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The effects of CYP1A2 and ADORA2A genotypes association with acute caffeine intake on physiological effects and performance: A systematic review

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Abstract

Introduction: This systematic review aims to examine the effects of the CYP1A2 −163C>A and *ADORA2A* 1976T>C polymorphism on physiological effects and performance relative to caffeine consumption. Material and Methods: In this study, electronic databases including PubMed, Web of Science Core Collection, Korean Journal Database, Russian Science Citation Index, SciELO Citation Index, Scopus, ScienceDirect, ProQuest Dissertations & Thesis Global and EBSCO were searched. Results: The results highlight that individuals with the TT or CT/CC genotype can have differences in caffeine consumption, and C carriers may have increases in the maximum oxygen uptake (VO_2max). The AA or AC/CC genotypes can have different caffeine consumption and VO_2max. In four studies, TT or CT/CC either in AA or CC genotype had different physiological effects. Regardless of the amount of caffeine (3 mg/kg^{-5} mg/kg), Carriers of the C allele in the genotype *ADORA2A* gene have higher sports performance. Six studies revealed a significant correlation between the AA genotype and performance following caffeine intake. Conclusions: Genotype variations in *ADORA2A* and *CYP1A2* may modulate the ergogenic effects of caffeine, but some physiological effects can occur for different genotypes.

Keywords

CYP1A2, ADORA2A, ergogenic substance, polymorphism, genetics

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Review

The effects of *CYP1A2* and *ADORA2A* genotypes association with acute caffeine intake on physiological effects and performance: A systematic review

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Abstract: Introduction: This systematic review aims to examine the effects of the CYP1A2 −163C>A and *ADORA2A* 1976T>C polymorphism on physiological effects and performance relative to caffeine consumption. Material and Methods: In this study, electronic databases including PubMed, Web of Science Core Collection, Korean Journal Database, Russian Science Citation Index, SciELO Citation Index, Scopus, ScienceDirect, ProQuest Dissertations & Thesis Global and EBSCO were searched. Results: The results highlight that individuals with the TT or CT/CC genotype can have differences in caffeine consumption, and C carriers may have increases in the maximum oxygen uptake (VO_2max). The AA or AC/CC genotypes can have different caffeine consumption and VO_2max. In four studies, TT or CT/CC either in AA or CC genotype had different physiological effects. Regardless of the amount of caffeine (3 mg/kg^{-5} mg/kg), Carriers of the C allele in the genotype *ADORA2A* gene have higher sports performance. Six studies revealed a significant correlation between the AA genotype and performance following caffeine intake. Conclusions: Genotype variations in *ADORA2A* and *CYP1A2* may modulate the ergogenic effects of caffeine, but some physiological effects can occur for different genotypes.

Keywords: *CYP1A2*, *ADORA2A*, ergogenic substance, polymorphism, genetics.

1. Introduction

Caffeine is widely used as an ergogenic aid in sports due to enhancing physical performance among athletes [1]. Low-medium doses of caffeine (3–6 mg.kg) have a potential to improve performance [2, 3]. Caffeine supplementation may be beneficial for muscle

power, timing, psychomotor, endurance, effort, physiological effects, exercise and cognitive performance [4]. The response to caffeine cannot be uniform in individuals. Caffeine supplementation can improve athletes' performance, but others may not change, or performance may remain stable [5].

Inter individual variation in caffeine response may be due to polymorphisms in the Cytochrome P450 Family 1 Subfamily A Member 2 (*CYP1A2*) gene (encoded enzyme responsible for up to 95% of caffeine metabolism) [A to C substitution at position 163C>A (rs762551)] and the Adenosine A2A Receptor (*ADORA2A*) gene (may affect the responses of acute caffeine ingestion) [T to C substitution at position 1976T>C (rs5751876)] [4, 6]. The AA genotype is considered "fast metabolizers" and AC/CC genotypes are considered as "slow metabolizers" of caffeine [6–8]. The TT genotype is considered as "high" and the CC/CT genotypes are considered as "low" responders to caffeine [4]. There are studies conducted with acute caffeine intake on the performance of athletes with *CYP1A2* polymorphism distributions [2], but their results are contradictory. Guest et al. reported that 4mg/kg caffeine supplementation improved the performance of those with the AA genotype, but had no positive effect on those with the AC/CC genotype [9]. On the other hand, apart from the *CYP1A2* gene, there are studies on performance changes of caffeine supplements on *ADORA2A* gene distributions [7]. Loy et al. reported that caffeine supplementation improved cycling performance in TT athletes compared to C-Carriers [10]. However, after acute caffeine intake, C-allele carriers can have an ergogenic response, or there are also studies with no effect [4, 11, 12]. Caffeine reduced the mean heart rate (HR) irrespective of *ADORA2A* or *CYP1A2* genotypes [13]. Thus, Womack et al. reported an increase in the mean HR during the time trial compared with placebo and also found no significance in the *CYP1A2* genotype [14]. Ratings in the perceived exertion (RPE) did not induce any changes with caffeine supplementation, and no significance was found with genotype *ADORA2A* [10] or reduced RPE [15]. Studies with *CYP1A2* and *ADORA2A* are limited, and there are contradictions in studies. Recently, Grgic et al. conducted a systematic review of the ergogenic effects of acute caffeine supplements according to *CYP1A2* gene polymorphism on sports performance [16]. However, *ADORA2A* gene polymorphism and physiological effects are also important in acute caffeine effects. We combined the *ADORA2A* and *CYP1A2* polymorphism results with physiological effect and sport performance data from randomize controlled trails (RTCs) to identify ergogenic effects which changed after acute caffeine intake and which harbored polymorphisms that showed evidence of association.

The ergogenic effects of caffeine intake in athletes and the genetic background effect on performance may be relevant [17]. The importance of this systematic review is to encourage more than multiple genetic polymorphisms of caffeine intake regarding different ergogenic effects, not just performance. Therefore, our results have implications not only for understanding individual differences in caffeine consumption and sport performance but also for many physiological effects such as the heart rate (HR), blood pressure (SBP), respiratory exchange ratio (RER), RPE, minute ventilation (VE), breathing frequency (BF), blood lactate concentration. This study will support new trials in this area and provide a prediction for determining appropriate genotype-specific values, such as the dose and frequency of caffeine intake, but it may also lead to new research on the effects of genetic variation between individuals on physiological effects altered by caffeine intake.

2. Materials and Methods

2.1. Literature search s

This review was performed while following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. A comprehensive search of the following databases. PubMed, Web of Science (Web of Science Core Collection, Korean Journal Database, Russian Science Citation Index, SciELO Citation Index), Scopus, ScienceDirect, ProQuest Dissertations & Thesis Global, EBSCO was performed. In all of these databases,

the following syntax was used: (*CYP1A2* OR *ADORA2A*) AND (caffeine) AND (exercise OR endurance OR ergogenic OR performance).

The search for studies concluded on 21 April 2021 and was performed independently by two authors of the review to minimize bias in the study selection.

2.2. Inclusion and Exclusion Criteria

Predefined inclusion and exclusion criteria were as follows: (a) English written peer-reviewed RTCs, dissertation or thesis on humans; (b) studies that specify the distinction between *CYP1A2* (AA or C carriers) and *ADORA2A* (TT or C carriers) genotype differences in daily caffeine consumption and maximum oxygen uptake (VO_2max); (c) studies that explore the influence of *CYP1A2*−163C>A polymorphism and ergogenic effects of acute caffeine supplement on performance parameters and physiological parameters compared to placebo; (d) studies that explore the effect of acute caffeine intake on physiological effects and performance in *ADORA2A*1976T>C polymorphism. Studies that had irrelevant title and abstract, reviews, editorials, conference abstracts, books, book chapters, commentaries, letters, errata, registration of trials, case reports, animal studies including in vivo and vitro, non-English articles and articles that do not meet the inclusion criteria were excluded.

2.3. Study Selection

All titles and abstracts obtained by electronic scanning were downloaded to the Zotero library. The duplicate results were removed through the Systematic Review Assistant-Deduplication Module (SRA-DM) [19] and via the Zotero software [20].

The following data were extracted: (a) author(s) (b) sample size, *ADORA2A* and *CYP1A2* genotype distribution, and participants' characteristics (sex, age, body mass, habitual caffeine intake, and training status); (c) exercise task(s) and caffeine supplementation protocol; (d) main outcomes for example caffeine/genotype, VO_2max/genotype and ergogenic effects of caffeine supplementations on performance/genotype interactions.

2.4. Calculation of Effect Sizes

Cohen's d effect sizes (ESs) were calculated by dividing the caffeine-placebo mean change by the pooled standard deviation for each genotype separately. ESs can be interpreted as "large" (> 0.80), "medium" (0.51–0.80), "small" (0.21–0.50), "unimportant" (0.20).

2.5. Quality Appraisal

PEDro scale (11-point) was used to measure the quality of the studies included [21]. Item 1 in the scale was excluded from total score according to recommendations. Randomization, hidden allocation, blinding, attrition and data reporting were included in the validation of studies. The scored table was assessed with 1 or 0 for meeting or not meeting the criteria respectively. 10 was the maximum score that could be assessed. Studies were classified as "poor" quality (3 points), "moderate" quality (4–5 points), "good" quality (6–8 points), "excellent" methodological quality (9–10 points) [37]. Two authors performed assessment independently, and final results were clarified by all authors.

