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# Doma, Kenji, Singh, Utkars, Boullosa, Daniel, and Connor, Jonathan (2021) *The effect of branched-chain amino acid on muscle damage markers and performance following strenuous exercise: a systematic review and meta-analysis.* Applied Physiology, Nutrition and Metabolism, 46 (11) pp. 1303-1313.

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Please refer to the original source for the final version of this work: <u>https://doi.org/10.1139/apnm%2D2021%2D0110</u>

- 1 The effect of branched-chain amino acid on muscle damage markers and performance
- 2 following strenuous exercise: a systematic review and meta-analysis
- 3
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17

#### 18 Abstract

19	This systematic review and meta-analysis determined whether the ergogenic effects of
20	branched-chain amino acids (BCAA) ameliorated markers of muscle damage and
21	performance following strenuous exercise. In total, 25 studies were included, consisting of
22	479 participants (age $24.3 \pm 8.3$ years, height $1.73 \pm 0.06$ m, body mass $70.8 \pm 9.5$ kg; females
23	26.3%). These studies were rated as fair to excellent following the PEDro scale. The outcome
24	measures were compared between the BCAA and placebo conditions at 24 and 48 hours
25	following muscle-damaging exercises, using standardised mean differences and associated p-
26	values via forest plots. Our meta-analysis demonstrated significantly lower levels of indirect
27	muscle damage markers (creatine kinase, lactate dehydrogenase and myoglobin) at 48 hours
28	(SMD = -0.41; $p < 0.05$ ) post-exercise for the BCAA than placebo conditions, whilst muscle
29	soreness was significant at 24 (SMD = $-0.28 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = $-0.41 \le d \le -0.61$ ; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48 (SMD = -0.41 \le -0.61; p < 0.05) and 48
30	0.92; $p < 0.01$ ) hours post-exercise. However, no significant differences were identified
31	between the BCAA and placebo conditions for muscle performance neither at 24 nor 48
32	hours post-exercise (SMD = $0.08 \le d \le 0.21$ ; p > 0.05). Overall, BCAA reduced the level of
33	muscle damage biomarkers and muscle soreness following muscle-damaging exercises.
34	However, the potential benefits of BCAA for muscle performance recovery is questionable,
35	and warrants further investigation to determine the practicality of BCAA for ameliorating
36	muscle damage symptoms in diverse populations.

37

38 Novelty

BCAA reduces the level of creatine kinase and muscle soreness following
 strenuous exercise with a dose-response relationship

41 • BCAA does not accelerate recovery for muscle performance

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#### 42 Introduction

Unfamiliar activities, particularly those that involve eccentric contractions, are known to 43 cause exercise-induced muscle damage (EIMD) (Clarkson et al., 1992). The signs and 44 symptoms of EIMD include prolonged impairment in muscle strength and joint range of 45 motion (ROM), proprioception, delayed onset of muscle soreness (DOMS) and elevated 46 47 muscle proteins in the blood (e.g., creatine kinase [CK]) (Ebbeling and Clarkson, 1989). The deterioration of muscular function and subsequent inflammatory response caused by EIMD 48 could compromise athletic performance during the subsequent days. In fact, several studies 49 have reported impairment in vertical jump (Byrne and Eston, 2002, Doma et al., 2017b), 50 sprint and agility (Khan et al., 2016, Doma et al., 2018), running economy (Doma and 51 Deakin, 2015, Doma and Deakin, 2013) and cycling power output (Hayter et al., 2016) 52 during periods of EIMD following strenuous exercises. Therefore, to maintain performance 53 levels, optimize the quality of subsequent training, and minimize the risks of injuries (Doma 54 et al., 2017a), recovery strategies that minimize the level of EIMD should be considered 55 (Doma et al., 2019a). One of various approaches could involve oral intake of legal 56 substances, with branched-chain amino acids (BCAA) as a potentially effective supplement 57 for this purpose. 58

