Review

Does ergogenic effect of caffeine supplementation depend on *CYP1A2 genotypes*? A systematic review with meta-analysis

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Abstract

Background: The ergogenic effects of caffeine intake on exercise performance are well-established, even if differences exist among individuals in response to caffeine intake. The genetic variation of a specific gene, human cytochrome P450 enzyme 1A2 (*CYP1A2*) (rs762551), may be one reason for this difference. This systematic review and meta-analysis aimed to comprehensively evaluate the influence of *CYP1A2* gene types on athletes' exercise performance after caffeine intake.

Methods: A literature search through 4 databases (Web of Science, PubMed, Scopus, and China National Knowledge Infrastructure) was conducted until March 2023. The effect size was expressed as the weighted mean difference (WMD) by calculating fixed effects meta-analysis if heterogeneity was not significant ($I^2 \leq 50\%$ and $p \geq 0.1$). Subgroup analyses were performed based on AA and AC/CC genotype of *CYP1A2*.

Results: The final number of studies meeting the inclusion criteria was 12 ($n = 666$ participants). The overall analysis showed that the cycling time trial significantly improved after caffeine intake (WMD = −0.48, 95% confidence interval (95%CI): −0.83 to −0.13, $p = 0.007$). In subgroup analyses, acute caffeine intake improved cycling time trial only in individuals with the A allele (WMD = −0.90, 95%CI: −1.48 to −0.33, $p = 0.002$), but not the C allele (WMD = −0.08, 95%CI: −0.32 to 0.17, $p = 0.53$). Caffeine supplementation did not influence the Wingate (WMD = 8.07, 95%CI: −22.04 to 38.18, $p = 0.60$) or countermovement jump test (CMJ) performance (WMD = 1.17, 95%CI: −0.02 to 2.36, $p = 0.05$), and these outcomes were not influenced by *CYP1A2* genotype.

Conclusion: Participants with the *CYP1A2 genotype* with A allele improved their cycling time trials after caffeine supplementation. However, compared to placebo, acute caffeine supplementation failed to increase the Wingate or CMJ performance, regardless of *CYP1A2 genotype*.

Keywords: Countermovement jump test; Endurance; Ergogenic aid; Gene polymorphism; Wingate

1. Introduction

Caffeine is a well-established ergogenic agent, known to enhance athletic performance.[1] In particular, endurance performance can be improved when a dose ranging from 3 to 6 mg per kilogram of body weight is consumed.[1,2] Although numerous studies have demonstrated an improvement in endurance performance (i.e., a reduction in time trial) and power performance (increase in jumping height) following caffeine supplementation,[2−4] a substantial interindividual variability still exists in response to caffeine ingestion.[5] Therefore, some individuals may experience beneficial effects from caffeine consumption, while others may experience no effects or even adverse reactions, such as palpitation and insomnia. In fact, a significant proportion of individuals fail to experience performance improvements, as nearly 30% of athletes report adverse effects (Table 1). This variability in responses could be partly attributed to genetic

Cite this article: Wang J, Dewi L, Peng Y, Hou C-W, Song Y, Condello G. Does ergogenic effect of caffeine supplementation depend on *CYP1A2 genotypes*? A systematic review with meta-analysis. *J Sport Health Sci* 2024;13:499−508.

Table 1
Individual responses to exercise performance after consuming caffeine with adverse effects.