3. Results

The initial study search resulted in 7,060 studies. After screening the titles and abstracts, removing duplicates from the original 3,998 studies, 348 articles were selected for full-text reading (Figure 1). The selection process led to the inclusion of twenty-five randomized controlled trials [2, 3, 4, 9–14, 22–36, 38]. Seven were included for the *ADORA2A* gene [4, 10, 11, 12, 13, 30, 34], and twenty-one were included for the *CYP1A2* gene [2, 3, 4, 9, 12–14, 22–29, 31–33, 35, 36, 38]. In three studies, *ADORA2A* and *CYP1A2* genes were studied together [4, 12, 13]. In all of the aforementioned studies, we analyzed data regarding a total number of 954 healthy individuals. In particular, of these 671 subjects, 332 were

AA genotype, 339 were C carriers of *CYP1A2* gene and of these 283 subjects, 82 were TT genotype, 201 were C carriers of *ADORA2A* gene.

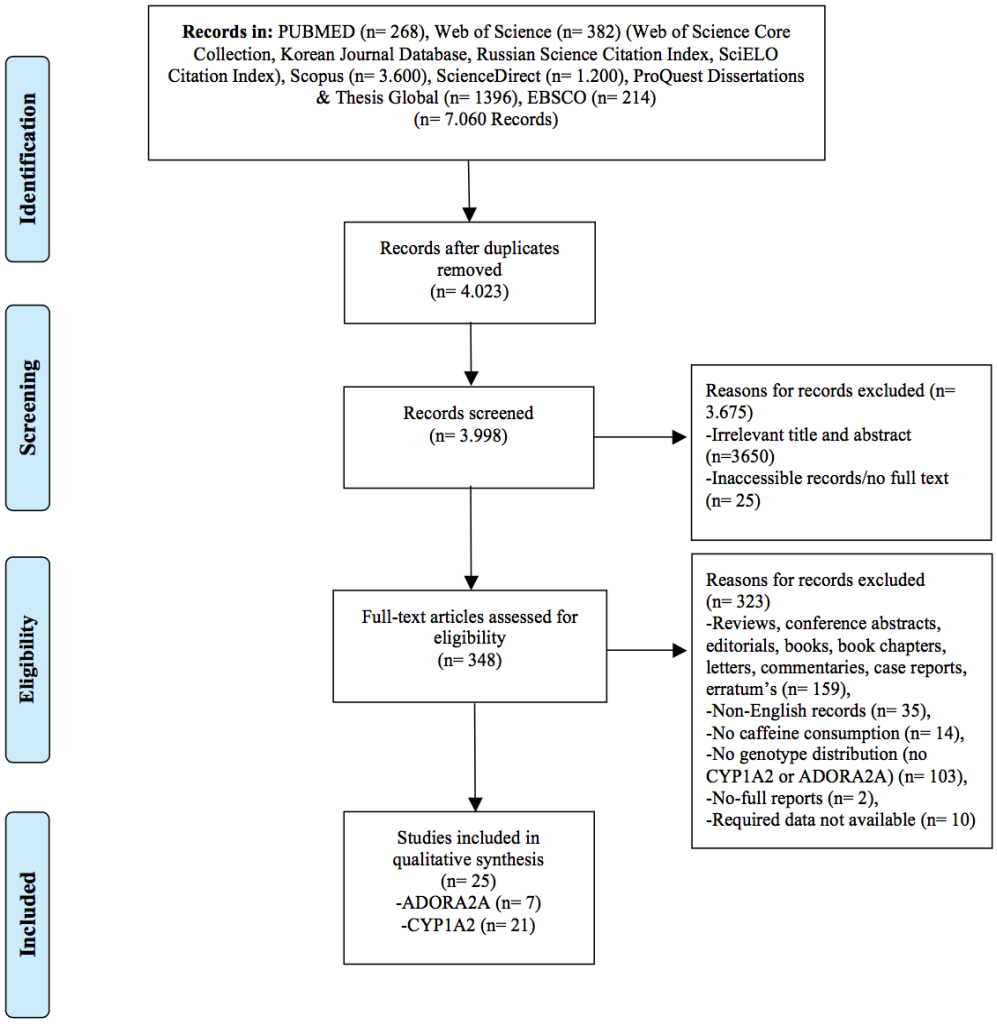

Fig. 1. PRISMA Flow diagram [18].

Caffeine Intake and VO_2max

ADORA2A: Four studies explored the effect of *ADORA2A* 1976T>C on caffeine consumption (Table 1). In two of these studies, the TT genotype was consuming more caffeine than C carriers [4, 13] with ESs 0.16–0.32; in one study, C carriers consumed more caffeine with the ES of 0.61 [10], and O'Connor et al. reported controversial results – the TT genotype consumed more caffeine than CC genotype but less than CT genotype with the ESs 0.14, 0.62 respectively [30]. Three studies examined the effect of *ADORA2A* 1976T>C on VO_2max; in all of them, C carriers were higher with ESs 0.44–0.68 [4, 10, 13].

CYP1A2: Nine studies reported the effect of *CYP1A2* −163C>A on caffeine consumption (Table 2). In four of them, C carriers consumed more caffeine in daily life with ESs 0.0071–0.12 [4, 13, 14, 24]. In four others, AA genotypes consumed more dietary caffeine with ESs 0.011–2.31 [9, 22, 27, 28]. On the other hand, the AC genotype consumed caffeine more than AA genotypes (ESs 1.85), and the CC genotype more than AA genotype (ESs 0.36) [9]. Also, Spineli et al. reported contrary results – the AC genotype consumed more caffeine than AA (ESs 0.38), and AA more than the CC genotype with ESs 0.50 [36].

Six studies detected the effect of *CYP1A2* −163C>A on VO_2max. In four, the AA genotype had higher VO_2max in C carriers in ESs 0.029–0.49 [4, 9, 13, 23]. Giersch et al. [27] reported a higher degree of C carriers (ESs 0.12), and there was no difference in the study by Pataky et al. [31].

Physiological Effects

ADORA2A: The study samples varied from 12–110 individuals; in some studies only men were included, but mostly the sexes were mixed (the total number of participants: 281). Out of six, four studies reported significant results on genotype distribution for physiological effects [10, 12, 30, 34] while in all studies caffeine affected HR, RER, VE, BF, blood lactate concentration, RPE with also contradictory results in HR, RPE, DBP, SBP [4,13]. HR increased more in C carriers (ESs TT:0.3, C carriers: 0.5) [10]. Peak change SBP increased in the TT genotype compared with C carriers [34]. Pain ratings (ESs TT: 0.033, CT: 0.36, CC:0.092) decreased in the TT genotype and increased in the CC genotype, RPE (ESs TT:0.12, CT:0.30, CC:0.057) and arm swelling decreased in the CC genotype, while caffeine sensitivity increased after the exercise with 5 mg/kg caffeine [30]. Increased activeness and urine production were seen in the TT genotype after ingesting 3 mg/kg CAF before the exercise [12].

CYP1A2: In sixteen studies, physiological effects were measured after caffeine intake. In seven studies, HR changed. Exercise HR increased in the AA genotype after ingesting 6 mg/kg caffeine [25, 28]. Guest et al. showed HR increases in AC genotypes after 4 mg/kg caffeine intake, while a decrease was seen in CC genotype, and no differences were seen in the AA genotype [9]. Meanwhile, a decrease in time for HR was detected in C carriers, so the recovery time improved [38]. Apart from genotype distributions, HR values were higher in the caffeine intervention group [4, 29, 35]. By contrast, it was low in another study [13]. RPE was measured in twelve studies. In seven of them, no difference was seen after acute caffeine consumption, and no effect was found in genotype distributions [2, 4, 14, 26, 32, 35, 36]. Two studies reported an increase in RPE in the placebo group [29, 32]. Guest et al. [9] found that 4mg/kg caffeine intake decreased RPE in AA genotype; moreover, Puente et al. suggested the same with 3 mg/kg of caffeine intake [33]. On the other hand, Fitzgerald reported that C allele carriers had a decrease in RPE after 6 mg/kg of caffeine intake [25], and also in 9-km Guest found no difference in genotype distributions; in general tests, RPE did not change in C carriers [9]. In four studies, RER was measured. Two studies supported that RER increased after 5 mg/kg of acute caffeine intake [13, 29]. Also being a C carrier can be more effective for RER increase after 5mg/kg of caffeine intake [13]. Fitzgerald detected RER decrease in C carriers after 6mg/kg of caffeine intake [25], while no effect in RER was found in study by Womack et al. [14]. When respiratory parameters were evaluated, Glaister et al. found minute ventilation and breathing frequency increased in the caffeine group. In addition, blood lactate levels increased, which is also supported in the study by Potgieter [13, 32]. In this study after 6 mg/kg, shakiness, heart palpitations and gastrointestinal system (GIS) disturbances were seen [32]. In general, insomnia was seen in C carriers after consuming 3 mg/kg [12], and also insomnia in AA genotypes was detected [33]. Puente et al. and Salinero et al. reported no side effects and stable fatigue index after 3 mg/kg caffeine intake, but nervousness was detected by Salinero et al. in C carriers [2, 33]. In four studies, the range of ESs in the AA genotype on HR is 0.080–0.86 and in C carriers 0.13–9.52. In six studies, the range of ESs for RPE is 0.0–0.45 in the AA genotype, and in six studies 0.0–1.34 in C carriers. In two studies, the range of in AC genotype was 0.12–0.37 and in an one study the Ess value was 0.16 in CC genotype [14] (see Table 2).

