

1 Abstract

2 **Objectives:** The aims of this paper are threefold: (1) to summarize the research examining the effects
3 of caffeine on isokinetic strength, (2) pool the effects using a meta-analysis, and (3) to explore if there
4 is a muscle group or a velocity specific response to caffeine ingestion.

5 **Design:** Meta-analysis.

6 **Methods:** PubMed/MEDLINE, Scopus, and SPORTDiscus were searched using relevant terms. The
7 PEDro checklist was used for the assessment of study quality. A random-effects meta-analysis of
8 standardized mean differences (SMDs) was done.

9 **Results:** Ten studies of good and excellent methodological quality were included. The SMD for the
10 effects of caffeine on strength was 0.16 (95% CI=0.06, 0.26; $p=0.003$; +5.3%). The subgroup analysis
11 for knee extensor isokinetic strength showed a significant difference ($p=0.004$) between the caffeine
12 and placebo conditions with SMD value of 0.19 (95% CI=0.06, 0.32; +6.1%). The subgroup analysis
13 for the effects of caffeine on isokinetic strength of other, smaller muscle groups indicated no
14 significant difference ($p=0.092$) between the caffeine and placebo conditions. The subgroup analysis
15 for knee extensor isokinetic strength at angular velocities of $60^{\circ}\cdot\text{s}^{-1}$ and $180^{\circ}\cdot\text{s}^{-1}$ showed a significant
16 difference between the caffeine and placebo conditions with SMD value of 0.21 (95% CI=0.07, 0.36;
17 $p=0.004$; +6.0%) and 0.23 (95% CI=0.07, 0.38; $p=0.005$; +5.5%), respectively. No significant effect
18 ($p=0.193$) was found at an angular velocity of $30^{\circ}\cdot\text{s}^{-1}$.

19 **Conclusions:** This meta-analysis demonstrates that acute caffeine ingestion caffeine may significantly
20 increase isokinetic strength. Additionally, this meta-analysis reports that the effects of caffeine on
21 isokinetic muscular strength are predominantly manifested in knee extensor muscles and at greater
22 angular velocities.

23 **Keywords:** caffeine; exercise; muscles; power; torque

24 **1. Introduction**

25 Caffeine, a trimethylxanthine, is one of the most commonly consumed drugs in the world.¹ The use of
26 caffeine is high both in the general population and among athletes.^{2,3} Van Thuyne and colleagues
27 reported that athletes in strength-based sports such as weightlifting and powerlifting are among the
28 highest users of caffeine.⁴ However, the effects of caffeine on strength performance remain a matter of
29 debate in the scientific literature. Several narrative reviews^{5,6} have highlighted that the effects of
30 caffeine ingestion on muscular strength remain unclear. Indeed, while some report an increase in
31 strength following caffeine ingestion^{7,8} others do not.⁹ Methodological differences between studies,
32 such as caffeine dose and training status of the participants, have been suggested as reasons for the
33 equivocal evidence on the topic⁶ (albeit, there is a lack of direct evidence to support these claims).¹⁰

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35 It needs to be acknowledged that small sample sizes are a mainstay in the research examining the
36 effects of caffeine on exercise performance. Therefore, it is possible that some studies lack sufficient
37 statistical power to observe significant effects. For instance, Astorino et al.¹¹ reported that the
38 ingestion of caffeine (in a dose of 6 mg·kg⁻¹) over placebo improved resistance exercise performance
39 in nine out of the 14 resistance-trained men included as participants, yet, no statistically significant
40 increases in weight lifted were found. Therefore, it is possible that the study was underpowered to find
41 significant effects.

42

43 Meta-analyses have helped to elucidate equivocal topics within nutritional supplement research as they
44 allow the pooling of outputs from many studies.¹² Such statistical procedures provide more conclusive
45 statements than individual trials and are set at the top of the hierarchy of evidence in the recent
46 International Olympic Committee consensus statement.¹² Two meta-analyses thus far have examined
47 the effects of caffeine on strength. Warren et al.¹³ found that caffeine ingestion can increase strength,
48 with the effect being predominantly in the knee extensor muscles, but not in smaller muscle groups
49 such as the elbow flexors. Of the 22 peer-reviewed studies included in the analysis by Warren et al.¹³
50 17 examined the effects of caffeine on isometric strength. Three included studies examined the effects
51 of caffeine on isokinetic strength, and two examined the effects of caffeine ingestion on one-repetition

