1  *CYP1A2* genotype and acute ergogenic effects of caffeine intake on exercise

2  performance: a systematic review

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10  **Running head:** *CYP1A2* genotype, caffeine, and exercise performance

11  **Number of figures:** 1

12  **Number of tables:** 3

13  **Abstract word count:** 246

14  **Manuscript word count:** 4334

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20     *CYP1A2* **genotype and acute ergogenic effects of caffeine intake on exercise**

21     **performance: a systematic review**

**Abstract**

**Purpose:** To systematically review studies that examined the influence of the *CYP1A2* −163C>A polymorphism on the ergogenic effects of caffeine and to discuss some of the reasons for the discrepancies in findings between the studies.

**Methods:** This review was performed in accordance with the PRISMA guidelines. The search for studies was performed through nine databases.

**Results:** Seventeen studies were included in the review. Based on the included studies, it seems that individuals with the AA or AC/CC genotype may experience an increase in performance following caffeine ingestion. Significant differences between genotypes were found in four studies, and all four reported a more favorable response in the AA vs. AC/CC genotype. These results suggest that if there is an actual genotype-related effect of acute caffeine supplementation, it might be in that direction. In the studies that reported such data for aerobic endurance, the findings are specific to male participants performing cycling time trials (distances of ≥10 km) and ingesting caffeine 60 minutes before exercise. For high-intensity exercise, two studies reported that genotype variations determined the response to caffeine ingestion, even though the differences were either small (~1 additional repetition in high-load resistance exercise set performed to muscular failure) or inconsistent (i.e., observed only in one out of eight performance tests).

**Conclusions:** *CYP1A2* genotype variations may modulate caffeine's ergogenic effects, but the differences between genotypes were small, inconsistent, or limited to specific exercise scenarios. Future studies with larger sample sizes are needed to fully elucidate this research area.

**Keywords:** supplements; ergogenic aid; genetics; responses

## Introduction

Caffeine is one of the most consumed psychoactive drugs in the world [1]. Besides the general population, caffeine is also widely used by athletes because of its ergogenic effects on exercise performance [2]. Based on the available evidence, caffeine ingestion may be ergogenic for different components of exercise performance, such as aerobic and muscular endurance, muscle strength, power, and speed [3]. Such effects are well-established and well-replicated in the scientific literature [3]. However, the response to caffeine ingestion does not seem to be uniform across individuals, with some experiencing increases in performance following acute caffeine ingestion, while others show no performance-related changes or even decrease following caffeine consumption [4].

The gene *CYP1A2* encodes cytochrome P450 1A2, an enzyme responsible for ~95% of caffeine metabolism [5]. An A to C substitution at position 163 (−163C>A; rs762551) in the *CYP1A2* gene impacts the speed of caffeine metabolism [6]. Individuals who possess the AA genotype are considered "fast metabolizers" of caffeine, given that this genotype codes for the highly inducible form of the CYP1A2 enzyme [5-8]. Individuals with AC or CC genotype (i.e., C allele carriers) tend to have slower caffeine metabolism and are considered as "slow metabolizers" of caffeine [5-8].

Several studies explored the effects of caffeine supplementation on exercise performance while considering *CYP1A2* −163C>A polymorphism [9-13]. The results of these studies, however, are equivocal. Some studies found genotype differences in caffeine's ergogenic effects, as individuals possessing the AA genotype experienced improvements in performance following caffeine ingestion, while those with the AC or CC genotype were not positively

69    impacted by caffeine ingestion [12]. In contrast to these findings, others have suggested that

70    individuals with the AC genotype experience greater improvements in performance following

71    caffeine ingestion than those who possess the AA genotype [13]. Finally, some studies did not

72    show significant differences in responses to caffeine supplementation between genotypes [9-

73    11].

74

75    Given the equivocal evidence presented in the literature, we aimed to: (a) systematically

76    review the available studies that have examined the influence of the *CYP1A2* −163C>A

77    polymorphism on the ergogenic effects of caffeine; and, (b) discuss some of the reasons for

78    the discrepancies between the studies. A systematic review of the evidence might be of high

79    practical importance as it may help to identify why some individuals have minimal ergogenic

80    or even ergolytic effects after acute caffeine intake. The presented findings might also be of

81    relevance if we consider that the number of companies that offer direct-to-consumer genetic

82    testing aimed to detect individual responses to caffeine and the subsequent popularity of such

83    testing has experienced a substantial increase in recent years [14].

84

85    **Methods**

86    *Search strategy*

87    This review was performed while following the Preferred Reporting Items for Systematic

88    Reviews and Meta-Analyses (PRISMA) guidelines [15]. The protocol was not registered. For

89    the purpose of this review, we performed a comprehensive search of the following databases:

90    CINAHL, ERIC, Open Dissertations, Networked Digital Library of Theses and Dissertations,

91    Open Access Theses and Dissertations, PubMed/MEDLINE, Scopus, SPORTDiscus, and

92    Web of Science. In all of these databases, we used the following syntax: (CYP1A2 OR

93    genotype OR genetics OR polymorphism) AND (caffeine) AND (exercise OR training OR

94    ergogenic OR performance). Secondary searches were performed by examining the reference

95    lists of all included studies and by performing forward citation tracking through Google

96    Scholar and Scopus. The search for studies concluded on August 28th, 2020 and was

97    performed independently by two authors (JG and CP) of the review to minimize bias in study

98    selection.

