60	Cycling time trial (Equivalent to 75% Wmax for 30 min.); DM: 33.3 min.	-3%
SANTOS et al. (2013) [64]	8♂; 32,6 ± 5,4 years	57,5 ±5,8	5	60	4 km cycling time trial; DM: 6.6 min.	+2,4%

 doi:10.20944/preprints202605.0463.v1

SANTOS et al. (2020) [65]	16♂; 33,5 ± 5,2 years	**High Performance Group:** 57,3 ± 8,1 **Low Performance Group:** 48,9 ±10	5	60	4 km cycling time trial; DM: 5,9 min.	**High Performance Group:** +1,6% **Low Performance Group:** +2,5%;
SILVA-CALVACANTE et al. (2013) [66]	7♂; 32,3 ± 5,4 years	VO_2peak: 58,1±6,3	5	60	4km cycling time trial; DM: ≈6.5 min.	+3,9%
SCOTT et al. (2015) [32]	13♂; 21 ± 2 years	39,6-52,8	1,3 ± 0,1	10	2 km rowing performance; MD: ≈7.3 min.	+1,1%
SKINNER et al. (2010) [67]	10♂; 20,6 ± 1,4 years	58,15 ± 6,8	2, 4, and 6	60	2 km rowing performance; DM: ≈6,4 min.	**2 mg.kg^{-1} :** +0,35% **4 mg.kg^{-1} :** +0,67% **6 mg.kg^{-1}:**+0,30%
SKINNER et al. (2013) [68]	14♂; 31 ± 5 years	69,5 ±6,1	6	60	40km cycling time trial; DM: 56.3 min.	+2%
SKINNER et al. (2019) [35]	27 (16♂ + 11♀); 32,6 ±8,3 years	**Women's VO2peak:** 51.9 ± 7.2 **Men's—VO2peak:** 60.4 ±4.1	3	90	Cycling time trial (work equivalent to 75% Wmax for 60 min); DM: ≈57.5 min	**Women's:** +2,75% **Men's:** +4.33%
SPENCE et al. (2013) [69]	10♂; 30 ± 2 years	VO_2peak: 58,9 ± 2	2.5 ± 0.1	60	40km cycling time trial; DM: ≈71.5 min.	+1,29%
STADHEIM et al. (2013) [70]	10♂; 20 ± 1 years	69,3 ± 1	6	75	8-km cross-country Double Poling; DM: ≈31.6 min.	+ 3,64%
TOMAZINI et al. (2022) [71]	11♂; 33 ± 7 years	56.1 ± 13.2	5	60	4 km cycling time trial; DM: 6.4 min.	+ 1,05%
WALKER et al. (2008) [33]	9♂; 23 ± 3 years	71,2 ± 6,8	6	60	Cycling time trial (work equivalent to 70% PP for 30 min); DM: 25.4 min.	+3,9%

3.3. Risk of Bias Assessment and Funnel Plots

Risk of bias assessment was conducted for the 48 placebo-controlled crossover trials included in this review (FIGURE 2 and to observe the individual assessment of each study in Supplementary Figure 01). Eleven trials (22.92%) were classified as having a low risk of bias, with clear descriptions of the methodological domains evaluated—selection bias, performance bias, attrition bias, reporting bias, detection bias, and other domains. In contrast, 37 studies (77.08%) were classified as having an unclear risk of bias due to insufficient detail regarding randomization procedures and/or allocation of participants. Eight studies (16.6%) were identified as having a high risk of bias related to blinding procedures, either because assessor blinding was not implemented (single-blind methodological design)[27,29–33] or because blinding was compromised in more than 50% of the sample (i.e., despite the double-blind design, over half of the participants correctly identified whether they had ingested caffeine or placebo)[34,35].

 doi:10.20944/preprints202605.0463.v1

Regarding outcome assessment, 42 studies (87%) were classified as having a low risk of bias, while only 6 were considered to have an unclear risk of bias. In the domain of data analysis, a single study (2.08%) was categorized as having a high risk of bias due to reporting participant attrition exceeding 20% of the initially described sample [36]. Finally, all studies evaluating time-trial performance (N = 48; 100%) were classified as having a low risk of bias for the domains of "selective reporting" and "other sources of bias."