Table 1. Characteristics and outcomes of included studies in the ADORA2A gene.

Author (year, location)	Study Design	Study Sample	Age year)	VO_2max	Intervention of the experimental group	Intervention of the control group	Genotype distribution	Caffeine intake (mg/day)	Outcomes	Effect Size
Carswell et al. (2020), U.K. [4]	RCT	Healthy active adults (N=18)	24 ± 4	TT (n=11): 46.8 ± 10.4 C allele carriers (n=7): 48.4 ± 6.8 *ml/kg/min	3 mg/kg BW CAF	3 mg/kg BW (microcrystalline)	TT (n=11), C allele carriers (n=7)	TT (n=11): 143 ± 139 C allele carriers (n=7): 104 ± 126	↑Performance (CAF intervention) *p<0.001 →Performance (CAF intervention x genotype distribution) *p>0.05 ↑Total work (CAF intervention) *p<0.001 →Total work (genotype distribution) *p<0.001 ↑Mean HR (CAF intervention during the TT) *p<0.01 →Mean HR (CAF intervention at %70 VO2max) *p>0.05 →Mean HR (genotype distribution) *p>0.05 →RPE (genotype distribution or CAF intervention) *p>0.05 ↑Cognitive performance with reaction time (CAF intervention) *p<0.01 ↑PVT (CAF intervention) *p<0.01	TT/C genotype: VO2max mL/kg/min 0.18 TT/C genotype: CAFF intake 0.29
Glaister et al. (2020), U.K. [13]	RCT	Cyclist (N=66)	41.9 ± 8.6	TT (n=16): 4.05 ± 0.45 CT (n=14): 4.07 ± 0.46 CC (n=10): 4.33 ± 0.37 *l/min	5 mg/kg BW CAF	Placebo (maltodextrin)	TT (n=24), C allele carriers (n=42)	TT (n=16): 359 ± 108 CT (n=14): 337 ± 158 CC (n=10): 326 ± 100	REST; ↑DBP, SBP (CAF intervention) *p<0.05 →DBP (Genotype distribution) *p=0.15 →SBP (Genotype distribution) *p=0.21 →BF, BGI, BLa, VO2, (CAF intervention) ↓HR (CAF intervention) *p<0.05 ↑RER, V̇E (CAF intervention) *p<0.05 →BF *p=0.305, BGI *p=0.494, BLa *p=0.874, HR *p=0.969, RER *p=0.140, V̇E *p=0.335, VO2 *p=0.903 (intervention x genotype distribution)	TT/TC genotype VO2max (L/min) 0.044 CAFF intake 0.16 TT/CC genotype VO2max (L/min) 0,68 CAFF intake 0.32

Author (year, location)	Study Design	Study Sample	Age year)	VO_2max	Intervention of the experimental group	Intervention of the control group	Genotype distribution	Caffeine intake (mg/day)	Outcomes	Effect Size
									INCREMENTAL EXERCISE; HR, BF, BGI, BLa, RER, V̇E, VO2 (CAF intervention x exercise intensity) *p<0.001 ↓HR (CAF intervention) *p <0.001 ↑BLa (CAF intervention) *p<0.001 ↓RPE (CAF intervention) *p<0.001 ↑V̇E (CAF intervention) *p=0.008 ↑RER (CAF intervention) *p=0.016 →HR, BF, BGI, BLa, RER, V̇E, VO2, RPE (CAF intervention or genotype distribution) TIME-TRIAL; ↑BF, BGI, BLa, mean HR, RER, mean V̇E (CAF intervention) *p<0.05 ↑Mean power output (CAF intervention) *p<0.001 ↓TT completion time (CAF intervention) *p<0.001 →TT completion time (Genotype distribution)*p=0.752 → VO2 (CAF intervention) *p=0.172 ↑BF, BGI, BLa, HR, RER, V̇E, (CAF intervention) *p<0.05	
Grgic et al. (2020), Australia [11]	RCT	Resistance-trained men (N=20)	29.3 ± 4.8	NA	3 mg/kg BW CAF	Placebo (dextrose)	C allele carriers (n=20)	C allele carriers (n=20): 143 ± 113	CAF INTERVENTION VS. PLACEBO IN C ALLELE CARRIERS; ↑Maximum repetitions at 85% 1RM *p<0.001 ↑Mean power matched for repetitions (W) *p<0.001 ↑Mean velocity matched for repetitions (m/s) *p<0.001 ↑Peak power matched for repetitions (W) *p<0.001 ↑Peak velocity matched for repetitions (m/s) *p<0.001	MUSCLE ENDURANCE TEST; Maximum repetitions at 85% 1RM C allele carriers 0.58 Mean power matched for repetitions (W) C allele carriers 0.56 Mean velocity matched for repetitions (m/s) C allele carriers 0.96

Author (year, location)	Study Design	Study Sample	Age year)	VO_2max	Intervention of the experimental group	Intervention of the control group	Genotype distribution	Caffeine intake (mg/day)	Outcomes	Effect Size
									↑Vertical jump height (cm) *p=0.034 ↑Peak power in the Wingate test (W) *p<0.001 ↑Mean power in the Wingate test (W) *p<0.001 ↑Minimum power in the Wingate test (W) *p=0.020	Peak power matched for repetitions (W) C allele carriers 0.27 Peak velocity matched for repetitions (m/s) C allele carriers 0.64 CMJ C allele carriers 0.13 WINGATE TEST (W) Peak power C allele carriers 0.37 Mean power C allele carriers 0.34 Minimum power C allele carriers 0.41
Loy et al. (2015), U.S. [10]	RCT	Tennis players (N=12)	NA	TT (n=6): 31.62 ± 4.35 C allele carriers (n=6): 33.78 ± 8.35 *ml/kg/min	5 mg/kg BW CAF	Placebo (flour)	TT (n=6), C allele carriers (n=6)	TT (n=6): 53.23 ± 76.57 C allele carriers (n=6): 102.02 ± 83.78	MODERATE EXERCISE; ↑%VO2peak (C allele carriers) *p=0.01 →%VO2 (CAF intervention vs PLA intervention) *p=0.60 →Mean VO2, HR, R, overall RPE, leg muscle pain intensity (group x condition) *p>0.43 PEAK EXERCISE; →VO2peak, Wpeak, HRpeak, RERpeak, overall RPEpeak, leg muscle pain peak (genotype distribution) *p>0.30 TIME TRIAL PERFORMANCE; ↑Total work (CAF intervention x genotype distribution) *p=0.03 →Mean VO2, HR, overall RPE or leg muscle pain (group x condition) *p>0.28 ↓%VO2 (TT group)	TT/C genotype CAFF intake 0.61 VO2max mL/kg/min 0.32 MODERATE EXERCISE; VO2 mean (mL/kg/min) TT genotype 0.2–C carriers 0.009 % VO2 peak mean (mL/kg/min) TT genotype 0.4–C carriers 0.06 Heart rate mean (bpm) TT genotyoe 0.3–C carriers 0.5 RPE mean (6–20) TT genotyoe 0.8–C carriers 0.5 Painmean (0–10) TT genotyoe 0.6–C carriers 0.16 TIME TRIAL PERFORMANCE Total work (kJ)

Author (year, location)	Study Design	Study Sample	Age year)	VO_2max	Intervention of the experimental group	Intervention of the control group	Genotype distribution	Caffeine intake (mg/day)	Outcomes	Effect Size
										TT genotype 0.27–C carriers 0.03 VO2mean (mL/kg/min) TT genotype 0.04–C carriers 0.001 % VO2peak mean (mL/kg/min) TT genotyoe 0.07–C carriers 0.11 Heart rate mean (bpm) TT genotyoe 0.2–C carriers 0.35 RPEmean (6–20) TT genotyoe 0.82–C carriers 0.71 Painmean (0–10) TT genotyoe 0.55–C carriers 0.28
Munoz et al. (2020), Spain [12]	RCT	Handball players (N=31)	23.7 ± 2.8	NA	3 mg/kg BW CAF	Placebo (cellulose)	TT (n=6), C allele carriers (n=25)	NA	↑Urine production (in TT genotype higher than C allele carriers) *p<0.001 ↑Increased activeness (in TT genotype higher than C allele carriers) *p=0.016 →Insomnia *p=0.174, GI problems *p=0.218, headache *p=0.108, irritability *p=0.558, muscular pain *p=0.094, tachycardia *p=0.282 (genotype distribution) →CMJ *p=0.602, SV *p=0.866, MATT *p=0.600, IHS *p=0.575, BT7M *0.879, BT7M+GK *p=0.151, BT9M *p=0.255, BT9M+GK *p=0.443 ACC *p=0.409, DEC *p=0.810, BI *p=0.753	CMJ (cm) TT genotype 0.08 –C carriers 0.018 SV (s) TT genotype 0.16 –C carriers 0.34 MATT (s) TT genotype 0.016 –C carriers 0.044 IHS (kg) TT genotype 0.27 –C carriers 0.036 BT7M (km/h) TT genotype 0.12 –C carriers 0.14 BT7M + GK (km/h) TT genotype 0.12 –C carriers 0.14 BT9M (km/h) TT genotype 0.045 –C carriers 0.34