99

100    *Inclusion criteria and data extraction*

101    We included studies that satisfied the following criteria: (a) written in English as a peer-

102    reviewed paper, a thesis, or a dissertation; (b) explored the influence of any of the *CYP1A2*

103    −163C>A genotypes on the ergogenic responses to acute caffeine ingestion; (c) included

104    humans as study participants. We extracted the following data from the included studies: (a)

105    author(s) and publication status (i.e., published or unpublished); (b) sample size, *CYP1A2*

106    genotype distribution, and participants' characteristics (sex, age, body mass, habitual caffeine

107    intake, and training status); (c) caffeine supplementation protocol and exercise task(s); and (d)

108    main study findings (i.e., caffeine main effects and caffeine × genotype interaction, where

109    applicable).

110

111    *Calculation of effect sizes*

112    Where available, Cohen's *d* effect sizes were calculated as the caffeine-placebo mean change

113    divided by the pooled SD, separately for each genotype. Effect sizes were interpreted as:

114    "trivial" ($\leq$0.20), "small" (0.21–0.50), "medium" (0.51–0.80), and "large" (>0.80).

115

116   *Methodological quality*

117   The 11-point PEDro scale was used to assess the methodological quality of the included

118   studies [16]. In line with the recommendations, item 1 on the PEDro scale was not included in

119   the total score as it concerns external validity. Besides external validity, items on the checklist

120   refer to randomization, concealed allocation, blinding, attrition, and data reporting. Each item

121   is scored with a 1 (criterion satisfied) or with a 0 (criterion not satisfied or unclear). The

122   maximal score on the PEDro checklist was 10. We classified studies as "excellent" quality (9–

123   10 points), "good" quality (6–8 points), "fair" quality (4–5 points), or "poor" methodological

124   quality (≤3 points) [17]. Two authors (JG and PM) independently performed the

125   methodological quality assessment; any observed differences in the initial scoring were

126   resolved via discussion.

127

128   **Results**

129   *Study selection*

130   In the primary search, there was a total of 1621 potentially relevant references. Of the 1621

131   screened references, 1593 were excluded based on title or abstract; 28 full-text papers were

132   read, and 14 studies were included in the review. Secondary searches resulted in another 1684

133   search results, and with the inclusion of three additional studies (Figure 1). Therefore, the

134   final number of included studies was 17 [9-13, 18-29]. Fourteen studies were published in

135   peer-reviewed journals; two were theses [20, 25], and one was a dissertation [21].

136

137   *Aerobic endurance*

138 Eleven studies explored the influence of *CYP1A2* −163C>A polymorphism on the responses

139 to caffeine ingestion during aerobic exercise (Table 2). Of these studies, eight combined the

140 AC and CC genotype in one group and compared it to the AA genotype groups; two studies

141 compared the effects across all three genotypes (Table 1). Additionally, in one study, only a

142 main effect of caffeine was explored in a sample consisting exclusively of 14 participants

143 with the AC genotype [25]. Sample sizes in individual studies ranged from 11 to 101

144 participants (pooled number of participants: 396). All studies included either a mixed-sex

145 sample or included only men. A significant main effect of caffeine was observed in all

146 studies, except in the study by Algrain et al. [9], where there were no significant differences

147 between caffeine and placebo. A significant caffeine × genotype interaction was found in two

148 studies [12, 26]. In one, a greater ergogenic effect was found in the AA genotype as compared

149 to AC/CC genotype [26]. In another, an ergogenic effect was found in the AA genotype with

150 both used caffeine doses (2 and 4 mg/kg); no increases in performance in the AC genotype

151 occurred with any of the used caffeine doses, and decreases in performance in the CC

152 genotype with the consumption of 4 mg/kg of caffeine, but not 2 mg/kg of caffeine [12].

153 Across the individual studies, effect sizes of caffeine on performance for the AA genotype

154 ranged from 0.16 to 0.67 (Table 2). For the AC/CC genotype, effect sizes ranged from 0.07 to

155 0.36. In the two studies that presented data for the CC genotype, the effect size amounted to –

156 1.35 (favoring of placebo) in one study [12], and 0.12 (favoring of caffeine) in another [29].

157

158 ***High-intensity exercise***

159 Eight studies explored the influence of *CYP1A2* −163C>A polymorphism on the responses to

160 caffeine ingestion during high-intensity exercise (Table 2). The performance tests in these

161 studies included muscle endurance tasks in resistance exercise, isometric handgrip strength

162 tests, jumping (countermovement jump, spike jump, and squat jump), sprinting (Wingate test,

163   sprint velocity test), agility tests, and sport-specific (tennis and handball) skill tests. Of these

164   studies, six conducted a comparison of effects between the AA and AC/CC genotype, one

165   compared the effects across all three genotypes, and in one study [25], only a main effect of

166   caffeine was explored in a sample of participants with the AC genotype (Table 1). Across the

167   studies, sample sizes ranged from 14 to 100 participants (pooled number of participants: 253).

168   Four studies included a mixed-sex sample, and four included only men (Table 1). Significant

169   main effects of caffeine were observed in all studies, but not necessarily across all exercise

170   tasks, as some studies [22, 28, 29] did not find significant differences between caffeine and

171   placebo for agility tests, isometric handgrip strength, or ball velocity throw tests. A significant

172   caffeine × genotype interaction was found in two studies [23, 28]. In one study, resistance

173   exercise performance was enhanced following caffeine ingestion in the AA genotype, while

174   no ergogenic effects were observed in the AC/CC genotype [23]. In another study, a

175   significant caffeine × genotype interaction was found in one out of eight performance tests

176   (ball throw from 7-m), with ergogenic effects observed for the AA, but not AC/CC genotype

177   [28]. Effect sizes of caffeine on performance for the AA genotype ranged from 0.0 to 1.87

178   (Table 2). For the AC/CC genotype, effect sizes ranged from –0.23 to 1.27. In the only study

179   that presented data separately for the CC genotype, the effect sizes ranged from –0.37 to 0.36.