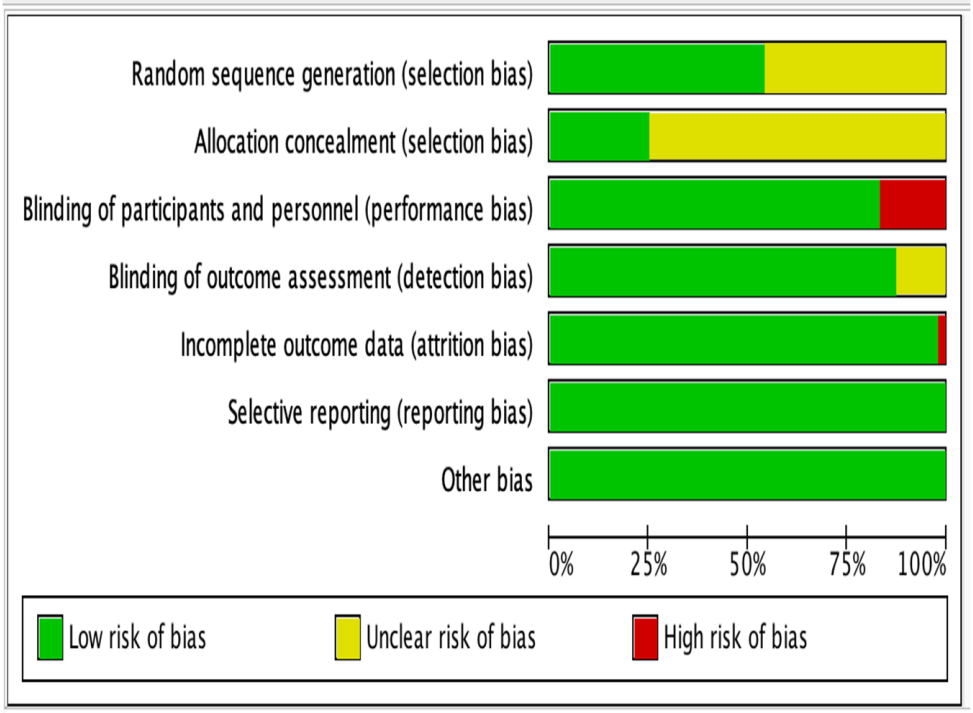

Figure 2. Global analysis by the authors on the risk of bias in studies that analyzed the influence of caffeine on aerobic performance. The analysis was performed using the Cochrane Risk of Bias analysis tool, version 2.0. The graph was created using the Review Manager 5.4.1 program, in its free version.

Analysis of the funnel plots for studies investigating low caffeine doses (N = 17; FIGURE 3.A) and moderate caffeine doses (N = 36; FIGURE 3.B) revealed that only two studies[23,31] fell outside the 95% confidence interval limits on the left side of the funnel plot. In part, the large number of articles included in the forest plot for studies administering moderate doses (3.1–6 $mg \cdot kg^{-1}$), as well as the substantially large sample size of one heterogeneous study[23], are factors that should be taken into consideration.

 doi:10.20944/preprints202605.0463.v1

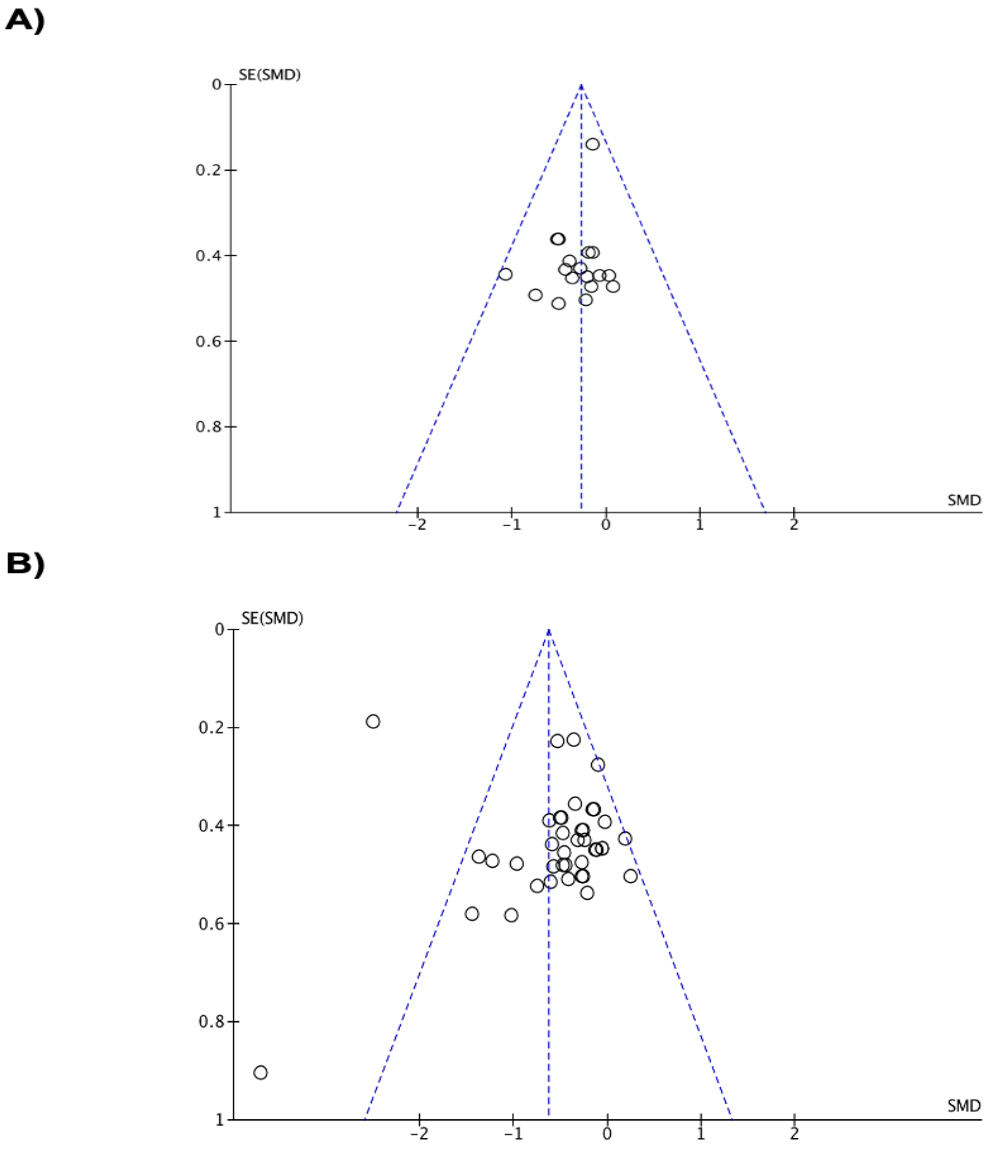

Figure 3. Funnel plot of studies comparing the use of caffeine treatment vs. control treatment (placebo) in aerobic performance tests. (A) Funnel plot of studies using low caffeine dosages (≤ 3 mg.kg-1) (B) Funnel plot of studies investigating the effects of moderate caffeine dosages (4-6 mg.kg-1) on time trial performance. Results from each of the analyzed studies are represented by circles, with the "y" axis representing the standard error of the data from each study and the "x" axis representing the difference from the standardized mean of their results. The graph was created using the Review Manager 5.4.1 program in its free version. The graph scale was represented as 4.5 SMD.