Study	Exercise mode	Caffeine dosage	Ingestion time	Sample size	Did not improve	Adverse effect
Acker-Hewitt et al. (2012)[60]	20-km cycling	6 mg/kg	60 min prior	10 male cyclists	4 participants	Not identified
Astorino et al. (2011)[61]	10-km cycling	5 mg/kg	60 min prior	12 male cyclists	4 participants	5 participants (increased energy, anxiety, mild tremor, and nausea)
Astorino et al. (2012)[62]	8.2-km cycling	6 mg/kg	60 min prior	10 young females	4 participants	Not identified
Beaumont et al. (2017)[63]	60-min cycling	6 mg/kg	60 min prior	8 healthy males	2 participants	No adverse effects
Christensen et al. (2014)[64]	6-min maximal test on a rowing ergometer	3 mg/kg	60 min prior	12 elite rowers (11 males and 1 female)	3 participants	Not identified
Church et al. (2015)[65]	5-km running	3 mg/kg	60 min prior	20 participants (10 males and 10 females)	8 participants (4 males and 4 females)	Not identified
Desbrow et al. (2012)[66]	Cycling time trial	3 mg/kg 6 mg/kg	90 min prior	16 well-trained male cyclists	2 participants 4 participants	Not identified
Giráldez-Costas et al. (2022)[67]	Backwards throw Standing shot put Complete shot put	3 mg/kg	45 min prior	13 trained shot putters	6 participants 2 participants 3 participants	3 participants (nervousness, gastrointestinal problems, activeness, muscular pain, headache, and increased urine production)
Gonçalves et al. (2017)[68]	Cycling time trial	6 mg/kg	60 min prior	40 male cyclists	20 participants	16 participants (tachycardia, increased wakefulness and attention)
Graham-Paulson et al. (2016)[69]	3 × 20-m sprint tests	4 mg/kg	70 min prior	12 male wheelchair rugby players	5 participants	5 participants (increased spasticity, struggling with decision-making, headaches, and nausea
Pitchford et al. (2014)[70]	Cycling time trial	3 mg/kg	90 min prior	9 well-trained male cyclists	3 participants	Not identified
Potgieter et al. (2013)[26]	Olympic-distance triathlon	6 mg/kg	60 min prior	26 triathlon athletes (14 males and 12 females)	6 participants	11 participants (shakiness, heart palpitations, and gastro-intestinal tract disturbances).
Richardson et al. (2016)[71]	Squat and bench press	5 mg/kg	60 min prior	9 resistance-trained males	3 participants	Not identified
Santos Rde et al. (2013)[72]	4-km cycling	5 mg/kg	60 min prior	8 trained male cyclists	2 participants	Not identified
Skinner et al. (2013)[73]	40-km cycling	6 mg/kg	60 min prior	14 trained male cyclists and triathletes	5 participants	4 participants (headaches, increased alertness, nausea, light-headedness, and muscle cramping)
			When peak serum caffeine concentrations will coincide with onset of exercise.		9 participants	4 participants (headaches, increased alertness, nausea, light-headedness, and muscle cramping)
Smirmaul et al. (2017)[74]	Incremental exercise test on a cycle ergometer	4 mg/kg	About 70 min prior	7 male adults	1 participant	Not identified
Stadheim et al. (2013)[75]	8-km cross-country double poling perfor-mance tests	6 mg/kg	75 min prior	10 trained male cross-country skiers	2 participants	Not identified
Dos Santos et al. (2023)[39]	8-km cross-country double poling time trial	4.5 mg/kg	73 min prior	13 sub-elite male cross-country skiers	3 participants	Not identified
Wang et al. (2022)[76]	Sprint triathlon	110 mg 220 mg	60 min prior	12 male triathlon athletes	5 participants 9 participants	Not identified

polymorphisms, which are among the factors contributing to individual differences.[6] In particular, genetic variation of the human cytochrome P450 enzyme 1A2 (*CYP1A2*) gene (rs762551) has a substantial impact on both caffeine intake and caffeine metabolism.[7]

The *CYP1A2* isozyme of cytochrome P450 is only present in the liver, where it represents around 15% of the total cyto-chromes. It is responsible for more than 90% of caffeine metabolism, and it decomposes caffeine into 3 metabolites: paraxanthine (81.5%), theobromine (10.0%), and theophylline

(5.4%).[8] The substitution of A to C at position 163 (rs762551) of the *CYP1A2 genotype* decreases enzyme inducibility after caffeine intake and determines the metabolic rate of caffeine.[9] This rate is reflected in the ratio of caffeine to metabolites in plasma or urine.[9] Individuals carrying the C allele (163A/C and 163C/C) are categorized as "slow metabolizers", which demonstrate a slow clearance of caffeine because they metabolize caffeine at a slower rate compared to individuals homozygous for the A allele (163A/A), who are classified as "fast metabolizers".[10] It is worth noting that fast metabolizers constitute approximately 46% of the overall population.[11] Therefore, the evidence shows that the A allele of the *CYP1A2 genotype* may be more responsive than the C allele is to caffeine ingestion.

The potential influence of polymorphism of *CYP1A2 genotype* on exercise performance in response to caffeine intake has been reviewed in previous work[12] that covered all sources of caffeine intake, including caffeine gum and mouth rinse. A preferential benefit of A/A genotype in response to caffeine ingestion was found for trained individuals in 5 studies.[13-17] However, one study showed that individuals with A/A genotype had a great occurrence of insomnia caused by caffeine intake compared with C allele carriers.[16] One study on *CYP1A2 genotypes* also found that individuals with A/A genotype performed better than those with C allele.[18] Contrary to this result, a study found that people with A/C genotype performed better in the 3-km time trial than those with A/A genotype.[19] In addition, other studies found that there was no difference in the performance of different genotypes after caffeine intake.[20-30] The inconclusive nature of these results could be attributed to factors such as small sample sizes, variations in caffeine delivery methods, differences in training status, and diverse exercise performance outcomes.

To comprehensively assess the impact of *CYP1A2 genotypes* on exercise performance following an acute caffeine supplementation, a systematic review with meta-analysis is essential. Since the variety of pre-exercise caffeine intervention (i.e., ingesting, mouth rinse) may cause different responses, we only focused on the intervention of caffeine ingestion. Moreover, subgroup analyses are required to account for genetic variations, ensuring a detailed evaluation of the role of *CYP1A2 genotypes* in athletes' performance enhancement through caffeine intake.

2. Methods

2.1. Study protocol and registration

The present work has been registered to the International Prospective Register for Systematic Reviews (PROSPERO; registration number: CRD42022376187).