180

181   *Methodological quality*

182   The average score on the PEDro checklist was 8.6 points (range: 7 to 9 points). Thirteen

183   studies were classified as "excellent" methodological quality, and four as "good"

184   methodological quality. Individual scores are presented in Table 3.

185

186   **Discussion**

187 Based on the results presented in the current literature, it generally seems that individuals with

188 the *CYP1A2* AA or AC/CC genotype may experience an increase in performance following

189 caffeine ingestion. Four included studies found significant differences between AA and AC or

190 CC genotype, and in all of these studies, the effects of caffeine favored the AA genotype.

191 These results suggest that if there is a true genotype effect in the population, it might be in

192 that direction. Still, several important factors that might be responsible for the discrepancies in

193 findings and the practical relevance of the results need to be considered when interpreting

194 these findings.

195

196 *Aerobic endurance*

197 Of the studies that examined the effects of caffeine on measures of aerobic endurance, only

198 two reported significant caffeine × genotype interaction, whereby individuals with the AA

199 genotype experienced greater improvements in exercise performance than the participants

200 with the AC/CC genotype [12, 26]. These studies used either 10-km or 40-km cycling time

201 trials. Some studies that reported no significant caffeine × genotype interaction used shorter

202 duration time trials (e.g., 3-km in two studies; [11, 13]). In the study by Pataky et al. [13], the

203 increases in performance even favored the AC genotype, even though the difference was not

204 statistically significant ($p = 0.12$). Therefore, significant between-genotype differences in

205 response to caffeine supplementation may be only present in longer duration aerobic events.

206 This hypothesis seems plausible, given that the effects of caffeine may increase with the

207 increase in the duration of the aerobic task [30]. However, one study explored the effects of

208 caffeine using Olympic-distance triathlons as the exercise task and did not find caffeine ×

209 genotype interaction (even though a main effect of caffeine was observed), suggesting that the

210 duration of the task might not be of such large importance [21].

211

212    In the two studies that reported significant differences between the genotypes, the samples

213    consisted exclusively of men [12, 26]. All studies that included a mixed-sex sample did not

214    report significant differences in response to caffeine ingestion between genotypes (Table 2).

215    As men and women seem to experience a similar response to caffeine ingestion during

216    aerobic exercise, it does not seem that the inclusion of a mixed-sex sample should be

217    considered as a limitation of these studies [31, 32]. Albeit speculative, it is conceivable that

218    genotype differences impact the individual variation in response to caffeine ingestion in men,

219    but not in women. In support of this hypothesis, there is evidence that CYP1A2 activity is

220    lower in women than men, which might explain these inconsistent findings [33]. Instead of

221    excluding females, future research should consider including both males and females and plot

222    the data separately to see if there indeed is a difference between sexes.

223

224    One potentially confounding issue is that studies generally did not report if the participants

225    were current smokers. This might be important given that smoking may affect CYP1A2

226    activity. A recent meta-analysis reported that only smokers demonstrated differences in

227    CYP1A2 activity between the AA vs. CC and AC vs. CC genotype [34]. In a subgroup of

228    studies that included non-smokers, no differences were found in CYP1A2 activity between

229    genotypes. In non-smokers, only in heavy coffee consumers (more than 3 cups per day), the

230    AA genotype had higher CYP1A2 activity than in C allele carriers [35]. In the two studies

231    that specifically noted that the participants were non-smokers, the authors did not find

232    significant caffeine × genotype interaction [9, 20]. Future studies on the topic should specify

233    the information on the smoking status of the participants to allow for a more informed

234    comparison of results between the studies. Other factors, such as vegetable intake [36], phase

235    of the menstrual cycle [37], and oral contraceptive use [38], may also affect caffeine

236    metabolism, and they should be considered in future studies. While potentially relevant, some

237 of these factors may not impact caffeine's ergogenic effects, as recent studies observed

238 similar improvements in exercise performance following caffeine ingestion in the early

239 follicular, pre-ovulatory, and mid-luteal phases of the menstrual cycle [39, 40].

240

241 Future research is needed to explore the influence of caffeine ingestion timing, as some have

242 hypothesized that different effects may be observed when using longer waiting times from

243 caffeine ingestion to the start of the exercise session [41]. Specifically, given that C allele

244 carriers are considered slow caffeine metabolizers, they might need to ingest caffeine 90 or

245 120 minutes before exercise to experience ergogenic effects [41]. There might be some

246 credence to this hypothesis if we consider the finding by McGrath [20]. In this study, the main

247 performance task consisted of a 30-minute cycling time trial performed 175 minutes

248 following caffeine ingestion. The participants ingested caffeine 60-minutes before performing

249 115-minutes of steady-state cycling. Only after steady-state cycling, the participants

250 performed the main performance trial. A main effect of caffeine was observed, but no caffeine

251 $\times$ genotype interaction, suggesting that similar responses to caffeine supplementation between

252 genotypes occurred, possibly because of the timing of caffeine supplementation. A limitation

253 of the study is that the participants first performed steady-state cycling. This aspect of the

254 study design is important to mention given that exercise may impact CYP1A2 activity [42].

255 Furthermore, the study by McGrath [20] had a small sample of 11 participants, and this

256 limitation should be considered when interpreting these findings.

257

258 Overall, there is some evidence that *CYP1A2* −163C>A polymorphism may impact the

259 ergogenic effects of caffeine on aerobic endurance. While individuals that possess the AC/CC

260 genotype still may experience improvements in performance, there is some evidence

261 indicating that AA homozygotes obtain a higher ergogenic effect from acute caffeine intake

262    than C allele carriers. However, to date, such findings are observed only in: (a) male

263    participants; (b) cycling time trials that included a ≥10 km distance; and (c) protocols that

264    included caffeine ingestion 60 minutes before exercise.