52 maximum (1RM). Therefore, it can be argued that the results provided by Warren et al.¹³ are specific
53 to the effects of caffeine on isometric strength. A recent meta-analysis by Grgic et al.¹⁴ focused on
54 1RM and found a significant ergogenic effect with caffeine ingestion. A subgroup analysis from their
55 review showed that caffeine ingestion had a significant effect on upper-body, but not on lower-body
56 strength; results which somewhat are in contrast to those presented for isometric strength by Warren et
57 al.¹³

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59 The assessment of strength forms an important component of monitoring the effects of various training
60 interventions.¹⁵ Additionally, assessment of strength is often used by researchers in order to
61 understand the relative significance of strength to a specific trait, outcome (such as falls in older
62 adults),¹⁶ and/or sports performance. Furthermore, assessing strength levels of an individual may be
63 utilized within talent identification,¹⁵ and to identify injury risk.^{17, 18} Strength can be assessed through a
64 variety of techniques, including isometric, 1RM, and isokinetic methods. An important consideration
65 is that the various types of strength assessment have different characteristics, and thus cannot be
66 considered as interchangeable or equivalent measures of strength.¹⁹ Moreover, they can even produce
67 conflicting results.²⁰

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69 Given that during an isometric muscle action the muscle-tendon unit does not change its length,
70 isometric strength only provides information regarding strength levels at a specific point of application
71 within a joint's range of motion.²¹ Also, isometric muscular actions might have less applicability to
72 most sporting situations as these commonly include dynamic muscle actions.¹⁰ While the 1RM test
73 includes dynamic muscle actions, in this test, velocity cannot be controlled, and, additionally, the
74 muscle can be overloaded only by the amount of weight that can be lifted through the weakest part of
75 the exercised range of motion.²¹ Furthermore, the complexity of some exercises (such as the free
76 weight barbell squat) used for the 1RM test may require several familiarization sessions to obtain a
77 reliable measurement given the considerable skill component of such movements.²²

78

79 While isokinetic strength assessment is not without its limitations, it does provide certain advantages
80 including: (1) maximal resistance throughout the exercised range of motion (i.e., no fixed resistance in
81 the weakest point of the movement); (2) the use of accommodating resistance, which provides a safety
82 mechanism given that the accommodating mechanism disengages when the participant senses pain; (3)
83 the use and control of different velocities; and (4) isokinetic assessments allow the quantification of
84 torque (the force measured about a joint's axis of rotation), work (force and distance of a given
85 muscular action), and power (time required to produce work).²¹ Furthermore, isokinetic assessment has
86 been shown to be a highly reliable measure of strength.^{21, 23}

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88 Several studies have previously investigated the effects of caffeine ingestion on isokinetic strength,
89 with equivocal findings.²⁴⁻³³ Thus, the aims of this paper are to: (1) summarize the research examining
90 the effects of caffeine on isokinetic strength, (2) pool the effects using a meta-analysis, and (3) to
91 explore if there is a muscle group or a velocity specific response to caffeine ingestion.

92

93 **2. Methods**

94 For this paper, peer-reviewed literature was searched on the effects of caffeine ingestion on isokinetic
95 strength, defined as the peak torque produced during an isokinetic maximal voluntary contraction. The
96 literature search was done on May 26th, 2018. The primary search occurred via Scopus,
97 PubMed/MEDLINE, and SPORTDiscus databases through titles, abstracts, and keywords. The search
98 syntax included the following words coupled with Boolean operators: caffeine AND (strength OR
99 force OR torque OR isokinetic). The secondary searchers consisted of: (1) examining the reference
100 lists of the studies found meeting the inclusion criteria, (2) examining papers that cited the included
101 studies through the Scopus database, and (3) scanning through the reference lists of relevant review
102 papers.^{1, 5, 6, 13, 14} In order to prevent any selection bias, the search was done independently by the two
103 authors of the review.

