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Title	CYP1A2 genotype and acute ergogenic effects of caffeine intake on exercise performance: a systematic review
Type	Article
URL	https://clock.uclan.ac.uk/35554/
DOI	https://doi.org/10.1007/s00394-020-02427-6
Date	2020
Citation	Grgic, Jozo, Pickering, Craig, Del Coso, Juan, Schoenfeld, Brad J and Mikulic, Pavle (2020) CYP1A2 genotype and acute ergogenic effects of caffeine intake on exercise performance: a systematic review. <i>European Journal of Nutrition</i> . ISSN 1436-6207
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<https://doi.org/10.1007/s00394-020-02427-6>

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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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19

- 20 ***CYP1A2* genotype and acute ergogenic effects of caffeine intake on exercise**
- 21 **performance: a systematic review**

22 **Abstract**

23 **Purpose:** To systematically review studies that examined the influence of the *CYP1A2*
24 $-163C>A$ polymorphism on the ergogenic effects of caffeine and to discuss some of the
25 reasons for the discrepancies in findings between the studies.

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

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

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

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

45 **Introduction**

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

55
56 The gene *CYP1A2* encodes cytochrome P450 1A2, an enzyme responsible for ~95% of
57 caffeine metabolism [5]. An A to C substitution at position 163 (-163C>A; rs762551) in the
58 *CYP1A2* gene impacts the speed of caffeine metabolism [6]. Individuals who possess the AA
59 genotype are considered “fast metabolizers” of caffeine, given that this genotype codes for the
60 highly inducible form of the CYP1A2 enzyme [5-8]. Individuals with AC or CC genotype
61 (i.e., C allele carriers) tend to have slower caffeine metabolism and are considered as “slow
62 metabolizers” of caffeine [5-8].

63
64 Several studies explored the effects of caffeine supplementation on exercise performance
65 while considering *CYP1A2* -163C>A polymorphism [9-13]. The results of these studies,
66 however, are equivocal. Some studies found genotype differences in caffeine’s ergogenic
67 effects, as individuals possessing the AA genotype experienced improvements in performance
68 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 \times 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" (≤ 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 \times 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 \times 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 \times 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 \times 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 \times 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 \times
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 \times 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 \times 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 \times 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 ×
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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558 **Acknowledgments:** none.

559 **Conflict of interest:** The authors declare that they have no competing interests. CP is a
560 former employee of DNAFit Ltd., a genetic testing company. He received no financial
561 incentives for the preparation of this manuscript.

562 **Funding:** none.

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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 ± 2 years; mass: 76 ± 5 kg)
			AC/CC genotype, $n = 9$ (age: 26 ± 1 years; mass: 77 ± 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 ± 3 years; mass: 68 ± 11 kg)
			AC/CC genotype, $n = 8$ (age: 25 ± 5 years; mass: 74 ± 8 kg)
Davenport et al. (2020)	Well-trained male and female cyclists ($n = 13$)	≥ 50 mg/day	AA genotype, $n = 7$ (age: 28 ± 2 years; mass: 71 ± 2 kg)
			AC genotype, $n = 6$ (age: 28 ± 2 years; mass: 71 ± 2 kg)
Giersch et al. (2018)	Recreationally-trained male cyclists ($n = 20$)	93 ± 111 mg/day (AA genotype); 92 ± 137 mg/day (AC/CC genotype)	AA genotype, $n = 8$ (age: 24 ± 8 years; mass: 72 ± 9 kg)
			AC/CC genotype, $n = 12$ (age: 25 ± 7 years; mass: 75 ± 12 kg)
Grgic et al. (2020)	Resistance-trained men ($n = 22$)	133 ± 123 mg/day (AA genotype), 117 ± 68 mg/day (AC/CC genotype)	AA genotype, $n = 13$ (age: 27 ± 6 years; mass: 78 ± 7 kg)
			AC/CC genotype, $n = 9$ (age: 30 ± 4 years; mass: 81 ± 15 kg)
Guest et al. (2018)	Male athletes from endurance, power, or mixed-sports ($n = 101$)	<i>For sport</i> 61 ± 13 mg/day (AA genotype), 89 ± 17 mg/day (AC genotype), 80 ± 74 mg/day (CC genotype) <i>Dietary</i> 87 ± 18 mg/day (AA genotype), 80 ± 20 mg/day (AC genotype), 38 ± 24 mg/day (CC genotype)	AA genotype, $n = 49$ (age: 24 ± 4 years; mass: 80 ± 12 kg)
			AC genotype, $n = 44$ (age: 25 ± 5 years; mass: 80 ± 10 kg)
			CC genotype, $n = 8$ (age: 25 ± 5 years; mass: 93 ± 25 kg)
Klein et al. (2012)	Collegiate male and female tennis players ($n = 16$)	104 ± 34 mg/day (AA genotype), 92 ± 64 mg/day (AC/CC genotype)	AA genotype, $n = 7$ (age: 21 ± 2 years; mass: 71 ± 13 kg)
			AC/CC genotype, $n = 9$ (age: 21 ± 2 years; mass: 71 ± 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 ± 3 years; mass: 77 ± 4 kg)
			AC/CC genotype, $n = 5$ (age: 31 ± 3 years; mass: 77 ± 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% $\text{VO}_{2\text{max}}$, 10 min of rest, and 15-min cycling time trial	No main effect of caffeine, and no caffeine \times 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 \times 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 \times genotype interaction	<i>35-minutes before exercise</i> Whole sample: 0.35 <i>Before 30-minutes of steady-state cycling</i> Whole sample: 0.17 <i>Before a 15-minute cycling time trial</i> 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 \times 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 \times genotype interaction	<i>Movement velocity and power in the bench press</i> AA genotype: 0.14–0.69 AC/CC genotype: 0.23–0.85 <i>Muscle endurance and velocity</i> AA genotype: 0.23–0.66 AC/CC genotype: 0.33–1.27 <i>CMJ</i> AA genotype: 0.19 AC/CC genotype: 0.15 <i>Power output in the Wingate</i> 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 \times 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 mg/kg 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 \times 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 \times 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 \times genotype interaction. No main effect of caffeine for time to complete the modified agility t-test, isometric handgrip strength,	<i>CMJ</i> AA genotype: 0.28 AC/CC genotype: 0.15 <i>Sprint velocity test</i> AA genotype: 0.84 AC/CC genotype: 0.15 <i>Modified agility t-test</i> AA genotype: 0.03 AC/CC genotype: -0.05 <i>Isometric handgrip strength</i> AA genotype: 0.00 AC/CC genotype: 0.23 <i>Ball throw from 7-m</i> AA genotype: 0.34