265

266    *High-intensity exercise*

267    Of the eight studies that used high-intensity exercise tasks, two reported a significant caffeine

268    × genotype interaction [23, 28]. In one study [28] conducted among 31 professional handball

269    players, significant genotype differences were observed in ball throw velocity from 7-m. This

270    study found improvements in individuals with the AA genotype following caffeine ingestion,

271    whereas participants with the AC/CC genotype did not benefit from caffeine ingestion on this

272    specific test. However, these results were inconclusive given that no significant genotype

273    differences were observed for other similar outcomes, such as ball throw velocity from 9-m,

274    and ball throw velocity from 7 and 9-m with a goalkeeper. In another study, individuals who

275    possessed the AA genotype experienced improvements in resistance exercise performance

276    following the ingestion of 6 mg/kg of caffeine [23]. Exercise performance did not improve

277    following caffeine ingestion in those with the AC/CC genotype. It should be noted, however,

278    that the difference in exercise performance was small. Specifically, following caffeine

279    ingestion, the AA genotype group completed an average of one repetition more (range: 0.3 to

280    1.1 repetitions) in a set with 85% of one-repetition maximum (1RM) performed to momentary

281    muscular failure. In the AC/CC group, the number of performed repetitions was the same

282    following placebo and caffeine ingestion. A subsequent study performed by Grgic et al. [18]

283    did not find a caffeine × genotype interaction using the same exercise task as Rahimi [23],

284    only a lower dose of caffeine (i.e., 3 mg/kg).

285

286 Besides assessing the number of repetitions, Grgic et al. [18] also assessed the velocity and

287 power output of each repetition. For the analysis, these authors also matched the number of

288 performed repetitions between caffeine and placebo conditions and observed that caffeine

289 ingestion substantially affected the "quality" of performed repetitions in both genotypes. In

290 the Rahimi [23] study, the only assessed outcome was the quantity of performed repetitions,

291 but not its overall quality. From a practical perspective, the quality of repetitions may be of

292 greater relevance. As shown by studies that used velocity-based training, training at a lower

293 velocity loss often produces similar or superior training adaptations as training at a higher

294 velocity loss, despite the higher number of repetitions performed when training at a higher

295 velocity loss [43, 44]. Future studies should assess both the quantity and quality of performed

296 repetition to reconcile these equivocal findings.

297

298 Besides resistance exercise, studies also utilized other high-intensity tasks, such as jumping

299 and Wingate test performance [18, 22, 24]. None of these studies found a significant caffeine

300 × genotype interaction in the analyzed outcomes, even though most reported a significant

301 main effect of caffeine. In line with these observations, the study by Southward [25]—that

302 included only 14 participants with the AC genotype—also reported improvements in

303 resistance exercise and jumping performance following caffeine ingestion. The effect size in

304 this study was similar to the effects of caffeine previously reported among samples with the

305 AA genotype and among those that were not genotype-specific [18, 22, 45, 46].

306

307 A limitation of the majority of studies conducted on the topic is pooling the AC and CC

308 genotype into a single group, which is relevant as the response may not be uniform across

309 these two genotypes [12]. Out of the studies that utilized high-intensity exercise tasks, only

310 one large sample size (*n* = 100) study examined the effects across all three genotypes [29].

311 This study did not find significant genotype differences, even though caffeine ingestion

312 enhanced muscular endurance (but not isometric strength, agility, and jump height). Still, this

313 study is also unique by the inclusion of adolescents as study participants, given that all other

314 studies included young adults. Overall, based on the current body of evidence, *CYP1A2*

315 genotype variations might impact the ergogenic effect of caffeine supplementation on high-

316 intensity exercise performance. However, the differences between genotypes were either

317 small or inconsistent, highlighting the need for future research.

318

319 *Methodological considerations*

320 Some of the discrepancies in findings between studies might also be related to the source and

321 dose of caffeine. Guest et al. [12] demonstrated ergolytic effects of caffeine in the CC

322 genotype with the consumption of 4 mg/kg of caffeine, but not 2 mg/kg of caffeine. Two

323 additional studies [23, 26] that observed genotype differences also used a higher dose of

324 caffeine (i.e., 6 mg/kg). These results suggest that the dose might influence *CYP1A2* genotype

325 responses to acute caffeine ingestion. Still, it should be noted that other studies [13, 29] also

326 used higher doses of caffeine and did not find genotype differences, suggesting that dose

327 alone is not likely the sole explanation for the differences in findings.

328

329 There is growing evidence that consuming alternate sources of caffeine such as chewing gums

330 and caffeine gels may enhance exercise performance [47]. One included study [9] used

331 chewing gums and did not observe general ergogenic effects of caffeine. The lack of an

332 ergogenic might be because an absolute dose of 255 mg was used, which might have created

333 differences in responses due to variation in body mass among participants. In contrast,

334 caffeine's ergogenic effect is most commonly observed when providing relative doses ranging

335 from 3 to 6 mg/kg [48]. To avoid confounding factors such as the absence of an ergogenic

336 effect (due to administration of absolute caffeine doses), future studies that aim to explore the

337 influence of genotype on the response to caffeine ingestion should strive to employ optimal

338 protocols of caffeine supplementation that include providing dose relative to body mass.