The bioactive constituents of BCAA includes leucine, isoleucine and valine, three essential 59 60 amino acids which are not synthesized in the body and must therefore be orally ingested (Mero, 1999). Of these amino acid compounds, leucine is known to offer the greatest 61 anabolic potential for proteostasis (Mero, 1999). Whilst not fully understood, it has been 62 speculated that supplemental amino acid after exercise may increase protein synthesis whilst 63 mitigating the deleterious effects of EIMD, such as muscle proteolysis, inflammation and 64 oxidative stress, by upregulating reactive oxygen species scavenging (Valerio et al., 2011). 65 Given that increased inflammation and oxidative stress post-exercise exacerbates the level of 66

EIMD via the secondary muscle damage response (Smith et al., 2008), BCAA 67 supplementation may enhance the recovery process associated with EIMD. In fact, evidence 68 over the last two decades suggest that oral supplements of BCAA may exhibit prophylactic 69 effects to ameliorate the signs and symptoms of EIMD. For example, several studies have 70 reported that supplementation of BCAA reduced the level of muscle damage biomarkers 71 (e.g., CK) (Coombes and McNaughton, 2000, Greer et al., 2007, Howatson et al., 2012, 72 73 Matsumoto et al., 2009, Osmond et al., 2019, Ra et al., 2013a, Sharp and Pearson, 2010, Shimomura et al., 2010) and DOMS (Howatson et al., 2012, Jackman et al., 2010, Leahy and 74 75 Pintauro, 2013, Matsumoto et al., 2009, Ra et al., 2013a, Reule et al., 2016, Shimomura et al., 2006), whilst improved muscular performance (e.g., isometric force) (Howatson et al., 2012, 76 Osmond et al., 2019, Reule et al., 2016, VanDusseldorp et al., 2018, Greer et al., 2007, 77 Waldron et al., 2017) for 24-48 hours post-exercise. However, BCAA supplementation has 78 79 also been reported to have no impact on outcome measures associated with EIMD (Foure et al., 2016, Kephart et al., 2016, Lin et al., 2017, Panahi et al., 2013, Sheikholeslami-Vatani 80 and Ahmadi, 2016). These equivocal findings may be attributed to the differences in study 81 protocol between studies, including the supplementation methods of BCAA, sample 82 characteristics, muscle-damaging protocols, and the type of EIMD outcome measures. Thus, 83 a systematic exploration of the current literature may identify the overall effectiveness of 84 BCAA supplement for post-exercise recovery by addressing the strengths and gaps in these 85 previous studies. 86 Recently, systematic reviews with meta-analyses have examined the effects of BCAA 87

supplementation on EIMD outcome measures. Previously, Rahimi et al. (2017) reported
significant reduction in the overall outcome measures for CK and DOMS with the ingestion
of BCAA. These findings were later confirmed by two other meta-analyses, with significantly
greater reductions in CK (Hormoznejad et al., 2019) and DOMS (Fedewa et al., 2019) for the

BCAA condition compared to the placebo condition. Collectively, the meta-analyses 92 published to date demonstrates the benefits of BCAA supplementation for muscle recovery 93 following EIMD. Surprisingly, the recovery periods in these meta-analyses were either not 94 reported, or combined from immediately post-exercise to several days post-exercise 95 (Hormoznejad et al., 2019). This is despite that the time course of recovery period varies 96 depending on the type of EIMD measured, which generally peaks at 24-48 hours post-97 98 exercise (Doma et al., 2019b, Doma et al., 2017b, Doma et al., 2015). When EIMD outcome markers were separated from 24 to 48 post-exercise in previous meta-analyses, the authors 99 100 solely reported DOMS (Fedewa et al., 2019), or included no more than six studies (Rahimi et al., 2017), even though research in this area has been continuing for several decades. 101 Furthermore, none of the existing meta-analyses have examined muscular performance 102 103 measures, which is critical, given that such outcomes provide the best method of determining muscle injury (Warren et al., 1999). Considering that studies often report biomarkers of 104 muscle damage (e.g., CK, lactate dehydrogenase [LDH] and myoglobin), DOMS and muscle 105 performance as measures of indirect muscle damage, all these outcome measures should be 106 examined during periods of EIMD. Thus, the current systematic review and meta-analysis 107 examined whether commonly supplemented and commercially available BCAA ameliorates 108 the signs and symptoms of EIMD and improve muscular function. 109

110

#### 111 Materials and methods

112 This systematic review has been registered with PROSPERO (registration number:

113 CRD42020191248), and the methodology was undertaken according to the PRISMA

114 guidelines (Moher et al., 2009).