Author (year, location)	Study Design	Study Sample	Age year)	VO_2max	Intervention of the experimental group	Intervention of the control group	Genotype distribution	Caffeine intake (mg/day)	Outcomes	Effect Size
										BT9M + GK (km/h) TT genotype 0.75 –C carriers 0.23 ACC (number/min) TT genotype 0.68 –C carriers 0.071 DEC (number/min) TT genotype 0.0038 –C carriers 0.34 BI (number/min) TT genotype 0.37 –C carriers 0.14
O'Connor et al. (2018), U.S [30]	RCT	Healthy individuals (N=26)		NA	5 mg/kg BW CAF	Placebo (flour)	TT (n=7), C allele carriers (n=19)	TT (n=7): 46 ± 68 CT (n=12): 93 ± 84 CC (n=7): 37 ± 56	↑Pain ratings (CC group) *p=0.056 ↓Pain ratings (TT group) *p=0.172 ↓Perceived exertion (CC group) *p>0.05 ↑Caffeine sensitivity (CC group) *p>0.05 ↓Caffeine consumption (CC group) *p>0.05 ↓Arm swelling (CC group vs CT/TT groups) *p>0.05	TT/CT Genotype: CAFF intake 0.62 TT/CC Genotype: CAFF intake 0.14 Perceived exertion (6–20): TT genotype 0.12, CT genotype 0.30, CC genotype 0.057 Pain (0–100): TT genotype 0.033, CT genotype 0.36, CC genotype 0.092
Renda et al. (2012), Italy [34]	RCT	Healthy men (N=110)	26.6 ± 4	NA	3 mg/kg CAF	Placebo (decaf preparation)	TT (n=28), C allele carriers (n=82)	NA	Mean SBP, DBP (CAF intervention) *p<0.001 ↑Peak SBP (CAF intervention) *p<0.001 Peak DBP (CAF intervention) *p=NS ↑peak ΔSBP (TT group) *p=0.024 SBP (intervention x time interaction) *p<0.01	Data not presented

Abbreviations: ACC: acceleration; BGI = blood glucose concentration; BF: breathing frequency; BI: body impacts; BLa: blood lactate concentration; BT7M: ball throw 7-m; BT7M+GK:ball throw 7-m with goalkeeper; BT9M: ball throw 9-m; BT9M+GK:ball throw 9-m with goalkeeper; BW: body weight; CAF: caffeine; CHO: carbohydrate; CMJ: countermovement jump; DBP: diastolic blood pressure; DEC: decelerations; GI: gastrointestinal; IHS: isometric handgrip strength; HR: heart rate; MATT: modified agility t-test; NA: Not applicable; NS: No significant; PLA: placebo; PVT: psychomotor vigilance test; RER: respiratory exchange ratio; RPE: rating of perceived exertion; SBP: systolic blood pressure; SV: sprint velocity test; TT: time-trial; VO_2: rate of oxygen uptake; V_E: minute ventilation; vs: versus; W: Watt.

Table 2. Characteristics and outcomes of included studies in the CYP1A2 gene.

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
Algrain et al. (2019), U.S. [23]	RCT	Young male (N=19)	25 ± 4	AA (n=10): 31.9 ± 5.69 C allele carriers (n=9): 31.7 ± 8.1 *ml/kg/min	3 gum x 100mg/piece CAF	Placebo (gum)	AA (n=10), C allele carriers (n=9)	NA	→Performance (CAF intervention) *p=0.258 →Ergogenic effect (CAF intervention x genotype distribution) *p≥0.861 →Absolute work (CAF intervention) *p=0.311 →Relative work (CAF intervention) *p=0.258 →Genotype distribution x CAF intervention interaction*p=0.861	AA/C genotype: VO2max mL/kg/min 0.029 Work (kJ) AA genotype 0.049 C carriers 0.15 Relative work(kJ/kg) AA genotype 0.24 C carriers 0.0
Carswell et al. (2020), U.K. [4]	RCT	Healthy active adults (N=18)	24 ± 4	AA (n=10): 48.5 ± 6.3 C allele carriers (n=8): 46.2 ± 11.9 *ml/kg/min	3 mg/kg BW CAF	3 mg/kg BW (microcrystalline)	AA (n=10), C allele carriers (n=8)	AA (n=10): 121 ± 128 C allele carriers (n=8): 135 ± 145	↑Performance (CAF intervention) *p<0.001 →Performance (CAF intervention x genotype distribution) *p>0.05 ↑Total work (CAF intervention) * p<0.001 →Total work (genotype distribution) * p>0,05 ↑Mean HR (CAF intervention during the TT) *p <0.01 →Mean HR (CAF intervention at %70 VO2max) *p>0.05 →Mean HR (genotype distribution) *p>0.05 →RPE (genotype distribution or CAF intervention) *p>0.05 ↑Cognitive performance with reaction time (CAF intervention) *p<0.01 ↓Reaction time (in AA group vs C allele carriers) *p <0.01 ↑PVT (CAF intervention) *p<0.01 ↑Slowest %10 speed response during exercise (in AA group vs C allele carriers) *p<0.01	AA/C genotype: VO2max mL/kg/min 0.24 AA/C genotype: CAFF intake 0.10

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									↓Fastest %10 reaction time at rest post supplementation (in AA group vs C allele carriers) *p<0.05 ↓Number of lapses (in AA group vs C allele carriers) *p<0.01	
Colquhoun (2019), U.S. [24]	RCT	Healthy males (N=42)	NA	NA	6 mg/kg BW CAF	Placebo (flour)	AA (n=26) C allele carriers (n=16)	AA (n=26): 290.6 ± 295.1 C allele carriers (n=16): 324.7 ± 276.3	↑VLEI (C allele carriers) *p=0.032 ↑MVIC (PLA intervention) *p=<0.001 →MVIC (CAF intervention) *p=0.094 ↓MVT (PLA intervention) *p=<0.001 Caffeine intake (AA genotype vs C allele carriers) *p=0.715	AA/C genotype: CAFF intake 0.12
Figueiredo et al. (2021), Brazil [26]	RCT	Well trained individuals (N=10)	30.1 ± 6.4	NA	300 mg CAF	Placebo (microcrystalline cellulose)	CC (n=9), AC (n=1)	NA	→TT performance (CAF intervention vs PLA intervention) *p=0.89 →RPE (CAF intervention vs PLA intervention) *p=0.34 →Vertical jump relative power (intervention or time or time x group) *p=0.67, p=0.4, p=0.66 Vertical jump relative power (CAF intervention vs PLA intervention) *p=0.34	Data not presented.
Fitzgerald (2014), U.S. [25]	RCT	Healthy men (N=12)	24±1	NA	6 mg/kg BW CAF	Placebo (flovured water)	AA (n=6) C (n=6)	NA	→Resting HR (CAF intervention) resting DBP in trials *p>0.05 ↑Resting SBP (CAF intervention) *p<0.05 ↓RPE in 300 WATT (CAF intervention) *p<0.10 ↓RPE in 300 WATT (CAF intervention) *p<0.10 RPE (time x genotype x intervention) RPE in trials (time x intervention) *p<0.05 ↓RPE (CAF intervention in C allele carriers) *p<0.05	Heart rate AA/C genotype 0.96 RPE (6–20 score) AA genotype 0.10 C carriers 1.34 RER C carriers 0.6

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									↑HR at peak exercise (AA genotype than C carriers) *p<0.05 →HR at peak exercise and peak power output →VO2max (genotype x condition x intervention) →RER (CAF intervention) ↓RER (CAF intervention in C allele carriers)	
Giersch et al. (2018), Canada [27]	RCT	Male (N=20)	NA	AA (n=8): 56.6±9.6 C allele carriers (n=12): 57.7±9.5 *ml/kg/min	6 mg/kg BW CAF	Placebo (flour)	AA (n=8), C allele carriers (n=12)	AA (n=8): 93.0 ± 111.2 C allele carriers (n=12): 91.6 ± 136.8	↑Average power output p=0,054 →Performance time (Genotype distribution) *p=0.42 →Power output (Genotype distribution) *p=0.98 TT performance (CAF intervention) *p=0.03	AA/C genotype: VO2max mL/kg/min 0.12 AA/C genotype: CAFF intake 0.011 Serum Caffeine AA/C genotype 1.4 Performance Time AA 0.36 C carriers 0.24 Power Output AA 0.23 C carriers 0.23
Glaister et al. (2020), U.K. [13]	RCT	Cyclist (N=66)	41.9 ± 8.6	AA (n=22): 4.20 ± 0.43 C allele carriers (n=18): 4.03 ± 0.44 *l/min	5 mg/kg BW CAF	Placebo (maltodextrin)	AA (n=41), C allele carriers (n=25)	AA (n=22): 340 ± 136 C allele carriers (n=18): 346 ± 110	REST. ↑DBP, SBP (CAF intervention) p*<0.05 →DBP (Genotype distribution) *p = 0.78 →SBP (Genotype distribution) *p = 0.68 →BF, BGI, BLa, VO2, (CAF intervention) ↓HR (CAF intervention) *p<0.05 ↑RER, V̇E (CAF intervention) *p<0.05 → BF *p=0.914, BGI *p=0.339, BLa *p=0.127, HR *p=0.401, RER *p=0.410, V̇E *p=0.153, VO2 *p= 0.076 (genotype distribution) INCREMENTAL EXERCISE.	AA/C genotype: CAFF intake 0.049 VO2max (l/min) 0.39