339

340 Factors such as participants' training status and their habitual caffeine intake should also be

341 considered when interpreting the evidence [49-51]. In all four studies [12, 23, 26, 28] that

342 reported significant between-genotype differences, the participants were either athletes or

343 resistance-trained individuals. This might suggest that caffeine's effects, according to the

344 *CYP1A2* genotype, might be related to training status. However, other studies [18, 29] also

345 included trained individuals but did not observe genotype differences, highlighting the

346 equivocal nature of the evidence. Future studies on the topic may consider including trained

347 and untrained individuals to establish a relationship between caffeine's ergogenic effects,

348 training status, and *CYP1A2* genotype. Most studies included participants that were "low"

349 habitual caffeine intake users (Table 2). Therefore, from this standpoint, the included studies

350 were reasonably uniform. Still, some studies [26, 27] included "low", "moderate", and "high"

351 habitual users as study participants, which might be a limitation as there is evidence indicating

352 that habitual caffeine intake may influence the ergogenic effects of acute caffeine ingestion

353 [50, 51]. Therefore, when conducting studies on this topic, it would be important to include a

354 sample with different *CYP1A2* genotypes but with homogeneous habitual caffeine intake.

355

356 Another important methodological aspect of the included studies is their sample size. Studies

357 that found significant genotype differences included sample sizes ranging from 30 to 101

358 participants. In contrast, most studies that did not find significant genotype differences

359 involved smaller sample sizes, with one study conducted among a cohort of 11 participants

360   [20]. Because of the small sample size, some of the included studies might have been

361   statistically underpowered to detect significant differences. While this might be the case, it

362   should also be considered that the study by Spineli et al. [29] included 100 participants and

363   did not find significant genotype differences, suggesting that the differences in sample sizes

364   alone cannot be the explanation for the divergent findings.

365

366   *Methodological quality of the included studies*

367   We included studies published in peer-reviewed journals as well as theses and dissertations in

368   this systematic review. This may be considered as a limitation given that studies published in

369   journals might be of higher methodological quality, as the peer-review process is considered

370   to present a form of quality control. Based on the PEDro checklist, however, all included

371   studies were of good or excellent methodological quality, regardless of their publication

372   status. Therefore, we believe that the inclusion of unpublished documents could be considered

373   as a strength of the review due to "publication bias," which dictates that studies reporting

374   larger and statistically significant effect sizes tend to be more often published than studies

375   reporting non-statistically significant data [52]. Therefore, basing the conclusions of a review

376   only on the published literature may introduce a source of bias. Indeed, of the three

377   unpublished documents included in the review, two did not report significant caffeine $\times$

378   genotype interaction, while one study was limited by the inclusion of only AC genotype in the

379   review (i.e., no between-genotype comparison could be performed) [20, 21, 25].

380

381   *Practical application*

382   Based on the current body of research, it is questionable if the knowledge of the *CYP1A2*

383   genotype represents a worthwhile means of informing caffeine-use strategies in sport. An

384    individual's response to caffeine, and optimal caffeine-use strategy to increase performance,

385    is likely complex, with aspects such as habitual caffeine use, method of caffeine intake, and

386    situational feelings of stress and anxiety potentially influencing the response to a given dose

387    of caffeine [7]. While there might be a genetic influence on the performance response to

388    caffeine in sport, *CYP1A2* represents only one such gene that has been demonstrated to

389    potentially play a role, with others, such as *ADORA2A* tentatively identified [27, 28, 53, 54].

390    Future research, on a wider panel of genetic variants, should help to provide greater clarity

391    here. For now, we suggest that athletes, coaches and support staff should take an evidence-

392    guided, experiential approach to caffeine, using current research-based guidelines as a starting

393    point, and then utilizing self-experimentation to settle on a caffeine dose optimized for their

394    unique make-up and circumstances. Finally, while the popularity of genetic testing in sport

395    has increased in recent years [14], for those interested in caffeine supplementation, it currently

396    seems that individual *CYP1A2* genotype identification might not provide a definitive answer

397    to the individual response to acute caffeine intake.

398

399    **Conclusion**

400    Based on the results of the studies included in the review, it seems that individuals with the

401    *CYP1A2* AA or AC/CC genotype may experience an increase in performance following

402    caffeine ingestion. Even though significant differences between genotypes were found only in

403    four studies, all four reported a more favorable response in the AA genotype. These results

404    suggest that if there is an actual genotype-related effect of acute caffeine supplementation in

405    the population, it is likely in that direction. In the studies that reported such data for aerobic

406    endurance, the findings are specific to male participants performing cycling time trials

407    (distances of ≥10 km) and ingesting caffeine 60 minutes before exercise. For high-intensity

408    exercise, two studies reported that genotype variations determined the response to caffeine

409    ingestion, even though the differences were either small (~1 additional repetition in high-load

410    resistance exercise set performed to failure) or inconsistent (i.e., observed only in one out of

411    eight performance tests). In summary, *CYP1A2* genotype variations may modulate caffeine's

412    ergogenic effects, but the differences between genotypes were small, inconsistent, or limited

413    to specific exercise scenarios.

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578  **Table 1.** Characteristics of the participants included in the studies