The literature search was performed for relevant studies (including a range of publications through to March 2023) across 4 databases: Web of Science, PubMed, Scopus, and China National Knowledge Infrastructure, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline.[31] The keywords included "exercise", "caffeine", "*CYP1A2*", and "genetic".

2.2. Inclusion and exclusion criteria

Studies were selected based on the Population, Intervention, Comparison, Outcomes and Study model (Table 2).[32] Intervention studies conducting caffeine ingestion were included. The primary outcome of the present meta-analysis included *CYP1A2 genotypes*, while the secondary outcome was exercise performances. Studies were excluded if: (a) *CYP1A2 genotypes* were not classified; (b) there was a mixed intervention (i.e., if caffeine was not the only supplement); (c) exercise performances were not measured; (d) placebo data were not available; and (e) there was a lack of detailed results and full-text data.

2.3. Data extraction

The initial review of records from all databases and the eligibility of studies were conducted by the primary investigator, then those results were confirmed by at least 2 separate investigators. The records were imported into Endnote (Version X9.3.3; Clarivate Analytic, Philadelphia, PA, USA) and were automated and manually screened. Once the screening of the included studies was finalized, the data were categorized by the characteristics of participants (sample size, age, and sex) and the exercise mode. The outcome data were expressed as the weighted mean difference (WMD). If the full-text article data were presented only in a figure format, WebPlotDigitizer (Ankit Rohatgi, 2019, V.4.2; WebPlotDigitizer, Pacifica, CA, USA) was used to extract the data from the figures.

2.4. Data analysis

A subgroup analysis was conducted to distinguish the outcomes based on different *CYP1A2 genotype* for individual exercise performance. *CYP1A2 genotypes* were categorized into AA and AC/CC. Exercise performance included aerobic endurance performance, anaerobic endurance performance, and strength performance. Aerobic endurance performance was determined as the completion time (expressed in min) during cycling time trial. Anaerobic endurance performance was measured by peak power (expressed in W) of Wingate test, while strength performance was defined by jumping height (expressed in cm) of a countermovement jump test (CMJ).

Table 2
Eligibility criteria of studies based on the PICOS model.

Parameter	Inclusion criteria
Population	Healthy individuals
Intervention	Acute caffeine ingestion
Comparator	Placebo
Outcome	Exercise performance
Study design	Randomized and non-randomized control trials

Abbreviation: PICOS = Population, Intervention, Comparator, Outcome, Study design.

2.5. Quality assessment

The quality of the included studies was assessed using 5 domains according to the revised Cochrane Risk of Bias tool for randomized trials: (a) randomization process, (b) deviations from intended interventions, (c) missing outcome data, (d) measurement of the outcome, and (e) selection of the reported result. The overall risk-of-bias was defined as "low risk" if all domains were at low risk of bias, "some concerns" if containing at least 1 domain at some concerns status but not at high risk of bias for any domain, and "high risk" if at least 1 study was judged in some concerns for multiple domains.[33]

2.6. Statistical analysis

Meta-analysis was performed using Review Manager (RevMan Version 5.4.1; Cochrane, London, UK). Due to the involvement of continuous data (mean ± SD), WMD with 95% confidence intervals (95%CIs) were used to represent the final analysis. Means and SD from placebo and caffeine conditions were collected. Subgroup analyses were performed for outcomes in relation to the type of *CYP1A2 genotype*. The forest plots were produced to display WMD, SD, and the overall effect of Z score. If publications reported the standard error only, the SD was calculated using the following formula, where n represented the number of participants:

$$SD = SE \times \sqrt{n}$$

To assess the heterogeneity, tau-squared (τ^2), χ^2 Cochran's Q (x^2) test, and I^2 statistic were performed. A value of $\tau^2 > 1$ indicated variability between studies. Q test measured the variation around a weighted mean, in which $p < 0.10$ was considered as significant heterogeneity.[34] I^2 statistic was used to assess the effect consistency across the studies, with I^2 interpreted as follows: (a) I^2: 0%−29% showing no important heterogeneity, (b) I^2: 30%−49% showing moderate heterogeneity, (c) I^2: 50%−74% showing substantial heterogeneity, (d) I^2: 75%−100% showing considerable heterogeneity.[35,36] Meta-analysis was performed using a fixed-effects model when heterogeneity was not significant ($I^2 \leq 50\%$ and $p \geq 0.1$) and a random-effects model was used when heterogeneity was significant ($I^2 > 50\%$ or $p < 0.1$). $p < 0.05$ was considered statistically significant.