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105 Studies meeting the following criteria were included in the present review: (1) published in a peer-
106 reviewed, English-language journal, (2) included humans as participants, (3) utilized a crossover

107 design with at least one placebo and one caffeine trial, and (4) isokinetic muscular strength was
108 assessed. Studies in which other potentially ergogenic compounds such as taurine were used were not
109 considered for the present review. Additionally, studies with a between-group design were not
110 included due to poor control of the inter-individual variability in response³⁴ to caffeine ingestion in
111 such study designs.

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113 The following data were extracted from the included studies: (1) authors and publication date, (2)
114 participants characteristics, (3) the tested muscle group, and (4) means and standard deviations for
115 isokinetic strength from the caffeine and placebo trials. If data were presented in figures, the Web Plot
116 Digitizer software (V.3.11. Texas, USA: Ankit Rohatgi, 2017) was used for the extraction of raw
117 values. Standard errors (SEs) were converted to standard deviations, using the following formula:
118 $(SE \cdot \sqrt{n})$.

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120 The Physiotherapy Evidence-Based Database Scale (PEDro) was used for the assessment of study
121 quality. This scale has a total of 11 items. The maximum possible score on the scale is 10 points as the
122 first item is not included in the total score. The full details regarding the PEDro scale can be found
123 elsewhere.³⁵ The study quality was classified as in the review by McKendry and colleagues³⁶ and by
124 others^{14,37} in which 9-10 points corresponds to excellent quality, 6-8 points correspond to good
125 quality, 4-5 points corresponds to fair quality, and less than 3 points correspond to poor
126 methodological quality.

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128 **2.1 Statistical analysis**

129 The extracted isokinetic muscular strength data were converted to standardized mean differences
130 (Hedge's g) and 95% confidence intervals (CIs). The following data were needed for the calculation of
131 standardized mean differences: (1) mean \pm standard deviation of the caffeine and placebo trials, (2)
132 sample size (n), and (3) inter-trial correlation. None of the included studies presented inter-trial
133 correlation. Therefore, as suggested in the Cochrane Handbook³⁸ the correlation was estimated using
134 the following formula:

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$$r = \frac{S_{\text{placebo}}^2 + S_{\text{caffeine}}^2 - S_D^2}{2 \cdot S_{\text{placebo}} \cdot S_{\text{caffeine}}}$$

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138 S represents the standard deviation while S_D is the standard deviation of the difference score, which
 139 was calculated as:

$$S_D = \left(\frac{S_{\text{placebo}}^2}{n} + \frac{S_{\text{caffeine}}^2}{n} \right)^{1/2}$$

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142 When a study measured strength under multiple conditions, such as multiple caffeine doses,
 143 standardized mean differences and variances were averaged across the different conditions and the
 144 average values were used for the analysis. The main analysis consisted of all isokinetic muscular
 145 strength data. A sensitivity analysis was performed by excluding the study with the lowest score on the
 146 PEDro checklist.²⁴ Two subgroup analyses that focused on the size of the assessed muscle group were
 147 performed, one in which only knee extensor data was analyzed, and one for all other muscle groups
 148 (such as knee flexors, elbow flexors, ankle plantar flexors, and wrist flexors). We analyzed knee
 149 extensor data in isolation to explore the impact of caffeine on individual muscle groups, with a
 150 previous meta-analysis¹³ suggesting that caffeine's positive impact on strength occurs predominantly
 151 within the knee extensors. In order to explore the effects of caffeine on different angular velocities,
 152 subgroup analyses were done for angular velocities of 30, 60, and 180°·s⁻¹. A subgroup analysis for
 153 other angular velocities such as 250°·s⁻¹ could not be explored due to the limited data.

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155 Hedge's g values of ≤0.2, 0.2-0.5, 0.5-0.8, and >0.8 were considered to represent small, medium,
 156 large, and very large effects, respectively.³⁹ Heterogeneity was assessed using the I^2 statistic. The
 157 following classification was used for heterogeneity: low levels (≤50%), moderate levels (50-75%), and
 158 high levels (>75%) of heterogeneity. Funnel plots were used for detecting publication bias with the
 159 Duval and Tweedie's trim and fill method. Percent changes between the placebo and caffeine

160 conditions were also calculated. The random-effects model was used for all analyses. The statistical
161 significance threshold was set at $p < 0.05$. All analyses were performed using the Comprehensive
162 Meta-analysis software, version 2 (Biostat Inc., Englewood, NJ, USA).