| Study | Study sample | Habitual caffeine intake | Genotype distribution |
|---|---|---|---|
| Algrain et al. (2015) | Recreationally active men and women ($n = 20$) | <300mg/day | AA genotype, $n = 11$ (age: $24 \pm 2$ years; mass: $76 \pm 5$ kg) |
| | | | AC/CC genotype, $n = 9$ (age: $26 \pm 1$ years; mass: $77 \pm 6$ kg) |
| Carswell et al. (2020) | Healthy active men and women ($n = 18$) | 13 participants were "low" users (0–150 mg/day), 2 participants were "moderate" users (151–300 mg/day), and 3 participants were "high" users (>300 mg/day) | AA genotype, $n = 10$ (age: $23 \pm 3$ years; mass: $68 \pm 11$ kg) |
| | | | AC/CC genotype, $n = 8$ (age: $25 \pm 5$ years; mass: $74 \pm 8$ kg) |
| Davenport et al. (2020) | Well-trained male and female cyclists ($n = 13$) | ≥50 mg/day | AA genotype, $n = 7$ (age: $28 \pm 2$ years; mass: $71 \pm 2$ kg) |
| | | | AC genotype, $n = 6$ (age: $28 \pm 2$ years; mass: $71 \pm 2$ kg) |
| Giersch et al. (2018) | Recreationally-trained male cyclists ($n = 20$) | $93 \pm 111$ mg/day (AA genotype); $92 \pm 137$ mg/day (AC/CC genotype) | AA genotype, $n = 8$ (age: $24 \pm 8$ years; mass: $72 \pm 9$ kg) |
| | | | AC/CC genotype, $n = 12$ (age: $25 \pm 7$ years; mass: $75 \pm 12$ kg) |
| Grgic et al. (2020) | Resistance-trained men ($n = 22$) | $133 \pm 123$ mg/day (AA genotype), $117 \pm 68$ mg/day (AC/CC genotype) | AA genotype, $n = 13$ (age: $27 \pm 6$ years; mass: $78 \pm 7$ kg) |
| | | | AC/CC genotype, $n = 9$ (age: $30 \pm 4$ years; mass: $81 \pm 15$ kg) |
| Guest et al. (2018) | Male athletes from endurance, power, or mixed-sports ($n = 101$) | *For sport* $61 \pm 13$ mg/day (AA genotype), $89 \pm 17$ mg/day (AC genotype), $80 \pm 74$ mg/day (CC genotype) *Dietary* $87 \pm 18$ mg/day (AA genotype), $80 \pm 20$ mg/day (AC genotype), $38 \pm 24$ mg/day (CC genotype) | AA genotype, $n = 49$ (age: $24 \pm 4$ years; mass: $80 \pm 12$ kg) |
| | | | AC genotype, $n = 44$ (age: $25 \pm 5$ years; mass: $80 \pm 10$ kg) |
| | | | CC genotype, $n = 8$ (age: $25 \pm 5$ years; mass: $93 \pm 25$ kg) |
| Klein et al. (2012) | Collegiate male and female tennis players ($n = 16$) | $104 \pm 34$ mg/day (AA genotype), $92 \pm 64$ mg/day (AC/CC genotype) | AA genotype, $n = 7$ (age: $21 \pm 2$ years; mass: $71 \pm 13$ kg) |
| | | | AC/CC genotype, $n = 9$ (age: $21 \pm 2$ years; mass: $71 \pm 13$ kg) |
| McGrath (2015) | Well trained male endurance athletes ($n = 11$) | 27% "low" users, 45% "moderate" users, and 27% "high" habitual caffeine users | AA genotype, $n = 6$ (age: $31 \pm 3$ years; mass: $77 \pm 4$ kg) |
| | | | AC/CC genotype, $n = 5$ (age: $31 \pm 3$ years; mass: $77 \pm 4$ kg) |

| | | | |
|---|---|---|---|
| Muñoz et al. (2020) | Professional male and female handball players (*n* = 31) | 60 ± 25 mg/day | AA genotype, *n* = 14 (age: 24 ± 3 years; mass: 79 ± 16 kg) |
| | | | AC/CC genotype, *n* = 17 (age: 24 ± 3 years; mass: 79 ± 16 kg) |
| Pataky et al. (2016) | Recreationally-trained male and female cyclists (*n* = 38) | Average of 70 mg/day | AA genotype, *n* = 21 (age: 20 ± 1 years; mass: 68 ± 13 kg) |
| | | | AC genotype, *n* = 17 (age: 21 ± 1 years; mass: 74 ± 8 kg) |
| Potgieter (2013) | Male and female triathletes (*n* = 26) | 413 ± 505 mg/day | AA genotype, *n* = 16 (age: 38 ± 11 years; mass: 69 ± 11 kg) |
| | | | AC/CC genotype, *n* = 10 (age: 38 ± 11 years; mass: 69 ± 11 kg) |
| Puente et al. (2018) | Male and female elite basketball players (*n* = 19) | <100 mg per day | AA genotype, *n* = 10 (age: 27 ± 4 years; mass: 84 ± 19 kg) |
| | | | AC/CC genotype, *n* = 9 (age: 29 ± 6 years; mass: 78 ± 15 kg) |
| Rahimi (2018) | Resistance-trained men (*n* = 30) | "Light caffeine consumers" (<70 mg/day) | AA genotype, *n* = 14 (age: 21 ± 2 years; mass: 79 ± 19 kg) |
| | | | AC/CC genotype, *n* = 16 (age: 22 ± 5 years; mass: 77 ± 11 kg) |
| Salinero et al. (2017) | Recreationally active men and women (*n* = 21) | <60 mg per day | AA genotype, *n* = 5 (age: 29 ± 7 years; mass: 69 ± 10 kg) |
| | | | AC/CC genotype, *n* = 16 (age: 29 ± 7 years; mass: 69 ± 10 kg) |
| Southward (2016) | Recreationally trained male athletes (*n* = 14) | "All participants were regular users of caffeine" | AC genotype, *n* = 14 (age: 27 ± 8 years; mass: 77 ± 9 kg) |
| Spineli et al. (2020) | Male adolescents engaged in competitive sports (*n* = 100) | 42 ± 39 mg/day (AA genotype), 59 ± 45 mg/day (AC genotype), 33 mg/day (CC genotype) | AA genotype, *n* = 49 (age: 15 ± 2 years; mass: 58 ± 10 kg) |
| | | | AC genotype, *n* = 42 (age: 16 ± 2 years; mass: 58 ± 13 kg) |
| | | | CC genotype, *n* = 9 (age: 16 years; mass: 68 kg)[a] |
| Womack et al. (2012) | Male competitive cyclists (*n* = 35) | 86 ± 107 mg/day (AA genotype), 87 ± 145 mg/day (AC/CC genotype) | AA genotype, *n* = 16 (age: 24 ± 7 years; mass: 74 ± 13 kg) |
| | | | AC/CC genotype, *n* = 19 (age: 26 ± 8 years; mass: 74 ± 12 kg) |
| All studies were randomized double-blinded; [a] no standard deviation reported | | | |