3. Results

3.1. Literature search

3.1.1. Selection process

The number of identified articles from the 4-database search and selection process are shown in Fig. 1. A total of 609 intervention studies were retrieved from the database search, and 292 duplicated and ineligible articles were excluded. After the screening phase, including title and abstract screening, 26 articles were left. The authors excluded 14 articles from this meta-analysis due to: (a) lack of sufficient data,[14,20,21,25] (b) caffeine supplement type was mouthwash and gum,[19,37,38] (c) *CYP1A2 genotypes* were not clearly provided,[26,28,39,40] and (d)
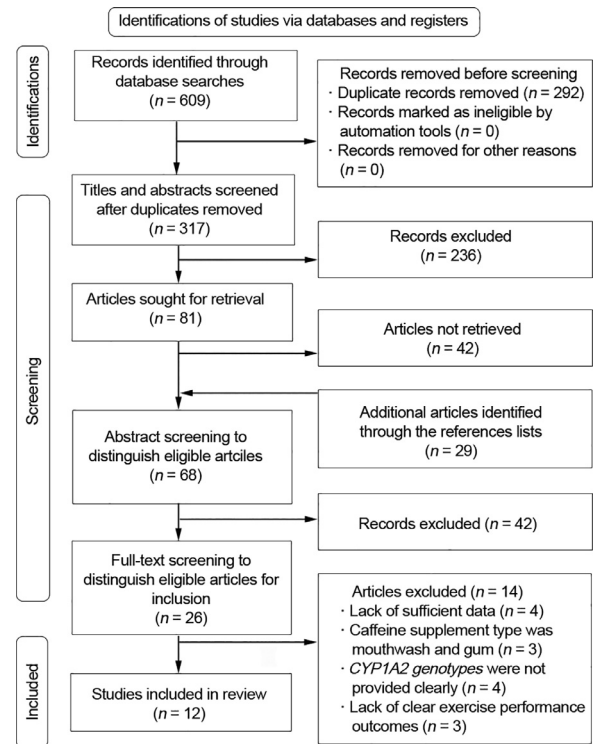

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram defining the electronic search and selection process.

lack of clear exercise performance outcomes.[24,41,42] The screening resulted in 12 eligible articles that were used for the current quantitative analysis.

3.1.2. Quality assessment in individual studies

Among the included studies, no study scored in the high-risk bias, 3 studies scored in the moderate-risk bias,[15,29,43] and 9 studies scored in the low-risk bias.[13,16−18,22,23,27,30,44] Results of the quality assessment are shown in Supplementary Fig. 1.

3.1.3. Characteristics of studies

The characteristics of the studies included in the meta-analysis are summarized in Table 3.[13,15−18,22,23,27,29,30,43,44] For all studies the sample was composed of young adults (aged 15 ± 2 to 29 ± 7 years) comprising active ($n = 525$) and sedentary ($n = 141$) individuals. The dosages of caffeine supplementation varied from 2 mg/kg to 6 mg/kg and were ingested acutely before conducting the performance test. The exercise regimen in the current meta-analysis consisted of cycling time trial ($n = 4$),[13,17,22,44] Wingate test ($n = 4$),[18,23,27,30] and CMJ test ($n = 5$).[15,16,23,29,43]

3.2. The effect of caffeine on the time trial

A total of 4 studies measured *CYP1A2 genotype* differences for cycling time trial after caffeine supplementation (Fig. 2).[13,17,22,44] Regardless of the allele genotype, caffeine supplementation showed a small but significant effect on time

Table 3
Characteristics of studies included in the meta-analysis.

Study	Information of participants			Dosage (mg/kg)	Exercise mode	Outcome	Conclusion
	Sample size and sex (male/female)	Genetic ratio A/C	Age (year) (mean ± SD)				
Giersch et al. (2018)[22]	20 participants (20/0)	8/12	25 ± 8	6	3-km cycling	Caffeine ingestion made a 2.2% improvement	Serum caffeine concentration C > A after 1 h; caffeine improved performance, but no difference between allele types
Grgic et al. (2020)[23]	22 trained males (20/0)	13/9	28 ± 5	3	CMJ test; Wingate test	Caffeine ingestion enhanced power output in the Wingate test and vertical jump height	Caffeine improved performance, but no difference between allele types
Guest et al. (2018)[13]	101 athletes (101/0)	49/52	24 ± 5	2; 4	10-km cycling	Performance increased 4.8% for 2 mg/kg caffeine and 6.8% for 4 mg/kg caffeine in participants with AA; performance decreased 13.7% for 4 mg/kg caffeine in participants with CC	Only those with the A allele improved
Guest et al. (2022)[44]	100 athletes (100/0)	49/51	25 ± 4	2; 4	10-km cycling	2 mg/kg caffeine decreased completion time by 1.7 min for participants with AA	Only those with the A allele improved
Minaei et al. (2022)[18]	16 trained males (16/0)	6/10	22 ± 7	6	Wingate test	Participants with AA improved 5.8% following caffeine ingestion	Only those with the A allele improved
Muñoz et al. (2020)[15]	31 handball players (16/15)	14/17	24 ± 3	3	CMJ test; sprint test; handgrip strength test	Jump height increased 3.4% for participants with AA and 4.3% for those with the C-allele	A > C when pitching 7 m after caffeine intake
Puente et al. (2018)[16]	19 basketball athletes (10/9)	10/9	28 ± 5	3	CMJ test	Caffeine increased jump height 2.9% in participants with AA; no significant effect for those with the C-allele	Only those with the A allele improved
Salinero et al. (2017)[27]	21 participants (14/7)	5/16	29 ± 7	3	Wingate test	Caffeine ingestion increased peak power by 1.7%	Caffeine improved performance, but no difference between allele types
Sicova et al. (2021)[30]	100 athletes (100/0)	46/53	25 ± 4	2; 4	Wingate test	No difference	Caffeine had no effect, and genes did not modify the effects of caffeine
Spineli et al. (2020)[29]	100 adolescents (no mention)	49/51	16 ± 2	6	handgrip strength test; CMJ test;	No difference	Caffeine improved performance, but no difference on between allele types
Womack et al. (2012)[17]	35 cyclists (35/0)	16/19	25 ± 7	6	40-km cycling	4.9% decrease in completion time for participants with AA; completion time increased 1.8% in those with the C allele	The A allele showed a greater ergogenic effect
Wong et al. (2021)[43]	102 athletes (102/0)	50/52	25 ± 4	2; 4	CMJ test; handgrip strength test	Participants with CC experienced a 12.8% decrease in handgrip strength with 4 mg/kg of caffeine	Handgrip strength in those with the CC genotype declined in response to 4 mg/kg of caffeine