163

164 3. Results

165 The search through the three databases resulted in a total of 3283 relevant publications. Of the total
166 number, 3238 items were excluded after reading the title or the abstract which left 45 full-text papers
167 to be examined. Out of the 45 full-text papers, 35 were excluded as they did not meet the inclusion
168 criteria, leaving a total of ten included studies.²⁴⁻³³ The secondary searches did not result in any
169 additional inclusion of studies.

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171 A summary of all study details can be found in Table 1. In total, 133 participants were included across
172 the studies (men = 120 *n*; women = 13 *n*). The median number of participants per study was 13. In five
173 of the studies,^{24, 25, 29-31} the participants were reported as athletes or resistance-trained while in the
174 remaining five the participants were either recreationally trained or untrained individuals.^{26-28, 32, 33} In
175 nine of the ten studies, the participants were of young age, while one study included older adults.²⁸
176 Seven studies measured only lower-body strength,^{24-26, 27, 29, 31, 32} two examined both lower and upper-
177 body strength,^{30, 33} while one study measured only upper-body strength.²⁷

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179 *****Insert Table 1 about here*****

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181 Based on the PEDro checklist, six studies^{25, 27-29, 31, 33} were classified as excellent quality while four^{24, 26,}
182 ^{30, 32} were classified as good quality. The mean \pm standard deviation score was 9 ± 1 (range = 6 to 10
183 points). Individual scores for the quality assessment can be found in Table 2.

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185 *****Insert Table 2 about here*****

186

187 The main meta-analysis results showed a significant difference ($p = 0.003$) between the caffeine and
188 placebo conditions. The standardized mean difference for the effects of caffeine on strength was 0.16
189 (95% CI = 0.06, 0.26; +5.3%; $I^2 = 15\%$). The sensitivity analysis in which the study with the lowest
190 quality was excluded changed the standardized mean difference value to 0.19 (95% CI = 0.10, 0.28; p
191 < 0.001). The forest plot of the analysis is presented in Figure 1. The subgroup analysis for knee
192 extensor isokinetic strength showed a significant difference ($p = 0.004$) between the caffeine and
193 placebo conditions. The standardized mean difference for the effects of caffeine on strength was 0.19
194 (95% CI = 0.06, 0.32; +6.1%; $I^2 = 11\%$). The subgroup analysis for the isokinetic strength of other
195 muscle groups indicated no significant difference ($p = 0.092$) between the caffeine and placebo
196 conditions with the standardized mean difference value of 0.10 (95% CI = -0.02, 0.21; +3.9%; $I^2 =$
197 19%).

198

199 The subgroup analysis for isokinetic strength at $30^\circ \cdot s^{-1}$ indicated no significant difference ($p = 0.193$)
200 between the caffeine and placebo conditions with the standardized mean difference value of 0.16 (95%
201 CI = -0.08, 0.39; +6.2%; $I^2 = 0\%$). The subgroup analysis for isokinetic strength at $60^\circ \cdot s^{-1}$ showed a
202 significant difference ($p = 0.004$) between the caffeine and placebo conditions. The standardized mean
203 difference for the effects of caffeine on strength was 0.21 (95% CI = 0.07, 0.36; +6.0%; $I^2 = 7\%$). The
204 subgroup analysis for isokinetic strength at $180^\circ \cdot s^{-1}$ showed a significant difference ($p = 0.005$)
205 between the caffeine and placebo conditions. The standardized mean difference for the effects of
206 caffeine on strength was 0.23 (95% CI = 0.07, 0.38; +5.5%; $I^2 = 0\%$). No asymmetry was noted in the
207 funnel plots in any of the analyses and the Duval and Tweedie's trim and fill correction did not have
208 any effect.

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211 *****Insert Figure 1 about here*****

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214 **4. Discussion**

215 The main finding of the present meta-analysis suggests that acute caffeine ingestion may increase
216 isokinetic strength when compared to placebo. Furthermore, it appears that caffeine improves strength
217 predominantly in the knee extensors and at higher angular velocities. Given its performance-enhancing
218 effect, caffeine may be used as an effective aid for an amplified acute training stimulus. Based on the
219 good and excellent quality of the included studies it can be concluded that the results of the present
220 analysis are not confounded by studies with poor methodological quality.