3.4. Meta-Analyses: Effect of Different Caffeine Dosages on Aerobic Time-Trial Performance

Sixteen clinical trials (33.3% of the eligible studies) investigated the effects of low caffeine dosages (≤3 mg·kg^{-1}) on time-trial performance, comprising a total of 287 participants in the caffeine-treated groups. The meta-analysis of these studies demonstrated that the ingestion of low caffeine doses (ranging from approximately 1.3 to 3 mg·kg^{-1}) resulted in a significant improvement in total time to complete aerobic time-trial tests (SMD = −0.27, 95% CI = −0.44 to −0.11, p = 0.001, I^2 = 0%)—For more details, see the FIGURE 4.

 doi:10.20944/preprints202605.0463.v1

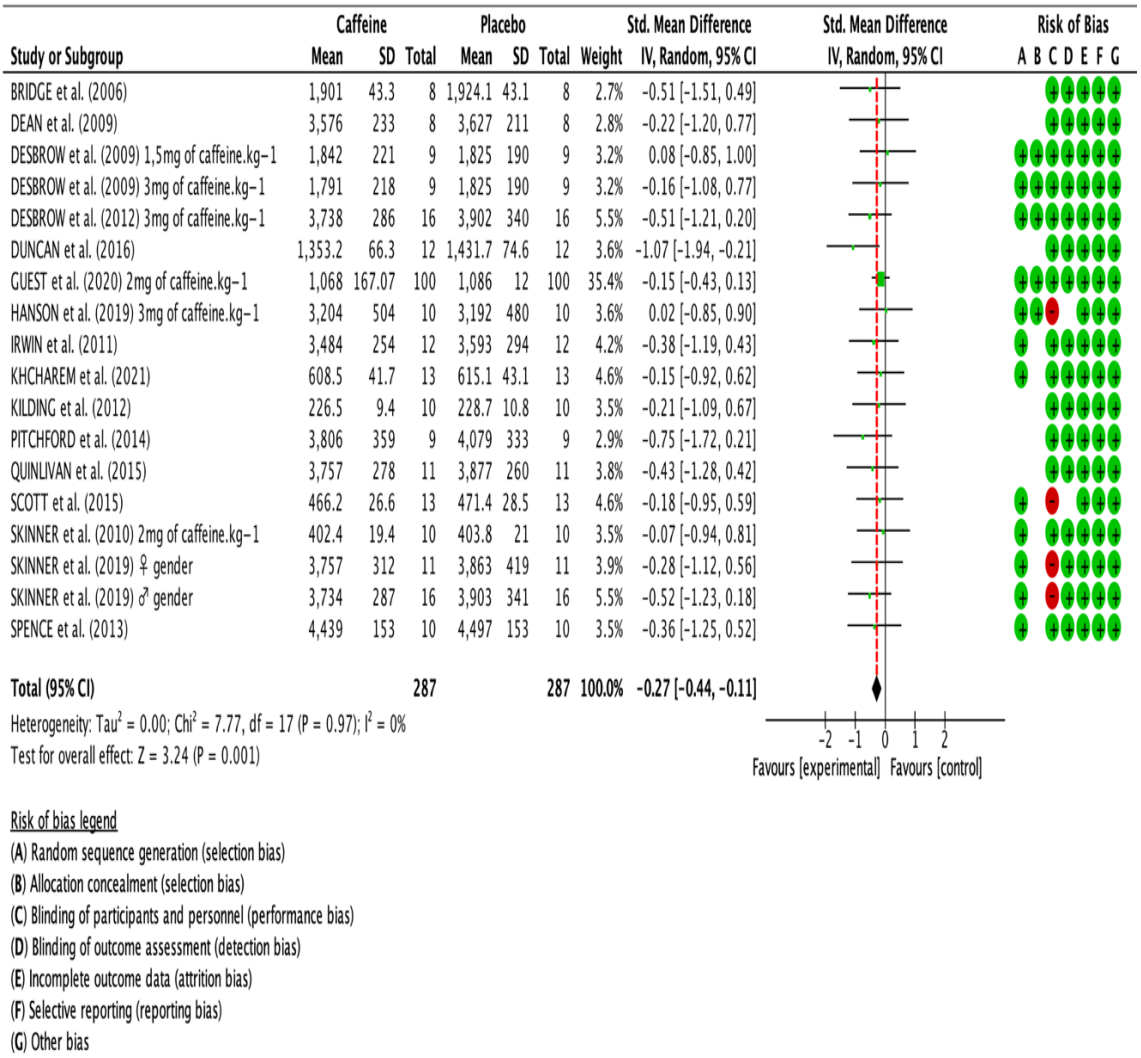

Figure 4. Forest plot for the effect of interventions using low doses of caffeine (~1.3 to 3 mg.kg-1) vs. the control group (placebo) on in aerobic time trials performance tests. The analysis of the effects of the data was performed randomly, with the overall mean effect and respective standard deviation represented by a 95% CI. The chi-square (I2) percentage value represents the percentage of heterogeneity among the samples of the studies included in this meta-analysis. All time measurements computed in this meta-analysis were parameterized in seconds, with the mean performance time values for each treatment condition placed in the "Mean" column and their respective standard deviations in the "SD" column. The graph scale was set to 3.99 for better comparison with other analyses.