Abbreviation: CMJ = countermovement jump test.

trial improvement (WMD = −0.48, 95%CI: −0.83 to −0.13, $p = 0.007$). However, the subgroup analysis demonstrated a large effect size among individuals with the A allele who ingested caffeine (WMD = −0.90, 95%CI: −1.48 to −0.33, $p = 0.002$) compared to individuals with the C allele, who did not confirm the effect on time trial when caffeine was ingested (WMD = −0.08, 95%CI: −0.32 to 0.17, $p = 0.53$). In the present meta-analysis, the average decrease in completion time among individuals with the A allele following caffeine ingestion across the included studies was 5.8%, whereas it was only 0.6% for individuals with the C allele.

3.3. The effect of caffeine on the Wingate test

Four studies measured *CYP1A2 genotype* differences for the Wingate test after caffeine supplementation (Fig. 3).[18,23,27,30] When gene type was not considered, caffeine supplementation did not have a beneficial effect on the
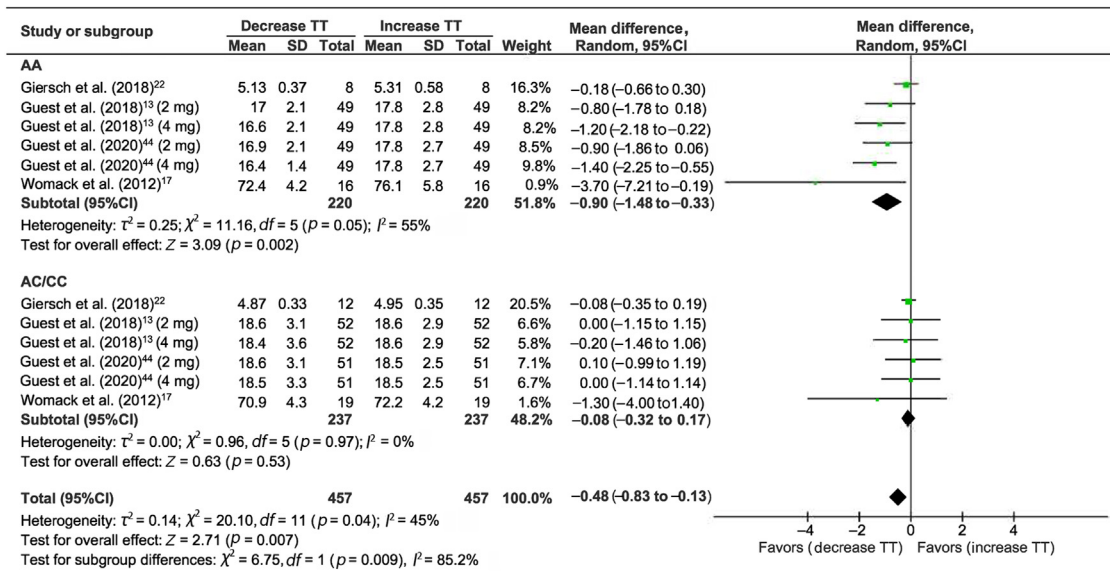
Fig. 2. Forest plot of standardized mean difference for caffeine intake on TT outcome. 95%CI = 95% confidence interval; df = degree of freedom; I^2 = inconsistency between studies; TT = time trial; WMD = standardized mean difference.

Wingate performance (WMD = 8.07, 95%CI: −22.04 to 38.18, p = 0.60). Subgroup analysis confirmed the lack of effect in both AA (WMD = 29.83, 95%CI: −16.77 to 76.44, p = 0.21) and AC/CC (WMD = −7.52, 95%CI: −46.96 to 31.92, p = 0.71) allele types.