221

222 The results presented herein corroborate previous meta-analytic data by Warren et al.¹³ and Grgic et
223 al.¹⁴ As previously discussed, Warren et al.¹³ found that caffeine may have a greater effect on the knee
224 extensor musculature than on smaller muscle groups such as elbow flexors. Knee extensor activation
225 is usually around 85 to 95% of its maximal capacity during a maximal voluntary contraction.⁴⁰ In
226 contrast to knee extensors, smaller muscle groups such as the plantar flexors are activated up to 99%
227 of their maximum during a maximal voluntary contraction.⁴⁰ Thus, given the possible ceiling effect of
228 activation in smaller muscle groups, Warren et al.'s suggestion was that the enhancement of central
229 excitability^{41,42} and increase in motor unit recruitment^{41,42} with caffeine ingestion might predominately
230 be manifested in the knee extensors.¹³ Our results appear to confirm such an effect. The work by Black
231 et al.⁴³ provided some further support for these results. The authors used the interpolated-twitch
232 electrical stimulation protocol and examined the percentage of motor-unit recruitment of the knee
233 extensors and the elbow flexors during a strength assessment. Before the ingestion of caffeine, the
234 mean percentage of motor-unit recruitment of the elbow flexors during a maximal voluntary
235 contraction was at 97%. However, for the knee extensors, the values were only 83%. Likely because
236 of these differences at baseline, after the ingestion of caffeine, a significant increase ($p = 0.014$;
237 +6.3%) in maximal voluntary contraction was seen in the knee extensors, but not in the elbow flexors.
238 While the present meta-analysis does show that caffeine ingestion may have a significant effect on the
239 strength of knee extensors, given the small number of studies (i.e., seven) that are directly comparing
240 the effects of caffeine on smaller vs. larger muscle groups, future work is warranted.

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242 Besides the increases in motor-unit recruitment, it has been suggested that a decrease in pain
243 perception might contribute to the enhanced strength with caffeine ingestion.^{41, 42} Caffeine is a
244 competitive adenosine receptor antagonist, and thus, after ingestion, binds to A₁ and A_{2a} adenosine
245 receptors.⁴⁴ Due to its analgesic properties (which are likely due to the modification of caffeine on
246 nociceptive processing),¹ caffeine is used in a variety of pain medications.^{41, 42} Motl and colleagues
247 reported a reduction in pain perception after the ingestion of caffeine in prolonged, aerobic exercise.⁴⁵
248 Only one of the ten included studies in the present review examined the effects of caffeine on strength
249 and the associated pain perception values. Tallis and Yavuz³³ reported no effect of caffeine on pain
250 perception, even though significant increases in peak torque of the knee extensors was seen both with
251 the 3 mg·kg⁻¹ and 6 mg·kg⁻¹ caffeine dose. These results would suggest that different mechanism(s)
252 other than reductions in pain perception contributed to the enhanced performance. One often proposed
253 mechanism is that caffeine increases intracellular calcium ion concentrations,⁴⁶ which in turn enhances
254 cross-bridge attachment and hence force production (as reviewed by Sökmen and colleagues).⁴⁷
255 However, it is evident that future work is needed in this area before making any firm conclusions.

256

257 The effects of caffeine on isokinetic strength as assessed by different angular velocities may not be
258 uniform.³³ To explore this matter, we conducted a subgroup analysis focusing on the effects of
259 caffeine on strength at different angular velocities. The results of this analysis indicated that caffeine
260 ingestion may have a more pronounced effect on strength when assessed at greater velocities (such as
261 60 and 180°·s⁻¹) as compared to a lower angular velocity of 30°·s⁻¹. These results provide some
262 support for the findings by Tallis and Yavuz³³ who also observed that caffeine ingestion may have a
263 greater effect at higher velocities. While this is indeed an exciting finding, given the small number of
264 studies, these results should be interpreted with a degree of caution. Specifically, the analyses for
265 angular velocities of 30, 60, and 180°·s⁻¹ included only six, three, and three studies, respectively.
266 Given this limitation, future work on this topic is needed.