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									HR, BF, BGI, BLa, RER, V̇E, VO2 (CAF intervention x exercise intensity) *p<0.001 →BF, BGI, VO2 (CAF intervention or genotype distribution) ↓HR (CAF intervention) *p <0.001 ↑BLa (CAF intervention) *p<0.001 ↓RPE (CAF intervention) *p<0.001 ↑V̇E (CAF intervention) *p=0.008 →BLa, RPE, V̇E, (genotype distribution) ↑RER (CAF intervention) *p=0.016 →HR, BF, BGI, BLa, V̇E, VO2, RPE (CAF intervention or genotype distribution) RER (C allele carriers) *p=0.004 RER (AA group) *p=0.628 TIME-TRIAL. ↑BF, BGI, BLa, mean HR, RER, mean V̇E (CAF intervention) *p<0.05 ↑Mean power output (CAF intervention) *p<0.001 ↓TT completion time (CAF intervention) *p<0.001 →TT completion time (Genotype distribution) *p=0.286 → VO2 (CAF intervention) *p=0.172 ↑BF, BGI, BLa, HR, RER, V̇E, (CAF intervention) *p<0.05	
Grgic et al. (2020), Australia [22]	RCT	Resistance-trained men (N=22)	NA	NA	3 mg/kg CAF	Placebo (dextrose)	AA (n=13), C allele carriers (n=9)	AA (n=13): 133 ± 123 C allele carriers (n=9): 117 ± 68	↑Movement velocity, power output (CAF intervention) *p<0.05 ↑Vertical jump height (CAF intervention) *p=0.017 ↑Power output in Wingate test (CAF intervention) *p<0.05	AA/C genotype: CAFF intake 0.16 Movement velocity and power in the bench press AA genotype 0.22–0.9 AC/CC genotype 0.14–0.68

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									→Mean power, mean velocity, peak power, peak velocity at 25, 50, 75, and 90% 1RM (genotype distribution or CAF intervention x genotype interaction) *p>0.05 ↑Mean power, mean velocity, peak velocity at 50% 1RM (CAF intervention) *p<0.05 →Maximum number of repetitions in the bench press exercise with 85% 1RM (genotype distribution or CAF intervention x genotype interaction) *p=0.454 ↑Maximum number of repetitions in the bench press exercise with 85% 1RM (CAF intervention) *p<0.001 ↑Mean velocity (C allele carriers) *p<0.001 Mean velocity (Genotype distribution) *p=0.034 →Mean velocity (CAF intervention x genotype) *p=0.094, Genotype x Caffeine interaction *p=0.094 →Peak velocity, mean power output, and peak power output (Genotype distribution or CAF intervention x genotype interaction) p>0.05 ↑Peak velocity, mean power output, and peak power output (CAF intervention) *p<0.001 →CMJ (Genotype distribution) *p=0.447 →CMJ (Genotype distribution x CAF intervention) *p=0.752 ↑CMJ (CAF intervention) *p=0.017 →Peak power in Wingate (Genotype distribution) *p=0.998	Muscle endurance and velocity AA genotype 0.62–1.25 AC/CC genotype 0.33–1.27 CMJ AA genotype 0.13 AC/CC genotype 0.19 Power output in the Wingate AA genotype 0.34–0.43 AC/CC genotype 0.32–0.57

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									→Peak power in Wingate (Genotype x CAF interaction) *p=0.542 ↑Peak power in Wingate (CAF intervention) *p< 0.001 →Mean power (Genotype distribution) *p=0.517 →Mean power (CAF intervention x genotype interaction) *p=0.583 ↑Mean power (CAF intervention) *p<0.001 →Minimum power (CAF intervention x genotype interaction) *p=0.396 →Minimum power (Genotype distribution) *p=0.505 ↑Minimum power (CAF intervention) *p=0.011 ↑Vigor/activeness, perception of improved performance (C allele carriers)	
Guest et al. (2019), Canada [9]	RCT	Competitive male (N=101)	25 ± 4	AA (n=49): 3.9 ± 0.8 AC (n=44): 3.8 ± 0.7 CC (n=8): 3.9 ± 0.6 *l/min AA (n=49): 49 ± 8 AC (n=44): 47 ± 12 CC (n=8): 44 ± 12 *ml/kg/min	2 and 4 mg/kg CAF	Placebo (dextrose)	AA (n=49), C allele carriers (n=52)	AA (n=49): 87 ± 18 AC (n=44): 80 ± 20 CC (n=8): 38 ± 24 *dietary AA (n=49): 61 ± 13 AC (n=44): 89 ± 17 CC (n=8): 80 ± 74 *sport	↓Cycling time (2–4 mg/kg BW CAF intervention vs PLA intervention) *p=0.04 ↓10-km time (4 mg/kg BW CAF intervention vs PLA intervention) *p=0.01 ↓Cycling time (4 mg/kg BW CAF intervention in AA group vs PLA) *p<0.0001 ↓Cycling time (2 mg/kg BW CAF intervention in AA group vs PLA) *p=0.0005 →Cycling performance (2–4 mg/kg BW CAF intervention in AC group) *p=0.43 ↑Cycling time (4 mg/kg BW CAF to CC group) *p=0.04	AA/CA genotype: VO2max mL/kg/min 0.20 VO2ma l/min 0.13 CAFF intake dietary 0.37 CAFF intake sport 1.85 AA/CC genotype: CAFF intake dietary 2.31 CAFF intake sport 0.36 VO2max mL/kg/min 0.49 VO2ma l/min 0.0 Cycling time 2 mg/kg CAF AA 2.26 4 mg/kg CAF AA 3.39 4 mg/kg CAF CC 3.75 Improvement 4 mg/kg AA 0.63

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									Greatest change in 10-km time (4 mg/kg BW CAF to CC group vs AA and AC) *p=<0.0001, *p=0.0015 ↓5-km RPE (4 mg/kg BW CAF intervention in AA genotype) *p=0.03 ↑HR (4 mg/kg BW CAF intervention in AC genotype vs 2mg/kg BW CAF and PLA intervention) *p=0.007, *p=0.005 ↓HR (4 mg/kg BW CAF intervention in CC genotype vs 2mg/kg BW CAF and PLA intervention) *p=0.05, *p=0.03 →9-km RPE (genotype distribution) →Total RPE (CAF intervention in C allele carriers) →HR (CAF intervention in AA genotype)	2 mg/kg AA 0.4 4 mg/kg CC 1.3
Klein et al. (2012), U.S. [28]	RCT	Tennis players (N=16)	20.7 ± 1.7	NA	6 mg/kg CAF	Placebo (shots)	AA (n=7), C allele carriers (n=9)	AA (n=7): 104.21 ± 33.78 C allele carriers (n=9): 91.94 – 64.23	↑Total success shots in TST (CAF intervention) *p=0.029 ↑HR in TM test (AA genotype) *p=0.052	AA/C Genotype CAFF intake 0.24 RPE AA genotype 0.11 (TM) – 0.20 (TST) C carriers 0.23(TST)– 0.38(TM) HR AA genotype 0.11(TST)– 0.37 (TM) C carriers 0.13(TST)–0.17 (TM)
McGrath (2015), New Zealand [29]	RCT	Healthy well trained male cyclists and triathletes (N=11)	31 ± 3	NA	5 mg/kg BW CAF	Placebo (flour)	AA (n=6), C allele carriers (n=5)	NA	↑Self-paced cycling performance *p=0.037 →Performance in TT (caffeine × genotype) *p=0.343 →RPE (caffeine x genotype interaction) *p=0.484 No caffeine x ergogenic effect x trial interaction *p=0.147	Data not presented