Thirty-six eligible clinical trials (75% of the included studies) examined the effects of moderate caffeine dosages (3.1–6 mg·kg^{-1}) on time-trial performance, comprising a total of 584 participants across the various caffeine treatment conditions. The meta-analysis of these studies demonstrated that the ingestion of moderate caffeine doses (ranging from 4 to 6 mg·kg^{-1}) produced a significant improvement in total time to complete aerobic time-trial tests (SMD = −0.52, 95% CI = −0.77 to −0.28, $p < 0.0001$, $I^2 = 73\%$)—Further details are presented in FIGURE 5.

 doi:10.20944/preprints202605.0463.v1

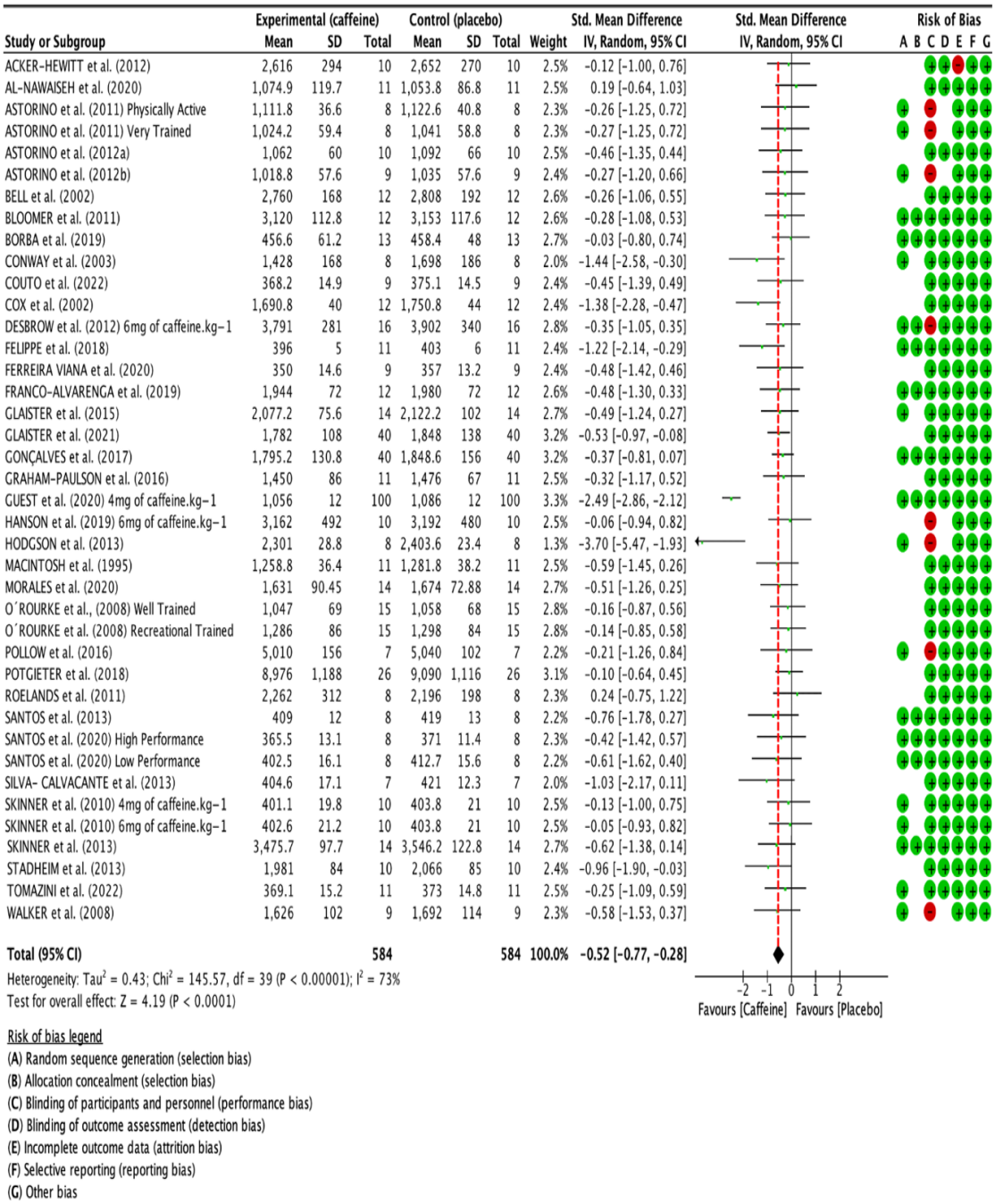

Figure 5. Forest plot for the effect of interventions using moderate doses of caffeine (4 to 6 mg.kg^{-1}) and placebo control in aerobic time trials performance tests. The analysis of the effects of the data was performed randomly, with the overall mean effect and respective standard deviation represented by a 95% CI. The chi-square (I2) percentage value represents the percentage of heterogeneity among the samples of the studies included in this meta-analysis. All time measurements computed in this meta-analysis were parameterized in seconds, with the mean performance time values for each treatment condition placed in the "Mean" column and their respective standard deviations in the "SD" column. The graph scale was set to 3.99 for better comparison with other analyses.

4. Discussion

The purpose of this systematic review and meta-analysis was to evaluate the effects of low (≤3 mg·kg^{-1}), moderate (4–6 mg·kg^{-1}), and high (>6 mg·kg^{-1}) caffeine doses on performance in aerobic-dominant time-trial events, such as long-distance running, cycling, swimming, and rowing. One of

 doi:10.20944/preprints202605.0463.v1

our primary findings was that the acute ingestion of low caffeine doses (~1.3 to 3 mg·kg^{-1}) can enhance aerobic time-trial performance (SMD = −0.27, 95% CI = −0.44 to −0.11), corresponding to an average performance improvement of 2.14% across the included tests. Complementarily, we observed that this performance enhancement was consistently identified with the use of moderate caffeine dosages (SMD = −0.52, 95% CI = −0.77 to −0.28), resulting in a mean improvement of 2.18% across all eligible studies. Notably, although the effect size associated with moderate caffeine doses was classified as moderate (Mean Effect Size: 0.52) and greater than the small effect observed with low caffeine doses (Mean Effect Size: 0.27), sensitivity analyses indicate that this difference is influenced by the data representation of the studies by Guest et al. (2020) [23] and Hodgson et al. (2013) [31], highlighting the need for additional consideration regarding the current state of the literature -for further details, see SUPPLEMENTARY FIGURE 02. Regardless, our findings align with the expected performance improvements (2–4%) reported by major international organizations [5].