			<p>ball throw velocity from 7-m with a goalkeeper, ball throw velocity from 9-m with a goalkeeper, and no caffeine \times genotype interaction. No main effect of caffeine for ball throw velocity from 7-m, but a caffeine \times genotype interaction whereby participants with the AA genotype improved performance following caffeine ingestion while those with the AC/CC genotype did not</p>	<p>AC/CC genotype: -0.02 <i>Ball throw from 7-m with a goalkeeper</i> AA genotype: 0.39 AC/CC genotype: -0.23 <i>Ball throw from 9-m</i> AA genotype: 0.40 AC/CC genotype: 0.22 <i>Ball throw from 9-m with a goalkeeper</i> AA genotype: 0.47 AC/CC genotype: 0.05</p>
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 \times 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 \times genotype interaction; no main effect of caffeine for sprint time in the “Change-of-	<p><i>Abalakov jump</i> AA genotype: 0.15 AC/CC genotype: 0.14 <i>“Change-of-Direction and Acceleration Test” without the ball</i> AA genotype: 0.12 AC/CC genotype: -0.06</p>

			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	<i>Bench press</i> AA genotype: 0.88–1.87 AC/CC genotype: –0.05 to 0.09 <i>Leg press</i> AA genotype: 0.48–1.22 AC/CC genotype: –0.12 to 0.44 <i>Seated row</i> AA genotype: 0.87–1.30 AC/CC genotype: 0.17–0.27 <i>Shoulder press</i> 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	<i>Peak power</i> AA genotype: 0.04 AC/CC genotype: 0.15 <i>Mean power</i> 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	<i>10-km running time trial</i> AC genotype: 0.34 <i>Concentric knee extensor torque</i> AC genotype: 0.25 <i>Eccentric knee extensor torque</i> AC genotype: 0.44 <i>SJ height</i> AC genotype: 0.33 <i>CMJ height</i> 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	<i>CMJ</i> AA genotype: 0.11 AC genotype: 0.13 CC genotype: 0.04 <i>Spike jump</i> AA genotype: 0.14 AC genotype: 0.05 CC genotype: 0.01 <i>Agility test</i> AA genotype: 0.10

			caffeine × genotype interaction for CMJ height, spike jump height, and time in the agility test	AC genotype: 0.07 CC genotype: -0.37 <i>Isometric handgrip strength</i> AA genotype: 0.17 AC genotype: 0.07 CC genotype: 0.06 <i>Push-up</i> AA genotype: 0.09 AC genotype: 0.24 CC genotype: 0.36 <i>Sit-up</i> AA genotype: 0.24 AC genotype: 0.32 CC genotype: 0.28 <i>Yo-Yo IRI</i> AA genotype: 0.31 AC genotype: 0.36 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 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