3.4. The effect of caffeine on the CMJ test

Five studies measured *CYP1A2 genotype* differences for the CMJ test after caffeine supplementation (Fig. 4).[15,16,23,29,43] CMJ performance was not improved by caffeine supplementation (WMD = 1.17, 95%CI: −0.02 to 2.36, p = 0.05). Subgroup analysis confirmed the lack of effect in both AA

(WMD = 1.14, 95%CI: −0.41 to 2.68, p = 0.15) and AC/CC (WMD = 1.23, 95%CI: −0.63 to 3.09, p = 0.20) allele types.

4. Discussion

To our knowledge, the present review provides a comprehensive quantitative analysis to confirm the polymorphism effect of *CYP1A2 genotype* on exercise performance in response to caffeine intake. In the current meta-analysis, we found that acute caffeine supplementation significantly decreased the completion time during a cycling time trial in individuals with the A allele but not in individuals with the C allele. We observed no significant effects of acute caffeine supplementation on peak power in the Wingate test or on the
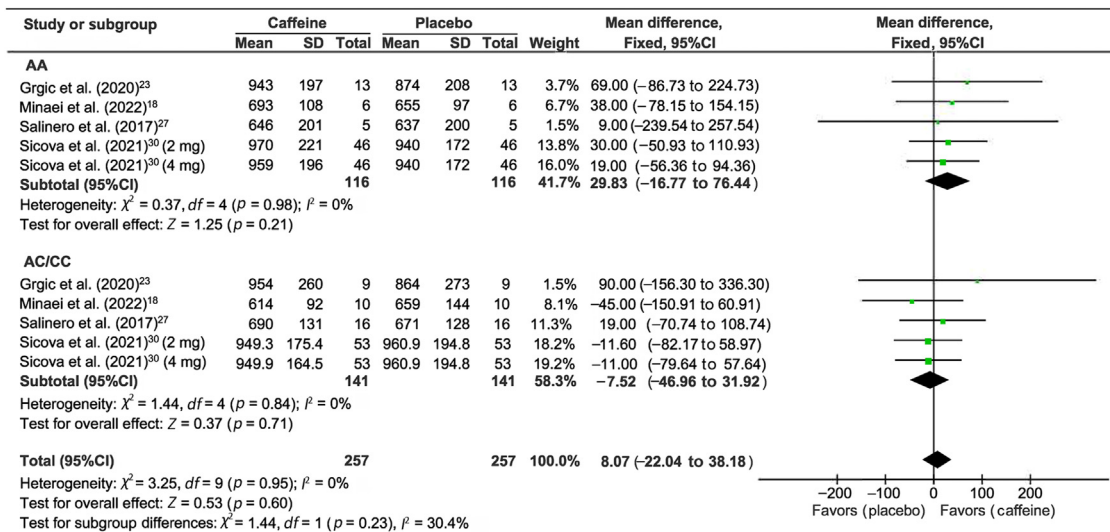

Fig. 3. Forest plot of standardized mean difference for caffeine intake on Wingate test outcome relative to placebo. 95%CI = 95% confidence interval; df = degree of freedom; I^2 = inconsistency between studies; WMD = standardized mean difference.

Study or subgroup	Caffeine			Placebo			Weight	Mean difference, Fixed, 95%CI
	Mean	SD	Total	Mean	SD	Total		
AA								
Grgic et al. (2020)[23]	35.6	5.9	13	34.8	6.2	13	6.5%	0.80 (−3.85 to 5.45)
Muñoz et al. (2020)[15]	34.02	4.44	14	32.91	3.52	14	16.1%	1.11 (−1.86 to 4.08)
Puente et al. (2018)[16]	40.7	7.3	10	39.6	7.2	10	3.5%	1.10 (−5.25 to 7.45)
Spineli et al. (2020)[29]	48.6	12.3	49	47.2	13.3	49	5.5%	1.40 (−3.67 to 6.47)
Wong et al. (2021)[43] (2 mg)	43	7	50	41	8	50	16.3%	2.00 (−0.95 to 4.95)
Wong et al. (2021)[43] (4 mg)	41	10	50	41	8	50	11.2%	0.00 (−3.55 to 3.55)
Subtotal (95%CI)			186			186	59.1%	1.14 (−0.41 to 2.68)
Heterogeneity: χ^2 = 0.75, df = 5 (p = 0.98); I^2 = 0%								
Test for overall effect: Z = 1.44 (p = 0.15)								
AC/CC								
Grgic et al. (2020)[23]	37.6	5.4	9	36.6	5.2	9	5.9%	1.00 (−3.90 to 5.90)
Muñoz et al. (2020)[15]	33.25	9.18	17	31.88	9.22	17	3.7%	1.37 (−4.81 to 7.55)
Puente et al. (2018)[16]	37.2	6.9	9	36.3	5.9	9	4.0%	0.90 (−5.03 to 6.83)
Spineli et al. (2020)[29]	50	13.2	51	48.5	14.6	51	4.8%	1.50 (−3.90 to 6.90)
Wong et al. (2021)[43] (2 mg)	40.7	9.5	52	40.5	10.9	52	9.2%	0.20 (−3.73 to 4.13)
Wong et al. (2021)[43] (4 mg)	42.5	5.1	52	40.5	10.9	52	13.2%	2.00 (−1.27 to 5.27)
Subtotal (95%CI)			190			190	40.9%	1.23 (−0.63 to 3.09)
Heterogeneity: χ^2 = 0.51, df = 5 (p = 0.99); I^2 = 0%								
Test for overall effect: Z = 1.29 (p = 0.20)								
Total (95%CI)			376			376	100.0%	1.17 (−0.02 to 2.36)
Heterogeneity: χ^2 = 1.27, df = 11 (p = 1.00); I^2 = 0%								
Test for overall effect: Z = 1.93 (p = 0.05)								
Test for subgroup differences: χ^2 = 0.01, df = 1 (p = 0.94), I^2 = 0%								