In part, our results corroborate the average effect size reported for acute caffeine ingestion in the meta-analysis conducted by Chen and colleagues (2024)[11], reinforcing that pre-exercise caffeine consumption appears to enhance generalized aerobic time-trial performance (e.g., running, cycling, swimming) in a manner comparable to its effect on cycling specifically (moderate effect size reported: 0.5 vs. 0.52 observed in the present analysis). In contrast to the earlier meta-analysis [11], our study is the first to indicate that low caffeine doses statistically improve aerobic time-trial performance. This discrepancy may be partially explained by the inclusion of rowing and/or running performance tests in our review, which accounted for 37.5% of all eligible studies using low caffeine doses, whereas Chen et al. (2024) [11] evaluated only cycling performance—which inherently limited the pool of eligible clinical trials.

There is substantial evidence that low caffeine doses (0.5–3 mg·kg^{-1}) exert central nervous system (CNS) effects capable of increasing alertness, vigilance, and attention, as well as reducing reaction time and enhancing cognitive focus in humans [72]. Even in studies where caffeine dosage was not standardized relative to body mass, time-trial performance tests have demonstrated that the use of low doses of caffeine (100–200 mg) can improve performance and reduce ratings of perceived exertion [73,74]. Although the results of our meta-analysis reinforce that the ergogenic effects of caffeine on aerobic time-trial performance occur with low doses and increase with the use of moderate doses, it is important to highlight that this dose–benefit pattern was not consistently observed across all studies that examined more than one caffeine dosage. Two studies found no dose-dependent improvements in performance [46,67], whereas three studies [23,26,27] reported greater performance gains with higher caffeine doses. In part, this variability in the effectiveness of different caffeine doses may be explained by genetic polymorphisms affecting caffeine metabolism (particularly within the CYP1A2 gene), as well as by the small sample sizes frequently observed in clinical studies on this topic [5,8]. Future research should investigate the impact of low and moderate caffeine doses among fast and slow CYP1A2 metabolizers to provide more precise insights into caffeine's dose–response relationships.

Finally, we emphasize that no eligible clinical trials were identified using high caffeine doses (>6 mg·kg^{-1}) before aerobic time-trial performance tests. This scarcity of studies in the academic literature was also noted in a recent meta-analysis [11] and may be attributable either to the absence of time-based performance outcomes [75] or to the lack of available mean and standard deviation values [76] in the few studies that have been conducted. From this perspective, it is essential that future clinical trials examine the risk–benefit profile of high caffeine doses (>6 mg·kg^{-1}), both in terms of aerobic time-trial performance and in relation to the potential adverse effects commonly associated with high caffeine intake, such as: anxiety, heart palpitations, headaches, insomnia, and gastrointestinal disorders [77].

5. Conclusions

This systematic review and meta-analysis demonstrated that the pre-exercise use of low caffeine doses (1.3–3 mg·kg^{-1}) can enhance generalized aerobic time-trial performance (Mean Effect Size: 0.27;

 doi:10.20944/preprints202605.0463.v1

p = 0.001). In addition, the use of moderate caffeine doses (4–6 mg·kg^{-1}) appears to promote a more consistent ergogenic effect, reducing total completion time in aerobic time-trial tests (Mean Effect Size: −0.5; p < 0.0001). Although a dose–response effect was observed, studies employing moderate caffeine doses displayed high heterogeneity (I^2 = 73%) and a wider range of effect sizes (−0.77 to −0.28). This variability may be partly attributable to the limited number of published studies using moderate doses, as well as the substantial statistical influence of one eligible study. Finally, no previously published studies investigating the use of high caffeine doses (>6 mg·kg^{-1}) in aerobic time-trial performance were deemed eligible. This finding underscores the lack of high-quality research examining the effects of high caffeine dosages.

Supplementary Materials: The supplementary figure, representing a sensitivity analysis of studies using moderate caffeine doses can be accessed at Preprints.org.

Author Contributions: GM: TF and AL are responsible for the conception of this present work. GM, JA, MM, CF, LM and MF were responsible for reviewing the literature and data curation. GM writing—original draft preparation and created the images and tables. AL, TF and JA reviewed and made significant contributions to the manuscript. All authors approved the final version of this manuscript.

Funding: A.H.L.J. is supported by the National Council for Scientific and Technological Development (CNPq) Bolsa Produtividade 1A #302706/2020-8 and Financial Support CNPq #437801/2018-7. T. F. is supported by CNPq grants (#409629/2021-9; #312628/2023-4; #408899/2024-7) and São Paulo Research Foundation (FAPESP) grants (#2022/03138-2; #2023/14680-5). GM was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Financial Support: 88887.357773/2019-00. CAPES-PROEX-Finance Code 001.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: The original version of this manuscript was written in Portuguese without the use of generative artificial intelligence (GenAI). The manuscript was subsequently translated and adapted into English without the use of GenAI tools. After the manuscript was completed, GenAI was used solely for language refinement and editing to improve clarity and fluency in English, with the assistance of the paid version of ChatGPT (Thinking 5.4).