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269 Only two studies examined the effects of caffeine on both upper and lower-body strength in the same
270 cohort, with equivocal findings.^{30, 33} Due to the lack of such studies, it could not be explored whether
271 there is a differential response to caffeine ingestion between upper and lower-body. Timmins and
272 Saunders³⁰ investigated the effect of 6 mg·kg⁻¹ of caffeine on isokinetic strength of knee extensors,
273 ankle plantar flexors, elbow flexors, and wrist flexors. The authors reported that caffeine ingestion
274 improved strength in all muscle groups, with the increases ranging from +6.3% to +13.7%. In contrast
275 to these results, Tallis and Yavuz³³ reported that 3 mg·kg⁻¹ and 6 mg·kg⁻¹ of caffeine increased strength
276 only in the knee extensors, but not in the upper-body musculature (i.e., elbow flexors). It might be that
277 these differences in results are due to the training status of the participants as Timmins and Saunders³⁰
278 included resistance-trained men, while Tallis and Yavuz³³ included individuals without any previous
279 resistance exercise experience. That said, this remains speculative at this point and thus, this area
280 merits further research.

281

282 Besides the effects of caffeine on pain perception, the effects of caffeine on strength at different
283 velocities, and the effects of caffeine on upper vs. lower-body strength, several interesting areas could
284 be explored in future research. For instance, future studies are needed among women as, out of the 133
285 pooled participants across the studies, 120 of them were men. Also, none of the studies explored
286 whether there is a sex-specific response to caffeine ingestion, which is something that might be of
287 interest for future studies. Furthermore, most of the studies used only a single dose of caffeine, most
288 commonly between 3-7 mg·kg⁻¹. Of the two studies that did utilize multiple caffeine doses, Tallis and
289 Yavuz³³ reported that both the lower (3 mg·kg⁻¹) and the higher (6 mg·kg⁻¹) caffeine doses enhanced
290 strength in the lower-body musculature. Astorino and colleagues compared 2 and 5 mg·kg⁻¹ caffeine
291 doses, while finding that only the higher dose enhanced performance. As such, it is not clear what the
292 optimal caffeine dose is for enhancing strength, and indeed this may even differ for both contraction
293 type³³ and individuals.³⁴ Thus, future research may wish to explore the dose-response of caffeine

294 ingestion of isokinetic performance. Also, given that only two studies compared the effects of caffeine
295 on concentric vs. eccentric muscle actions,^{31,33} future studies addressing this subject are also needed.

296

297 It is well-established that there is a considerable inter-individual variation in the responses to caffeine
298 ingestion.³⁴ Using a 10-km cycling time trial, Guest et al.⁴⁸ recently reported that the *CYP1A2* gene
299 impacts the ergogenic effects of caffeine on performance. The results showed that the AA genotype
300 increased performance following caffeine ingestion, while the C allele carriers either showed no
301 improvement (AC genotype) or even decreases in performance (CC genotype) with caffeine. Similar
302 results have been reported in terms of the effect of acute caffeine ingestion on muscular endurance,⁴⁹
303 although the impact on maximum strength is currently unexplored, representing a future avenue for
304 exploration.

305

306 Finally, only one of the studies in this meta-analysis examined the impact of caffeine in older adults,
307 reporting no significant effects of caffeine on isokinetic strength in the knee extensors. Using a mice
308 model, the same research group reported a reduction (but not an elimination) of the ergogenic effects
309 of caffeine on strength performance in older muscles.⁵⁰ These results tentatively suggest the potential
310 for a reduction in caffeine sensitivity, mediated by a reduction in excitation-contraction coupling, with
311 age.⁵⁰ Again, future research in this area is required to confirm these initial findings.

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313 From a practical standpoint, the main use of isokinetic tests is in assessing strength, as opposed to its
314 use as a training aid. These results suggest that the outcomes of such an assessment could be modified
315 by caffeine ingestion. As such, when utilizing isokinetic strength assessments, researchers and
316 practitioners should attempt to control for caffeine intake, particularly when seeking to explore
317 differences between individuals.

318

319 5. Conclusion

320 In conclusion, this meta-analysis demonstrates that acute caffeine ingestion may lead to significant
321 increases in isokinetic strength performance. Additionally, this meta-analysis reports that the effects of
322 caffeine on isokinetic muscular strength are predominantly manifested in knee extensor muscles and at
323 higher angular velocities. Finally, these conclusions are based on studies with excellent to good
324 methodological quality, and on analyses with low levels of heterogeneity.

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