−4 −2 0 2 4
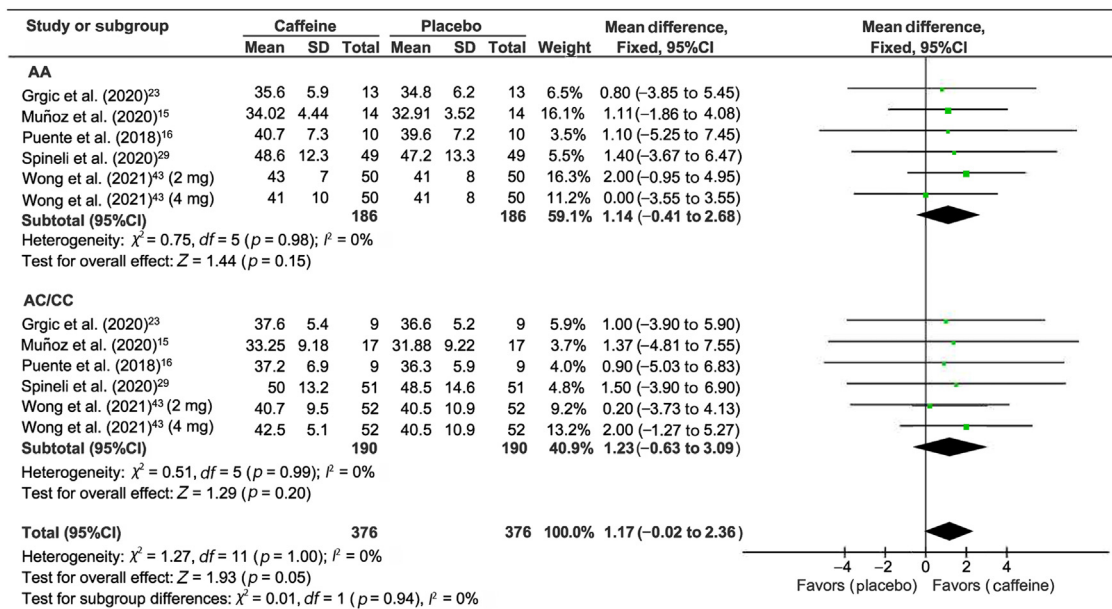Favors (placebo) Favors (caffeine)

Fig. 4. Forest plot of standardized mean differences for caffeine intake on CMJ outcome relative to placebo. 95%CI = 95% confidence interval; CMJ = counter-movement jump test; *df* = degree of freedom; I^2 = inconsistency between studies; WMD = standardized mean difference.

CMJ test, and these outcomes were not influenced by *CYP1A2* genotype. These findings suggest that the influence of *CYP1A2* genotype on caffeine metabolism is complex and may interact with specific aspects of athletic performance.

The current meta-analysis elucidated the impact of *CYP1A2* genotype polymorphism on aerobic endurance. Notably, caffeine intake demonstrated performance improvements exclusively for participants with the AA genotype. In a 10 km cycling time trial, distinct genetic profiles revealed discernible disparities. Despite C allele carriers' demonstrated higher serum caffeine concentrations compared to that of A allele carriers 1 h after intake, AA homozygotes exhibited a performance enhancement of approximately twice the amount as the C allele carriers.[22] The greater magnitude of the effect was particularly pronounced among A allele carriers, suggesting a potential association with exercise duration.[13,17,44] Although the precise mechanism through which caffeine enhances exercise performance remains to be fully elucidated, a leading hypothesis suggests that caffeine exerts a central effect by antagonizing adenosine receptors.[45] This action inhibits the adverse effects of adenosine on nerve transmission, arousal, and pain perception. Additionally, caffeine stimulates skeletal muscle contractility through the excitation-contraction coupling mechanism.[46,47] Biologically, caffeine acts as an adenosine receptor antagonist, alleviating endogenous adenosinergic inhibition, thereby triggering muscle contraction via calcium release.[48,49] The genetic variability in *CYP1A2* genotype may determine the 10-km cycling time trial outcome, as A allele carriers exhibit faster metabolism, resulting in a more rapid biological effect. Conversely, C allele carriers may necessitate a longer ingestion period to induce performance-enhancing effects. Moreover, theophylline and 1,7-dimethylxanthine (paraxanthine), which are metabolites of caffeine and adenosine antagonists, exhibit higher binding affinities for adenosine receptors and may play a bigger role in improving exercise performance than caffeine itself.[50] This could explain the greater benefits for AA homozygotes compared to C allele carriers. Across the studies included in this meta-analysis, caffeine ingestion typically occurred about 60 min prior to exercise. Future research should consider both the duration of endurance exercise and the timing of caffeine intake before exercise to optimize performance outcomes.