Conflicts of Interest: The authors declare that the research was conducted in the absence of any financial or professional relationships that could be construed as a potential conflict of interest.

References

1. Diel, P. Caffeine and doping—What have we learned since 2004. *Nutrients* **2020**, 12, 2167.
2. Goldstein, E.R.; Ziegenfuss, T.; Kalman, D.; et al. International Society of Sports Nutrition position stand: Caffeine and performance. *J. Int. Soc. Sports Nutr.* **2010**, 7, 5.
3. Maughan, R.J.; Shirreffs, S.M. IOC consensus conference on nutrition in sport. *J. Sports Sci.* **2011**, 29, S1.
4. Maughan, R.J.; Burke, L.M.; Dvorak, J.; et al. IOC consensus statement: Dietary supplements and the high-performance athlete. *Int. J. Sport Nutr. Exerc. Metab.* **2018**, 28, 104–125.
5. Guest, N.S.; VanDusseldorp, T.A.; Nelson, M.T.; et al. International Society of Sports Nutrition position stand: Caffeine and exercise performance. *J. Int. Soc. Sports Nutr.* **2021**, 18, 1.
6. Grgic, J. Exploring the minimum ergogenic dose of caffeine on resistance exercise performance: A meta-analytic approach. *Nutrition* **2022**, 97, 111604.
7. Grgic, J. Effects of caffeine on resistance exercise: A review of recent research. *Sports Med.* **2021**, 51, 2281–2298.
8. Martins, G.L.; Guilherme, J.P.L.F.; Ferreira, L.H.B.; de Souza-Junior, T.P.; Lancha, A.H., Jr. Caffeine and exercise performance: Possible directions for definitive findings. *Front. Sports Act. Living* **2020**, 2, 574854.

 doi:10.20944/preprints202605.0463.v1

9. Ferreira, L.H.B.; de Souza Gonçalves, L.; dos Santos, M.G.; et al. High doses of caffeine increase muscle strength and calcium release in plasma of recreationally trained men. *Nutrients* **2022**, 14, 4921.
10. Grgic, J.; Trexler, E.T.; Lazinica, B.; Pedisic, Z. Wake up and smell the coffee: Caffeine supplementation and exercise performance—An umbrella review of 21 meta-analyses. *Br. J. Sports Med.* **2020**, 54, 681–688.
11. Chen, B.; Nakagawa, A.; Hongu, N.; et al. Effect of caffeine ingestion on time trial performance in cyclists: A systematic review and meta-analysis. *J. Int. Soc. Sports Nutr.* **2024**, 21, 2363789.
12. Ribeiro, B.G.; Carvalho, T.; Schwingel, P.A.; et al. Acute effects of caffeine intake on athletic performance: A systematic review and meta-analysis. *Rev. Chil. Nutr.* **2017**, 44, 283–291.
13. Chester, N.; Wojek, N. Caffeine consumption amongst British athletes following changes to the WADA prohibited list. *Int. J. Sports Med.* **2008**, 29, 524–528.
14. Bravo, J.; Juániz, I.; Monente, C.; et al. Evaluation of spent coffee obtained from common coffeemakers as a source of hydrophilic bioactive compounds. *J. Agric. Food Chem.* **2012,** 60, 12565–12573.
15. Desbrow, B.; Hall, S.; Irwin, C. Caffeine content of Nespresso pod coffee. *Nutr. Health* **2019**, 25, 3–7.
16. McCusker, R.R.; Goldberger, B.A.; Cone, E.J. Caffeine content of specialty coffees. *J. Anal. Toxicol.* **2003**, 27, 520–522.
17. Moher, D.; Shamseer, L.; Clarke, M.; et al. Preferred reporting items for systematic reviews and meta-analyses statement. *Ann. Intern. Med.* **2014**, 151, 264–269.
18. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan: A web and mobile app for systematic reviews. *Syst. Rev.* **2016**, 5, 210.
19. Gastin, P.B. Energy system interaction and relative contribution during maximal exercise. *Sports Med.* **2001**, 31, 725–741.
20. Sterne, J.A.C.; Savović, J.; Page, M.J.; et al. RoB 2: A revised tool for assessing risk of bias in randomized trials. *BMJ* **2019**, 366, l4898.
21. Higgins, J.P.T.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, 327, 557–560.
22. Guest, N.; Corey, P.; Vescovi, J.; El-Sohemy, A. Caffeine, CYP1A2 genotype, and endurance performance in athletes. *Med. Sci. Sports Exerc.* **2018**, 50, 1570–1578.
23. Guest, N.S.; Corey, P.N.; El-Sohemy, A. Effect of caffeine on endurance performance in athletes may depend on HTR2A and CYP1A2 genotypes. *J. Strength Cond. Res.* **2020**, 1–7.
24. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Syst. Rev.* **2021**, 10, 89.
25. Al-Nawaiseh, A.M.; Al-Khazaleh, A.; Al-Kaabi, A.; et al. No significant effect of caffeine on five kilometer running performance after muscle damage. *Int. J. Vitam. Nutr. Res.* **2020**, 1–9.
26. Desbrow, B.; Anderson, S.; Barrett, J.; et al. Caffeine, cycling performance, and exogenous carbohydrate oxidation: A dose-response study. *Med. Sci. Sports Exerc.* **2009**, 41, 1744–1751.
27. Hanson, N.J.; Scheadler, C.M.; Larson, S.K.; et al. Increased rate of heat storage and no performance benefits with caffeine ingestion before a 10 km run in hot conditions. *Int. J. Sports Physiol. Perform.* **2019**, 14, 196–202.
28. Roelands, B.; Goekint, M.; Buyse, L.; et al. No effect of caffeine on exercise performance in high ambient temperature. *Eur. J. Appl. Physiol.* **2011**, 111, 3089–3095.
29. Astorino, T.A.; Rohwer, K.; Bartolini, A. Ergogenic effects of caffeine on simulated time trial performance are independent of fitness level. *J. Caffeine Res.* **2011**, 1, 179–185.
30. Astorino, T.A.; Cottrell, T.; Talhami Lozano, A.; Aburto-Prins, Z. Increases in cycling performance in response to caffeine ingestion are repeatable. *Nutr. Res.* **2012**, 32, 78–84.
31. Hodgson, A.B.; Randell, R.K.; Jeukendrup, A.E. The metabolic and performance effects of caffeine compared to coffee during endurance exercise. *PLoS ONE* **2013**, 8, e59561.
32. Scott, A.T.; Slivka, D.; Esposito, P.; et al. Improvement of 2000 m rowing performance with caffeinated carbohydrate gel ingestion. *Int. J. Sports Physiol. Perform.* **2015**, 10, 464–468.
33. Walker, G.J.; Hull, S.M.; Sweeting, A.J.; et al. The effect of caffeine ingestion on human neutrophil oxidative burst responses following time trial cycling. *J. Sports Sci.* **2008**, 26, 611–619.
34. Pollow, D.J., Jr.; Brubaker, P.H.; Del Coso, J.; et al. Caffeine does not affect improvements in cognition during prolonged high-intensity exercise. *J. Caffeine Res.* **2016**, 6, 163–171.