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586 **Table 2.** Summary of the caffeine intake protocols, exercise task(s), and main findings from
587 the studies included in the review

| Study | Caffeine supplementation protocol | Exercise task(s) | Main findings | Effect sizes |
|-------|-----------------------------------|------------------|---------------|--------------|
| Algrain et al. (2015) | 255 mg of caffeine consumed in a chewing gum 15-minutes before starting the exercise session | 15-min of cycling at 75% $VO_{2max}$, 10 min of rest, and 15-min cycling time trial | No main effect of caffeine, and no caffeine × genotype interaction | AA genotype: 0.16 AC/CC genotype: 0.29 |
| Carswell et al. (2020) | 3 mg/kg of caffeine consumed in capsules 70-minutes before starting the exercise session | 15-min cycling time trial | A main effect of caffeine, but no caffeine × genotype interaction | Data not presented |
| Davenport et al. (2020) | 200 mg of caffeine consumed in a drink either 35-minutes before exercise, before 30-minutes of steady-state cycling, or immediately before a 15-minute cycling time trial [a] | 30 min of steady-state cycling followed by and a 15-minute cycling time trial | A main effect of caffeine when caffeine was ingested 35-minutes before the start of the exercise session, but no caffeine × genotype interaction | *35-minutes before exercise* Whole sample: 0.35 *Before 30-minutes of steady-state cycling* Whole sample: 0.17 *Before a 15-minute cycling time trial* Whole sample: 0.06 |
| Giersch et al. (2018) | 6 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | 3-km cycling time trial | A main effect of caffeine, but no caffeine × genotype interaction | AA genotype: 0.37 AC/CC genotype: 0.25 |
| Grgic et al. (2020) | 3 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | Movement velocity and power in the bench press with different loads, one set of bench press with 85% 1RM performed to muscle failure, CMJ, and 30-second Wingate | A main effect of caffeine in all exercise tests, but no caffeine × genotype interaction | *Movement velocity and power in the bench press* AA genotype: 0.14–0.69 AC/CC genotype: 0.23–0.85 *Muscle endurance and velocity* AA genotype: 0.23–0.66 AC/CC genotype: 0.33–1.27 *CMJ* AA genotype: 0.19 AC/CC genotype: 0.15 *Power output in the Wingate* AA genotype: 0.31–0.57 AC/CC genotype: 0.34–0.43 |

| Guest et al. (2018) | 2 or 4 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | 10-km cycling time trial | A main effect of caffeine and caffeine × genotype interaction, whereby participants with the AA genotype improved performance following caffeine ingestion (both 2 and 4 mg/kg), those with the AC genotype did not improve performance with any of the caffeine doses, and performance of those with the CC genotype was worse with the ingestion of 4 kg/mg but not 2 mg/kg of caffeine | *2 mg/kg* AA genotype: 0.33 AC genotype: 0.07 CC genotype: (data not presented) *4 mg/kg* AA genotype: 0.49 AC genotype: 0.20 CC genotype: –1.35 |
|---|---|---|---|---|
| Klein et al. (2012) | 6 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | 45-minutes of intermittent treadmill exercise followed by a tennis skill test | A main effect of caffeine, but no caffeine × genotype interaction | AA genotype: 0.48 AC/CC genotype: 0.62 |
| McGrath (2015) | 5 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | 115-minutes of steady-state cycling followed by a 30-minute time trial | A main effect of caffeine, but no caffeine × genotype interaction | Whole sample: 0.59 |
| Muñoz et al. (2020) | 3 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | CMJ, sprint velocity test, modified agility t-test, isometric handgrip strength, ball throw from 7-m, ball throw from 7-m with a goalkeeper, ball throw from 9-m, and ball throw from 9-m with a goalkeeper | A main effect of caffeine for CMJ height, time in the sprint velocity test, and ball throw velocity from 9-m, but no caffeine × genotype interaction. No main effect of caffeine for time to complete the modified agility t-test, isometric handgrip strength, | *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 |

| | | | | |
|---|---|---|---|---|
| | | | <span style="color:red">ball throw velocity from 7-m with a goalkeeper, ball throw velocity from 9-m with a goalkeeper, and no caffeine × genotype interaction. No main effect of caffeine for ball throw velocity from 7-m, but a caffeine × genotype interaction whereby participants with the AA genotype improved performance following caffeine ingestion while those with the AC/CC genotype did not</span> | <span style="color:red">AC/CC genotype: –0.02<br>*Ball throw from 7-m with a goalkeeper*<br>AA genotype: 0.39<br>AC/CC genotype: –0.23<br>*Ball throw from 9-m*<br>AA genotype: 0.40<br>AC/CC genotype: 0.22<br>*Ball throw from 9-m with a goalkeeper*<br>AA genotype: 0.47<br>AC/CC genotype: 0.05</span> |
| Pataky et al. (2016) | 6 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session, with or without additional caffeine mouth rinsing | 3-km cycling time trial | A main effect of caffeine when caffeine ingestion was combined with mouth rinsing; using MBI, the effects favored the AC genotype, but the effect was not statistically significant ($p = 0.12$) | Data not presented |
| Potgieter (2013) | 6 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | Olympic-distance triathlons | A main effect of caffeine, but no caffeine × genotype interaction | Whole sample: 0.10 |
| Puente et al. (2018) | 3 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | Abalakov jump test and the "Change-of-Direction and Acceleration Test" with and without the ball | A main effect of caffeine for Abalakov jump height, but no caffeine × genotype interaction; no main effect of caffeine for sprint time in the "Change-of- | *Abalakov jump*<br>AA genotype: 0.15<br>AC/CC genotype: 0.14<br>*"Change-of-Direction and Acceleration Test" without the ball*<br>AA genotype: 0.12<br>AC/CC genotype: –0.06 |