For the current meta-analysis, peak power during the Wingate test was not improved by caffeine supplementation regardless of gene type. Caffeine doses may influence the efficacy of caffeine supplementation for improving anaerobic performance in individuals with the A allele. Among them, the study conducted by Sicova et al.[30] demonstrated that performance did not improve in both supplemented groups with caffeine dosages of 2 mg/kg or 4 mg/kg. However, when participants ingested 6 mg/kg of caffeine, A allele carriers improved their anaerobic capacity.[18] In addition, an improvement in exercise performance was obtained with the ingestion of 3 mg/kg of caffeine in 2 studies, without any influence of gene type.[23,27] Up to now, the influence of genetic variability for the effect of caffeine ingestion on anaerobic capacity have remained inconclusive. A meta-analysis measuring the effect of caffeine ingestion on Wingate performance regardless of gene variability has been conducted previously, and it showed a small effect on enhancing power output.[51] The discrepancy between our results and those of the previous meta-analysis can be explained by the fact that only studies considering gene variability were included in our meta-analysis.

When jumping performance was evaluated, the current meta-analysis demonstrates that caffeine intake did not improve jumping height, regardless of genotype. Among the

included studies, caffeine intake increased jumping height of A allele participants only in the Puente study,[16] while *CYP1A2 genotype* did not influence jumping height in most other studies.[15,23,29,43] Although jumping ability after caffeine intake is not affected by gene type, improved sport-related performances in handball and basketball were observed in individuals with the A allele compared to those with the C allele after caffeine was supplemented.[15,16]

Our meta-analysis confirmed that the ergogenic effect of caffeine is associated with *CYP1A2 genotype* variability, providing evidence of the benefits of caffeine supplementation (with proper dosage and timing) before exercise training. The *CYP1A2* activity influenced by the A allele has been previously reported.[9] In addition, other factors can affect the activity of *CYP1A2 genotypes*,[10,52] such as diet (cruciferous vegetables: broccoli and cabbage,[53] and high curcumin foods[54]), smoking status,[8] drinking habits,[55] exogenous estrogens,[53,56] oral contraceptives, and other drugs (fluvoxamine, omeprazole).[57] In a previous meta-analysis, smoking habits was associated with the *CYP1A2* activity in individuals with homozygous AA and heterozygous A/C.[58] Therefore, it is crucial to note that dietary control and habits may influence study outcomes. However, for the studies included in the present meta-analysis, dietary records and smoking status were not reported. The choice of caffeine delivery method for enhancing exercise performance assumes an important value, given the varying absorption rates between ingestion and the chewing method.[59] Importantly, ingestion involves an interaction with the gastrointestinal tract, potentially leading to an extended absorption period. Increasing peak power output in participants with the A allele after an acute caffeine supplementation with dosage 6 mg/kg had showed similar improvement with C allele.[18] Therefore, more studies are required to confirm the results.

The limited number of included studies may lead to inaccurate interpretations of the anaerobic and power outcomes. Therefore, more studies are required to obtain consistency in the results. Our meta-analysis offers a comprehensive estimation of the effect for individual exercise categories, as well as an aggregated effect for subgroup analysis, to derive conclusions regarding caffeine's ergogenic effects with respect to distinct genetic alleles.

The results of previous studies collected up to the present time could guide us toward a new approach: Profiling endurance athletes with an aim to enhance the impact of caffeine consumption on their endurance performance, particularly before a competition. A higher caffeine dose could compensate for the slower metabolism associated with the C allele, potentially improving endurance performance in athletes who possess this genetic variant.

5. Conclusion

Regardless of the *CYP1A2* variability, an acute caffeine supplementation improved cycling time trial but not Wingate or CMJ performance. When considering *CYP1A2 genotype*, only A allele carriers improved their performance in the cycling time trial; the Wingate and CMJ performances had no associations with gene type. Therefore, individual differences should be considered when consuming caffeine to enhance exercise performance.

Authors' contributions

JW conceived the study, took part on the screening process and data extraction, and drafted the manuscript; LD took part on the screening process and data process and participated in writing the first draft on the manuscript; YP helped to draft the manuscript and performed the statistical analysis; CWH participated in its design; YS also participated in its design and assisted in drafting the manuscript; GC formulated the review criteria and helped to revise the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2023.12.005.

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