 doi:10.20944/preprints202605.0463.v1

35. Skinner, T.L.; Desbrow, B.; Arapova, J.; et al. Women experience the same ergogenic response to caffeine as men. *Med. Sci. Sports Exerc.* **2019**, 51, 1202.
36. Acker-Hewitt, T.L.; Heigenhauser, G.J.F.; Hargreaves, M.; Spriet, L.L. Independent and combined effects of carbohydrate and caffeine ingestion on aerobic cycling performance. *Appl. Physiol. Nutr. Metab.* **2012**, 37, 276–283.
37. Astorino, T.A.; Roupoli, L.R.; Valdivieso, B.R. Caffeine does not alter perceived exertion or pain during intense exercise in active women. *Appetite* **2012**, 59, 585–590.
38. Bell, D.G.; McLellan, T.M.; Sabiston, C.M. Effect of ingesting caffeine and ephedrine on 10 km run performance. *Def. Civ. Inst. Environ. Med.* **2002**.
39. Bloomer, R.J.; Canale, R.E.; McCarthy, C.G.; Farney, T.M. Effect of caffeine and 1,3-dimethylamylamine on exercise performance and blood markers of lipolysis and oxidative stress. *J. Caffeine Res.* **2011**, 1, 169–177.
40. Borba, G.L.; Moreira, O.C.; Azevedo, L.M.; et al. Acute caffeine and coconut oil intake, isolated or combined, does not improve running times: A randomized, placebo-controlled crossover study. *Nutrients* **2019**, 11, 1661.
41. Bridge, C.A.; Jones, M.A. The effect of caffeine ingestion on 8 km run performance in a field setting. *J. Sports Sci.* **2006**, 24, 433–439.
42. Conway, K.J.; Orr, R.; Stannard, S.R. Effect of a divided caffeine dose on endurance cycling performance, postexercise urinary caffeine concentration, and plasma paraxanthine. *J. Appl. Physiol.* **2003**, 94, 1557–1562.
43. Couto, P.G.; Silva-Cavalcante, M.D.; Coelho, D.B.; et al. Effects of caffeine on central and peripheral fatigue following closed and open loop cycling exercises. *Braz. J. Med. Biol. Res.* **2022**, 55, e11969.
44. Cox, G.R.; Desbrow, B.; Montgomery, P.G.; et al. Effect of different protocols of caffeine intake on metabolism and endurance performance. *J. Appl. Physiol.* **2002**, 93, 990–999.
45. Dean, S.; Braakhuis, A.; Paton, C. The effects of EGCG on fat oxidation and endurance performance in male cyclists. *Int. J. Sport Nutr. Exerc. Metab.* **2009**, 19, 624–644.
46. Desbrow, B.; Barrett, J.; Leveritt, M. The effects of different doses of caffeine on endurance cycling time trial performance. *J. Sports Sci.* **2012**, 30, 115–120.
47. Duncan, M.J.; Clarke, N.D.; Cox, M.; Tallis, J. The effect of caffeine and *Rhodiola rosea*, alone or in combination, on 5 km running performance. *J. Caffeine Res.* **2016**, 6, 40–48.
48. Felippe, L.C.; Ferreira, G.A.; Learsi, S.K.; Bertuzzi, R.; Lima-Silva, A.E. Caffeine increases total work performed above critical power and peripheral fatigue during a 4 km cycling time trial. *J. Appl. Physiol.* **2018**, 124, 1491–1501.
49. Ferreira Viana, B.; Aoki, M.S.; Silva-Cavalcante, M.D.; et al. Caffeine increases motor output entropy and performance in 4 km cycling time trial. *PLoS ONE* **2020**, 15, e0236592.
50. Franco-Alvarenga, P.E.; Brietzke, C.; Canestri, R.; et al. Caffeine improves cycling time trial performance in mentally fatigued cyclists. *Physiol. Behav.* **2019**, 204, 41–48.
51. Glaister, M.; Gissane, C.; Dempster, M.; et al. Effects of dietary nitrate, caffeine, and their combination on 20 km cycling time trial performance. *J. Strength Cond. Res.* **2015**, 29, 165–174.
52. Glaister, M.; Patterson, S.D.; Foley, P.; et al. Caffeine, exercise physiology, and time trial performance: No effect of ADORA2A or CYP1A2 genotypes. *Appl. Physiol. Nutr. Metab.* **2021**, 46, 541–551.
53. Gonçalves, L.S.; Painelli, V.S.; Yamaguchi, G.; et al. Dispelling the myth that habitual caffeine consumption influences the performance response to acute caffeine supplementation. *J. Appl. Physiol.* **2017**, 123, 213–220.
54. Graham-Paulson, T.; Perret, C.; Goosey-Tolfrey, V.L. Improvements in cycling but not handcycling 10 km time trial performance in habitual caffeine users. *Nutrients* **2016**, 8, 393.
55. Irwin, C.; Leveritt, M.; Shum, D. Caffeine withdrawal and high-intensity endurance cycling performance. *J. Sports Sci.***2011**, 29, 509–515.
56. Khcharem, A.; Kachouri, M.; Borji, R.; et al. Acute caffeine ingestion improves 3 km run performance, cognitive function, and psychological state. *Pharmacol. Biochem. Behav.* **2021**, 207, 173219.
57. Kilding, A.E.; Overton, C.; Gleave, J. Effects of caffeine and sodium bicarbonate on high-intensity cycling performance. *Int. J. Sport Nutr. Exerc. Metab.* **2012**, 22, 221–229.
58. Macintosh, B.R.; Wright, B.M. Caffeine ingestion and performance of a 1500 m swim. *Can. J. Appl. Physiol.* **1995**, 20, 168–177.