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									↑ HR during the TT (CAF intervention) *p=0.003 →HR (CAF intervention x genotype interaction) *p=0.118 ↑During steady state exercise HR (No difference between CAF intervention and genotype distribution) *p=0.013 ↑RPE (time) *p=0.020 ↑RPE (PLA intervention) *p=0.010 ↑During steady state VO2 (CAF intervention) *p=0.047 ↑During steady state VO2 (time) *p=0.007 ↑RER (CAF intervention) *p=0.08 →RER (genotype distribution) *p=0.709 ↑VO2 (CAF intervention *p=0.757	
Munoz et al. (2020), Spanish [12]	RCT	Handball players (N=31)	23.7 ± 2.8	NA	3 mg/kg CAF	Placebo (cellulose)	AA (n=14), AC (n=15), CC (n=2)	NA	↑CMJ height *p=0.001, SV *p=0.022, BT9M *p=0.008 (CAF intervention) →Time to complete the MATT *p=0.686, strength in the IHS test *p=0.054, BT7M *p=0.065, BT7M+GK *p=0.492, BT9M+GK *p=0.093 ↑BT7M (CAF intervention in AA genotype) *p=0.013 →BT7M (C allele carriers) *p=0.932 →ACC, DEC, BI frequency (CAF intervention or genotype distribution) *p=0.178, *p=0.051, *p=0.556 ↑Insomnia (C allele carriers) *p=0.023	CMJ AA genotype 0.28 AC/CC genotype 0.15 Sprint velocity test AA genotype 0.84 AC/CC genotype 0.15 Modified agility t-test AA genotype 0.03 AC/CC genotype − 0.05 Isometric handgrip strength AA genotype 0.00 AC/CC genotype 0.23 Ball throw from 7-m AA genotype 0.34 AC/CC genotype − 0.02 Ball throw from 7-m with a goalkeeper AA genotype 0.39 AC/CC genotype − 0.23 Ball throw from 9-m

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
										AA genotype 0.40 AC/CC genotype 0.22 Ball throw from 9-m with a goalkeeper AA genotype 0.47 AC/CC genotype 0.05 ACC (number/min) AA genotype 0.089 C genotype 0.52 DEC (number/min) AA genotype 0.57 C genotype 0.0061 BI (number/min) AA genotype 0.079 C genotype 0.31
Pataky et al. (2016), U.S. [31]	RCT	Recreationally trained men (N=38)	21 ± 1	AA (n=21): 51 ± 7, C (n=17): 51 ± 6 *ml/kg/min	6 mg/kg BW CAF	Placebo (flavor + saccharine)	AA (n=21), C (n=17)	NA	↑Power output (Ingestion+Rinse CAF intervention) *p=0.01 ↑Power output (Ingestion CAF intervention) *p=0.12 ↑Likely differences (Ingestion CAF intervention to AC genotype) *p=0.12 ↑Power output (Ingestion+Rinse CAF intervention in early subjects) *p=0.0001 ↑Power output (Ingestion CAF intervention in early subjects) *p=0.06 ↑Power output (Rinse CAF intervention in early subjects) *p=0.16 ↓Power output (Rinse CAF intervention in late subjects) *p=0.43	AA/C genotype: VO2max mL/kg/min 0.0
Potgieter (2013), South Africa [32]	RCT	Triathles (N=26)	37.8 ± 10.6	NA	6 mg/kg BW	Placebo (Canderel®)	AA (n=16), AC (n=5), CC (n=5)	NA	↓Swimming time (CAF intervention) *p=0.05 ↓Completion of the triathlon time *p=0.02 ↓RPE (CAF intervention) *p=0.87	Data not presented

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									↑Blood lactate levels (CAF intervention) *p=0.04 Shakiness *p = 0.00, heart palpitations *p = 0.01 and GIS disturbances *p=0.01 (CAF intervention)	
Puente et al. (2018), Spain [33]	RCT	Elite basketball players (N=19)	NA	NA	3 mg/kg BW CAF	Placebo (cellulose)	AA (n=10), C (n=9)	NA	↑Ablakov jump (AA genotype) *p=0.03 →Sprint time in the CODAT test with the ball (AA genotype) *p=0.15 →Sprint time in the CODAT test with the ball (C allele carriers) *p=0.49 →Sprint time in the CODAT test without the ball (AA genotype) *p=0.36 →Sprint time in the CODAT test without the ball (C allele carriers) *p=0.37 →HR in basketball game (Genotype distribution) * p >0.05 ↑Perceived muscle power (CAF intervention in AA genotype) *p=0.04 ↑Self-perceived endurance capacity (CAF intervention in AA genotype) *p=0.06 →Self-perceived endurance capacity (C allele carriers) *p=0.50 →Ratings of perceived fatigue (AA genotype or C allele carriers) *p=0.20, *p=0.50 ↑Insomnia (AA genotype) →Side effects (Genotype distribution) *p>0.05 ↑BI (CAFF intake) *p<0.05 ↑Mean jump height (CAF intervention in AA genotype) *p<0.05	Abalakov jump AA genotype 0.15 AC/CC genotype 0.14 “Change-of-Direction and Acceleration Test” without the ball AA genotype 0.12 AC/CC genotype − 0.06 “Change-of-Direction and AccelerationTest” with the ball AA genotype 0.44 AC/CC genotype 0.0 Mean HR AA genotype 0.21 C genotype 0.179 Peak HR AA genotype 0.080 C genotype 0.46 BI (number/min) AA genotype 0.38 C genotype 0.39 Perceived muscle power (A.U.) AA genotype 0.89 C genotype 0.65 Perceived endurance (A.U.) AA genotype 0.71 C genotype 0.0 Perceived exertion (A.U.) AA genotype 0.45 C genotype 0.0

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
Rahimi (2018), Iran [3]	RCT	Resistance-trained men (N=30)	NA	NA	6 mg kg BW CAF	Placebo (maltodextrin)	AA (n=14), C allele carriers (n=16)	NA	↑BP repetitions at S1, S2, S3 (AA genotype) *p=0.015 *p=0.0001 *p=0.001 ↑BP repetitions at S1, S2 (CAF intervention vs PLA intervention in AA genotype) *p=0.003 *p=0.001 ↑LP repetitions at S2, S3 (AA genotype) *p=0.001 *p=0.024 ↑LP repetitions at S2, S3 (CAF intervention vs PLA intervention in AA genotype) *p=0.012 *p=0.016 ↑SR repetitions at S1, S2, S3 (CAF intervention in AA genotype) *p=0.005 *p=0.001 *p=0.007 ↑SR repetitions at S1, S2, S3 (CAF intervention vs PLA intervention) *p=0.012 *p=0.027 *p=0.001 ↑SP repetitions at S2, S3 (CAF intervention vs PLA intervention in AA genotype) *p=0.0001, *p=0.012 ↑Total repetitions for BP *p=0.006, LP *p=0.03, SR *p=0.16 (CAF intervention in AA genotype vs C allele carriers) ↑Total repetitions for BP *p=0.004, LP *p=0.01, SR *p=0.001, SP *p=0.048 (CAF intervention vs PLA intervention in AA genotype) Total repetitions x genotype distribution x CAF *p=0.002	Data not presented
Salinero et al. (2017), Spain [2]	RCT	Healthy active participants (N=21)	28.9 ± 7.3	NA	3 mg/kg BW CAF	Placebo (??)	AA (n=5), C allele carriers (n=16)	NA	→Reaction time (CAF or PLA intervention) *p=0.31 →Reaction time (Genotype distribution) *p=0.681	Peak power AA genotype 0.04 AC/CC genotype 0.15 Mean power AA genotype 0.07 AC/CC genotype 0.10

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									↑Mean power output and peak power in Wingate test (CAF intervention) *p<0.001, *p=0.01 ↑Mean power output and peak power (CAF intervention) *p<0.05 ↑Mean and peak power (CAF intervention vs PLA intervention in C allele carriers) *p<0.05 →Mean power, peak power (Genotype distribution) *p>0.05 →Fatigue index (CAF intervention) *p=0.57 →Perceived muscle power, perceived exertion (CAF intervention) →Perceived muscle power, perceived exertion (Genotype distribution) *p>0.05 →Side effect (CAF intervention) *p>0.05 →Side effect (Genotype distribution) *p>0.05 ↑Nervousness (C allele carriers)	Perceived power AA genotype 0.5 C genotype 0.5 Perceived exertion AA genotype 0.0 C genotype 0.0 Fatigue Index AA genotype 0.01 C carriers 0.15
Southward (2016), New Zealand [35]	RCT	Recreationally trained athletes (N=14)	26.9 ± 7.93	NA	6 mg/kg BW CAF	Placebo (maltodextrin)	AC (n=14)	NA	→5 or 10-km TT (CAF intervention) *p=0.589, p=0.187 ↑During the exercise HR (CAF intervention) *p=0.062 →Intervention x HR x time *p=0.257 →Resting HR (CAF intervention) *p=0.25 →Concentric knee extensor torque (CAF intervention) *p<0.05 →Intervention x time x concentric knee extensor torque *p=0.808 ↑Eccentric knee extensor torque (CAF intervention) *p<0.05 →Eccentric knee extensor torque x time x intervention *p=0.195	10-km running time trial AC genotype 0.34 HR AC genotype 0.44 Concentric knee extensor torque AC genotype 0.25 Eccentric knee extensor torque AC genotype 0.44 SJ height AC genotype 0.33 CMJ height AC genotype 0.17 RPE AC genotype 0.12