| | | | Direction and Acceleration Test" with or without the ball and no caffeine × genotype interaction | *"Change-of-Direction and Acceleration Test" with the ball* AA genotype: 0.44 AC/CC genotype: 0.0 |
|---|---|---|---|---|
| Rahimi (2018) | 6 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | 3 sets performed to muscle failure with 85% 1RM in the bench press, leg press, seated row, and shoulder press | A main effect of caffeine and caffeine × genotype interaction in all exercises, whereby participants with the AA genotype improved performance following caffeine ingestion while those with the AC/CC genotype did not | *Bench press* AA genotype: 0.88–1.87 AC/CC genotype: –0.05 to 0.09 *Leg press* AA genotype: 0.48–1.22 AC/CC genotype: –0.12 to 0.44 *Seated row* AA genotype: 0.87–1.30 AC/CC genotype: 0.17–0.27 *Shoulder press* AA genotype: 0.57–1.86 AC/CC genotype: 0.12–0.48 |
| Salinero et al. (2017) | 3 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | 30-second Wingate | A main effect of caffeine for peak and mean power, but no caffeine × genotype interaction | *Peak power* AA genotype: 0.04 AC/CC genotype: 0.15 *Mean power* AA genotype: 0.07 AC/CC genotype: 0.10 |
| Southward (2016) | 6 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | 10-km running time trial, isokinetic knee extension, SJ and CMJ | A main effect of caffeine for eccentric knee extensor torque and SJ height; no significant difference for the 10-km time trial, concentric knee extensor torque and CMJ height | *10-km running time trial* AC genotype: 0.34 *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 |
| Spineli et al. (2020) | 6 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | CMJ, spike jump, agility test, isometric handgrip strength, push-up, sit-up, and Yo-Yo IR1 | A main effect of caffeine for push-up and sit-up repetitions and distance covered in the Yo-Yo IR1, but no caffeine × genotype interaction. No main effect and no | *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 |

| Study | Caffeine dose | Exercise test | Results | Effect sizes |
|---|---|---|---|---|
| | | | caffeine × genotype interaction for CMJ height, spike jump height, and time in the agility test | AC genotype: 0.07<br>CC genotype: −0.37<br>*Isometric handgrip strength*<br>AA genotype: 0.17<br>AC genotype: 0.07<br>CC genotype: 0.06<br>*Push-up*<br>AA genotype: 0.09<br>AC genotype: 0.24<br>CC genotype: 0.36<br>*Sit-up*<br>AA genotype: 0.24<br>AC genotype: 0.32<br>CC genotype: 0.28<br>*Yo-Yo IR1*<br>AA genotype: 0.31<br>AC genotype: 0.36<br>CC genotype: 0.12 |
| Womack et al. (2012) | 6 mg/kg of caffeine consumed in capsules 60-minutes before starting the exercise session | 40-km cycling time trial | A main effect of caffeine and caffeine × genotype interaction, whereby caffeine ingestion improved performance by a greater magnitude in the AA genotype in comparison with the AC/CC genotype | AA genotype: 0.67<br>AC/CC genotype: 0.34 |

SJ: squat jump; CMJ: countermovement jump; 1RM: one-repetition maximum; MBI: magnitude-based inferences; IR1: intermittent recovery test level 1; VO$_{2max}$: maximum rate of oxygen consumption; [a] the drink contained other substances such as beta-alanine and quercetin, which are not considered ergogenic when ingested acutely;

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597 **Table 3.** Results of the methodological quality assessment using the Physiotherapy Evidence-
598 Based Database (PEDro) scale.

| Reference | 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. (2015) | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Carswell et al. (2020) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Davenport et al. (2020) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Giersch et al. (2018) | No | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Grgic et al. (2020a) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Guest et al. (2018) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Klein et al. (2012) | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 7 |
| McGrath (2015) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 8 |
| Muñoz et al. (2020) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Pataky et al. (2016) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Potgieter (2013) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 7 |
| Puente et al. (2018) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Rahimi (2018) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Salinero et al. (2017) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Southward (2016) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Spineli et al. (2020) | No | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Womack et al. (2012) | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Yes: criterion is satisfied; No: criterion is not satisfied; Unclear: unable to rate | | | | | | | | | | | | |

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603    **Figure 1.** Flow diagram of the search process

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Identification

Screening

Eligibility

Included

Records identified through database searching
($n = 1621$)

Records screened
($n = 1621$)

Excluded based on title or abstract
($n = 1593$)

Full-text articles assessed for eligibility ($n = 28$)

Full-text articles excluded ($n = 14$), with the following reasons:

- Conference abstract ($n = 6$)
- Duplicate data ($n = 3$)
- No exercise tasks ($n = 3$)
- Unsuitable outcome ($n = 2$)

Studies included in the review from the primary search
($n = 14$)

Secondary searches
($n = 1684$)

Studies included in the review
($n = 17$)

Studies additionally included from the secondary searches
($n = 3$)