 doi:10.20944/preprints202605.0463.v1

59. Morales, A.P.; Silva-Cavalcante, M.D.; Lima-Silva, A.E.; et al. Caffeine supplementation does not induce tolerance to ergogenic effects in cyclists. *Nutrients* **2020**, 12, 2101.
60. O'Rourke, M.P.; O'Brien, B.J.; Knez, W.L.; et al. Caffeine has a small effect on 5 km running performance. *J. Sci. Med. Sport* **2008**, 11, 231–233.
61. Pitchford, N.W.; Fell, J.W.; Leveritt, M.; Sculley, D.V. Effect of caffeine on cycling time trial performance in the heat. *J. Sci. Med. Sport* **2014**, 17, 445–449.
62. Potgieter, S.; Wright, H.H.; Smith, C. Caffeine improves triathlon performance: A field study in males and females. *Int. J. Sport Nutr. Exerc. Metab.* **2018**, 28, 228–237.
63. Quinlivan, A.; Irwin, C.; Leveritt, M.; Desbrow, B. The effects of Red Bull energy drink compared with caffeine on cycling time trial performance. *Int. J. Sports Physiol. Perform.* **2015**, 10, 897–901.
64. Santos, R.A.; Silva-Cavalcante, M.D.; Correia-Oliveira, C.R.; et al. Caffeine alters anaerobic distribution and pacing during a 4000 m cycling time trial. *PLoS ONE* **2013**, 8, e75399.
65. Santos, P.S.; Aoki, M.S.; Silva-Cavalcante, M.D.; et al. Caffeine increases peripheral fatigue in low but not in high performing cyclists. *Appl. Physiol. Nutr. Metab.* **2020**, 45, 1208–1215.
66. Silva-Cavalcante, M.D.; Correia-Oliveira, C.R.; Santos, R.A.; et al. Caffeine increases anaerobic work and restores cycling performance following reduced carbohydrate availability. *PLoS ONE* **2013**, 8, e72025.
67. Skinner, T.L.; Jenkins, D.G.; Coombes, J.S.; et al. Dose response of caffeine on 2000 m rowing performance. *Med. Sci. Sports Exerc*. **2010**, 42, 571–576.
68. Skinner, T.L.; Jenkins, D.G.; Coombes, J.S.; et al. Coinciding exercise with peak serum caffeine does not improve cycling performance. *J. Sci. Med. Sport* **2013**, 16, 54–59.
69. Spence, A.L.; Sim, M.; Landers, G.; Peeling, P. A comparison of caffeine versus pseudoephedrine on cycling time trial performance. *Int. J. Sport Nutr. Exerc. Metab.* **2013**, 23, 507–512.
70. Stadheim, H.K.; Kvamme, B.; Olsen, R.; et al. Caffeine increases performance in cross-country double-poling time trial exercise. *Med. Sci. Sports Exerc.* **2013,** 45, 2175–2183.
71. Tomazini, F.; Pasqua, L.A.; Damasceno, M.V.; et al. Caffeine ingestion increases endurance performance when cycling against a virtual opponent. *Eur. J. Appl. Physiol.* **2022**, 122, 1915–1928.
72. McLellan, T.M.; Caldwell, J.A.; Lieberman, H.R. A review of caffeine's effects on cognitive, physical and occupational performance. *Neurosci. Biobehav. Rev.* **2016,** 71, 294–312.
73. Spriet, L.L. Exercise and sport performance with low doses of caffeine. *Sports Med.* **2014**, 44, 175–184.
74. Talanian, J.L.; Spriet, L.L. Low and moderate doses of caffeine late in exercise improve performance in trained cyclists. *Appl. Physiol. Nutr. Metab.* **2016**, 41, 850–855.
75. Wang, C.; Wang, S.; Chen, S.; et al. Effects of various doses of caffeine ingestion on intermittent exercise performance and cognition. *Brain Sci.* **2020**, 10, 595.
76. Cohen, B.S.; Johnson, J.L.; Coelho, A.J.; et al. Effects of caffeine ingestion on endurance racing in heat and humidity. *Eur. J. Appl. Physiol. Occup. Physiol.* **1996**, 73, 358–363.
77. de Souza, J.G.; Del Coso, J.; Fonseca, F.S.; et al. Risk or benefit? Side effects of caffeine supplementation in sport: A systematic review. *Eur. J. Nutr.* **2022**, 61, 1–12.