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									↑Eccentric knee extensor torque (CAF intervention vs PLA intervention) *p=0.015 ↑Knee extensor torque x time (CAF intervention) *p=0.081 ↑SJ height (CAF intervention) *p=0.017 →Intervention x time x SJ height *p=0.129 →CMJ height (CAF intervention) *p=0.325 →Intervention x time x CMJ height *p=0.209 →RPE (CAF intervention) *p=0.309 →Intervention x time x RPE *p=0.156 →Vigor (CAF intervention) *p=0.197 ↓Digit vigilance reaction times (CAF intervention) *p<0.05 ↓Rapid visual information processing (CAF intervention) *p<0.1 ↑Vigor (CAF intervention) *p=0.032 →Sleep quality *p=0.358, ease of awakening *p=0.790, behavior following sleep *p=0.457 (CAF intervention)	
Spineli et al. (2020), Brazil [36]	RCT	Competitive adolescents (N=100)	15 ± 2	AA (n=49): 44.3 ± 2.7 AC (n=42):43.2 ± 2.4 CC (n=9): 45.8 ± 3.5 *ml/kg/min	6 mg/kg BW CAF	Placebo (cellulose)	AA (n=49) AC (n=42) CC (n=9)	AA (n=49): 42.3 ± 39.8 AC (n=42): 58.6 ± 44.9, CC (n=9): 32.8 ± 23.9	→CMJ (CAF intervention x genotype distribution or genotype distribution) *p=0.935, *p=0.753 →SJ test (CAF intervention x genotype distribution or genotype distribution) *p=0.571, *p=0.832 →Agility time (CAF intervention) *p=0.736	AA/AC genotype: VO2max (ml/kg/min) 0.43 CAFF intake 0.38 AA/CC henotype VO2max (ml/kg/min) 0.50 CAFF intake 0.30 Handgrip strength test (kgf)

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
									↓Agility (AC vs AA or CC genotype) *AA p=0.037, *CC p=0.018 →Agility (CAF intervention x genotype distribution) *p=0.417 ↑Sit-up and push-up tests (CAF intervention) *p=0.001, p=0.004 →Sit-up and push-up tests (Genotype distribution) *p=0.122 ↑Total distance in Yo-Yo IR1 (CAF intervention) *p=0.019 ↓Yo-Yo IR1 (AC genotype) *p=0.068 →RPE (CAF intervention x genotype distribution or genotype) *p=0.466, *p=0.502 →Handgrip test (CAF intervention x genotype distribution or genotype distribution) *p=0.210, *p=0.096	AA genotype 0.26 AC genotype 0.065 CC genotype 0.062 CMJ AA genotype 0.11 AC genotype 0.13 CC genotype 0.04 Spike jump AA genotype 0.14 AC genotype 0.05 CC genotype 0.01 Agility test AA genotype 0.10 AC genotype 0.07 CC genotype − 0.37 Isometric handgrip strength AA genotype 0.17 AC genotype 0.07 CC genotype 0.06 Push-up AA genotype 0.09 AC genotype 0.24 CC genotype 0.36 Sit-up AA genotype 0.24 AC genotype 0.32 CC genotype 0.28 Yo–Yo IR1 AA genotype 0.31 AC genotype 0.36 CC genotype 0.12 RPE AA genotype 0.22 AC genotype 0.37 CC genotype 0.16
Thomas et al. (2020), Canada [38]	RCT	Healthy untrained adults (N=20)	25.5 ± 3.5	AA (n=11): 32.3 ± 5.4 C allele carriers (n=9): 32.1 ±	3x100mg/piece gum	Placebo (gum)	A (n=11) C allele carriers (n=9)	NA	C allele group, a main effect of time was detected for HR and all HRV indices during the PLA trial *p<0.05	AA/C genotype: VO2max (ml/kg/min) 0.030

Author (year, location)	Study Design	Study Sample	Age (year)	VO_2max	Intervention	Control	Genotype Distribution	Caffeine Intake (mg/day)	Outcomes	Effect Size
				7.8 *ml/kg/min					↓Time diffrence was detected for HR (CAFF trial) *p <0.05	
Womack et al. (2012), U.S. [14]	RCT	Recreationally competitive cyclists (N=35)	25.0 ± 7.3	VO2max (L/min) AA (n=16): 4.30 ± 0.45 C allele carriers (n=19): 4.31 ± 0.58 / VO2max (ml/kg/min) AA (n=16): 59.04 ± 9.29 C allele carriers (n=19): 59.61 ± 10.31	6 mg/kg BW CAF	Placebo (flour)	AA (n=16) C allele carriers (n=19)	AA (n=16): 85.71 ± 106.49 C (n=19): 86.62 ± 145.40	↓40-km times (CAF intervention vs PLA intervention and intervention x genotype distribution) *p<0.001, *0.005 ↓40-km times (CAF intervention in AA genotype vs C allele carriers) *p<0.001, *p=0.04 ↑VO2, HR (CAF intervention) *p<0.001 ↑VO2 (C allele carriers) *p=0.03 →RPE, RER (CAF intervention or genotype distribution) p=NS	AA/C genotype: CAFF intake 0.0071 AA/C genotype: VO2max (L/min) 0.019 AA/C genotype: VO2max (ml/kg/min) 0.058 RPE AA genotype 0.062 C genotype 0.071 VO2(L/min) AA genotype 0.44 C genotype 0.42 RER AA genotype 0.22 C genotype 0.0 HR AA genotype 0.86 C genotype 0.52

Abbreviations: 1RM: 1-repetition maximum; ACC: acceleration; A.U.; arbitrary units; BF: breathing frequency; BGI = blood glucose concentration; BI: body impacts; BLa: blood lactate concentration; BP: bench press; BT7M: ball throw 7-m; BT7M+GK: ball throw 7-m with goalkeeper; BT9M: ball throw 9-m; BT9 + GK: ball throw 9-m with goalkeeper; BW: body weight; CAF: caffeine; CODAT: change-of-direction and acceleration test; CMJ: countermovement jump; DBP: diastolic blood pressure; DEC: decelerations; GIS: gastrointestinal system; GK: goalkeeper; HR: heart rate; IHS: isometric handgrip strength; LP: leg press; MATT: modified agility t-test; MVIC: maximal voluntary isometric contraction; MVT: maximal voluntary torque; MUAP: motor unit action potential amplitude; NA: Not applicable; NS: No significant; PLA: placebo; PVT: psychomotor vigilance test; PX: paraxanthine; RER: respiratory exchange ratio; RPE: rating of perceived exertion; RT: recruitment threshold; SBP: systolic blood pressure; SP: shoulder press; SR; seated row; SV: sprint velocity test; HRV: post-exercise heart rate variability; TM: treadmill exercise; TST: tennis skill test; TT: time-trial; VL_{EI}: vastus lateralis echo intensity; VO_2: rate of oxygen uptake; V_E: minute ventilation; vs: versus.

Sport Performance

ADORA2A: Four studies reported performance changes after ingesting caffeine. The study samples ranged from 12–66 [10, 11, 12, 13]. Ergogenic effects on performance were seen after caffeine ingestion. No significant results were seen in genotype distribution after ingesting 3 mg/kg caffeine in countermovement jump (CMJ), sprint velocity test (SV), modified agility t-test (MATT), isometric handgrip strength (IHS), ball throw 7-m (BT7M), ball throw 7-m with goalkeeper (BT7M+GK), ball throw 9-m (BT9M), ball throw 9-m with goalkeeper (BT9M+GK) tests [12]. %VO_2max peak and VO_2max increased in C carriers after consuming 5 mg/kg caffeine, and total work done in the caffeine group increased, and in the TT genotype, %VO_2max decreased. Total work done by C carriers was greater than by the TT genotype [10]. Also, Glaister et al. reported significant changes in power output after 5 mg/kg of caffeine [13]. Importantly, in a study that Grgic et al. conducted on resistance-trained men, 3 mg/kg caffeine intake increased the muscular endurance, CMJ and Wingate tests measure in C allele carriers [11]. The ESs of the TT genotype in performance was 0.0038–0.75, while in C carriers they were 0.018–0.96 (see Table 1).

CYP1A2: In their systematic review, Grgic et al. [16] reported sixteen studies [2–4, 9, 12, 14, 22, 23, 27–29, 31–33, 35, 36] regarding the effect of acute caffeine consumption on performance in the *CYP1A2* gene that we also included in our systematic review. For this reason, the same results were not included as we wanted our study to be a complementary study. Four more studies were added [13, 24–26].

A total of 20 studies investigated performance changes after caffeine consumption. Different performance tests were implemented in studies, such as measuring VO_2max, time trial tests, muscle power tests, isometric handgrip tests, bench press, leg press, shoulder press, seated row, countermovement jump, abalakov jump, spike jump and squat jump, sprint velocity test, Wingate test, agility tests, different skill tests changing, reaction time, response speed, number of lapses. In six studies, no effect of the genotype distribution was seen, while acute caffeine intake was affected [4, 13, 27, 29, 33, 36]. In three studies, no difference was detected with both the genotype and caffeine intake [23, 25, 26]. Nine studies found significant results in the genotype distribution [2, 3, 4, 9, 12, 14, 24, 33, 36]. Carswell et al. detected that 3 mg/kg caffeine intake decreased the reaction time, the number of lapses and increased the slowest speed time in AA genotypes [4]. Guest found improvements in cycling performance in the AA genotype after ingesting 2mg/kg or 4mg/kg caffeine [9]. Respectively, performance improvements in ball throwing and abalakov jump were seen in the AA genotype after 3mg/kg caffeine [12, 33]. Also, Womack et al. reported improvements in cycling time after 6mg/kg caffeine on AA genotypes, and Rahimi reported increases in bench press, leg press, seated row, shoulder press repetitions in AA genotype [3, 14]. On the other hand, in C alleles, muscle power increased after ingesting 6 mg/kg [24]. Also an increase in mean and peak power after 3 mg/kg of caffeine intake was seen [2]. Spineli et al. reported that a decrease in the agility test in the AC genotype compared to the AA and CC genotypes [36]. Moreover, in four studies, VO_2max was measured after caffeine intake [13, 14, 25, 29]. Two of them reported no significant effects [13, 25]. McGrath reported an increase in VO_2max after 5 mg/kg caffeine, and Womack et al. reported an increase in VO_2max in C allele carriers after 6 mg/kg of caffeine [14, 29]. The range of ESs in 10 studies for the AA genotype in performance was 0.049–3.39; in 9 studies for C carriers these were 0.0–1.27; in one study for the AC genotype it was 0.065–0.37, and in two studies for the CC genotype it was 0.062–3.75 (see Table 2).

Quality Appraisal

The average score obtained from the PEDro checklist was calculated as 8.64 points (range 7–9 points). 18 studies were classified as "excellent" in their methodological quality and 7 as of "good" methodological quality. Individual scores are shown in Table 3.

Table 3. Quality appraisal of the included studies by the PEDro scale [21, 37].

References	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Score
Algrain et al. [23]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Carswell et al. [4]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Colquhoun [24]	No	Yes	Unclear	Yes	Yes	Unclear	Yes	No	Yes	Yes	Yes	7
Figueiredo et al. [26]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Fitzgerald [25]	Yes	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8
Giersch et al. [27]	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Glaister et al. [13]	No	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9
Grgic et al. [11]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Grgic et al. [22]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Guest [9]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Klein et al. [28]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Loy et al. [10]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
McGrath et al. [29]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Munoz et al. [12]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
O'Connor et al. [30]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Pataky et al. [31]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Potgieter [32]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Puente et al. [33]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Rahimi [3]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Renda et al. [34]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Salinero et al. [2]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Southward [35]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Spineli et al. [36]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Thomas et al. [38]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Womack et al. [14]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

4. Discussion

This systematic review finds that different doses of acute caffeine intake can affect the physiological state and performance of individuals with genotype distributions of the *CYP1A2* and *ADORA2A* gene. Studies acknowledged that there is no single gene that affects caffeine metabolism in the body [4, 10–13, 30, 34], but strategies are insufficient to definitely prove which gene is more efficient and also which genotype benefits more with caffeine's ergogenic use. In studies with the same study groups of in *CYP1A2* and *ADORA2A* gene polymorphisms [4, 12, 13], Carswell et al. did not find any difference in the *ADORA2A* gene, while in the *CYP1A2* gene, the AA genotype has significant improvements in performance following the 3mg/kg caffeine [4]. Also, Glaister et al. did not report any changes in the *ADORA2A* gene, but improvement in RER was observed in the *CYP1A2* gene [13]. On the other hand, according to the *ADORA2A* gene polymorphism, urine production and activeness increased in the TT genotype, while no differences were seen for the *CYP1A2* genotype distributions. Moreover, performance improvements were observed in 7-m ball throw in the AA genotypes of *CYP1A2* gene, and insomnia rates increased in C carriers, but no significant effects of the *ADORA2A* gene distributions were observed [12]. In one study with only C carriers of the *ADORA2A* gene, all performance tests (maximum repetitions at 85%, 1-repetition maximum (1RM), mean power matched for repetitions, mean velocity matched for repetitions, peak power matched for repetitions, peak velocity matched for repetitions, vertical jump height in the CMJ test, peak power in the Wingate test, mean power in the Wingate test, minimum power in the Wingate test) showed significant increases after 3mg/kg of caffeine intake [11]. With the same performance test in the *CYP1A2* gene distributions, only an increase in the mean velocity in C allele carriers was found; also increased vigor/activeness was observed [22]. A comparison of these two studies explains the importance of the *ADORA2A* gene in the ergogenic use of caffeine; therefore, more studies are needed with bigger study samples and in all genotypes for the *ADORA2A* gene polymorphisms.

Apart from gene variations, ergogenic responses to caffeine can change according to the amount, type of replacement, gender and age [4, 39–42]. Caffeine is classified as "generally considered safe" by the U.S. Food and Drug Administration (FDA) [43]. Caffeine can be unsafe for individuals with certain genetic polymorphisms or certain medical conditions (e.g., hypertension, heart conditions, gastrointestinal problems, diabetes), and it is difficult to predict its effects at higher doses [44]. In most people, caffeine contributes to a cognitive response that includes increased activeness and attention [45–47] and has roles mainly in an increase in blood pressure (BP) [48]. In the *ADORA2A* polymorphism, increased activeness and urine production were seen in the TT genotype after ingesting 3 mg/kg of caffeine before the exercise [12]. On the other hand, in the *CYP1A2* polymorphism, after 6 mg/kg of caffeine intake, shakiness, heart palpitations and gastrointestinal system (GIS) disturbances were seen [32]. Moreover, insomnia was seen in both the AA genotypes and C carriers after consuming 3 mg/kg [12, 33].

HR plays an important role in athletes' performance and training. Stork et al. [49] found that HR is always associated with physiological limits, and therefore the heart rate is suitable for measuring the performance of athletes. In the *ADORA2A* gene, HR increased more in C carriers after ingestion of 5 mg/kg of caffeine [10]. The peak change SBP increased in the TT genotype following 3 mg/kg of caffeine [34]. In the *CYP1A2* gene, exercise HR increased in the AA genotype after ingesting 6 mg/kg of caffeine [25,28]. Guest reported HR increases in the AC genotypes after 4 mg/kg of caffeine intake, while and a decrease was seen in the CC genotype [9]. Meanwhile, a decrease in time for HR was detected in C carriers so the recovery time was improved after 3x100mg/piece of gum caffeine [38]. The quick HR decrease, or decreased HR in exercise, is a wanted thing to compare the performance for an athlete. In a study, the top 5 athletes in a competition had higher HRs in exercise than other athletes [50]. Therefore, the decrease in HR in C carriers can be evidence of a probable performance increase. However, in all cases, HR data can only be measured in a limited number of aspects for performance or training response

and, therefore, need to be combined with additional parameters [51]. RPE is an indicator of how difficult the work is done, and in the study, 4mg/kg of caffeine intake decreased RPE in the *CYP1A2* gene AA genotype. Moreover, Puente et al. suggested the same about 3 mg/kg of caffeine intake [9, 33]. On the other hand, Fitzgerald reported that C allele carriers had a decrease in RPE after 6 mg/kg of caffeine intake [25]. Also, in the *ADORA2A* gene, pain ratings decreased in the TT genotype and increased in the CC genotype; RPE and arm swelling decreased in the CC genotype, while caffeine sensitivity increased after the exercise with 5 mg/kg of caffeine [30]. Therefore, caffeine can be a potential ergogenic for athletes. Furthermore, in the use of caffeine for ergogenic effects, tolerance may develop [52]. It has been shown that the suppressive effect of acute caffeine intake disappears after 3 to 5 days of repeated caffeine consumption [53]. In addition, studies indicated that a tolerance in HR and BP can occur after chronic caffeine intake, and Beaumont et al. demonstrated that regular daily consumption of 3 mg/kg of caffeine can reduce the response to ergogenic effects of acute 3 mg/kg of caffeine consumption before the exercise [54–56]. This indicates that genetic factors may be involved in developing incomplete tolerance. therefore, it is important to determine the proper dose, frequency and effects of the polymorphisms on the athletes for maximum performance and side effects.

Limitations

The significant limitations are small sample sizes in each study; most measured parameter were different and not suitable to processes of a quantitative appraisal. Most studies measured the effect of caffeine intake without applying any wash-out, which may affect the results obtained in the studies. By this, the probable tolerance that may occur and can affect the results of the trials. Fasting state of satiety or a different ergogenic supplement use is unknown. There are different doses of caffeine intake in studies, and there is no standardization in this regard. Different exercise types, durations and contributor groups (resistance trainer, strength sports, team sports, etc.) were used, so exercise type and the variations on the performance cannot be interpreted.

5. Conclusions

Even studies for caffeine metabolism are usually interpreted with the *CYP1A2* gene. This study provides the importance of the *ADORA2A* gene polymorphism. As explained, C alleles usually show performance improvements after caffeine intake. In the *CYP1A2* polymorphism, different performance changes were observed, and controversial results were inconsistent. On the other hand, many physiological and ergogenic effects can occur due to caffeine, but no consistent reports are presented for genotypes either. This study indicates the differences between the two genes, but the studies on genotypes are mostly inconsistent and unpredictable. It is important to determine the proper dose, frequency and effects of the polymorphisms on the athletes, for maximum performance, predict side effects and, more importantly, to specify a personalized ergogenic guideline. Consequently, significant results in genotype distributions in studies are detected; however, there are controversial results about which genotype may be affected more, so there is a need for efficient studies with a increased number of study samples.

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