115

116 Inclusion and exclusion criteria

We included studies based on the following criteria: 1) studies that investigated the acute 117 responses to various muscle-damaging exercises, such as eccentric contractions, resistance 118 training, ballistic jumping and long-distance running in humans only; 2) the outcome 119 measures were compared between the BCAA and placebo (PLA) conditions; 3) the outcome 120 121 measures consisted of either biomarkers of indirect muscle damage (e.g., CK), inflammation (e.g., interleukins), oxidative stress (e.g., malondialdehyde) and antioxidant status (e.g., total 122 antioxidant capacity), subjective measures of musculoskeletal pain and muscular performance 123 measures (e.g., isometric contractions, vertical jump); 4) the outcome measures (i.e., 124 biomarkers of muscle damage, inflammation, oxidative stress, antioxidant status and 125 subjective measures of musculoskeletal pain) were collected for at least 24 hours following 126 the muscle-damaging exercise; and 5) the supplement at least consisted of a combination of 127 valine, leucine and isoleucine in any ratio, given that these are the most typical biochemical 128 129 constituents of BCAA. We excluded studies if: 1) conducted in animal models; 2) the outcome measures were collected to determine chronic adaptations to training, rather than 130 acute responses; 3) a PLA condition was not included; 4) the paper was not written in 131 English; 5) findings were reported as a conference abstract, review or case report. 132

133

#### 134 Search strategy

The search was conducted on the 6<sup>th</sup> of April, 2020, via five electronic databases, including Cinhal, PubMed, Scopus, SPORTDiscus and Web of Science. Four strings of Mesh terms were combined in PubMed, and two strings were combined for free text search for all databases (refer to Supplementary 1 for full list of search terms). The reference lists of all included studies and Google Scholar were also screened as a supplementary search. 140

#### 141 Selection process

The abstract screening was independently completed by two authors (US and JC). Firstly, all abstracts were highlighted as either 'yes' (definitely meeting the criteria), 'maybe' (possibly meeting the criteria) or 'no' (not meeting the criteria) using the inclusion criteria. Any discrepancies in screening was consulted by a third reviewer (KD) until a consensus was reached. Following the abstract screening process, full text articles were further selected based on the inclusion criteria by the two authors (US and JC).

148

149 Data extraction, assessment of quality, risk of bias and reporting of data

The descriptive information from each study was extracted for the following: 1) study aims; 150 2) research design (i.e., randomized, placebo control or cross-over); 3) participant 151 characteristics; 4) the amount of BCAA; 5) the type of outcome measures; and 6) the post-152 exercise time points of when outcome measures were collected (i.e., 24- and 48-hours after 153 the muscle-damaging protocol). The quantitative results of the selected outcome measures 154 deemed appropriate for later meta-analyses was extracted as mean  $\pm$  standard deviation to 155 construct forest plots. Based on previous recommendations (Johnston et al., 2018), the PEDro 156 157 scoring tool was modified by including additional criteria that assesses the methodological quality of studies appropriate for oral supplements and EIMD responses. The PEDro scoring 158 tool originally consists of 11 items (Maher et al., 2003), with our additional items assessing 159 160 whether: 1) the supplements only consisted of leucine, isoleucine and valine; 2) the amount of each amino acid was reported; 3) previous exposure to resistance training was confirmed 161 for each participant; and 4) the participants refrained from ingesting oral supplements with 162 anti-inflammatory and antioxidant agents. Each PEDro item was scored a 'one' or 'zero' 163

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based on whether the item was met or not, respectively. The final additional item accounted 164 for whether 1) participants avoided additional oral supplementation and/or medication two 165 weeks prior to the study; 2) participants avoided additional oral supplementation and 166 medication during the study; and 3) dietary habits were monitored during the study. The 167 duration of refraining additional oral supplements prior to the study was set at 2-weeks, given 168 that previous studies have used durations as minimal as 7 days for wash-out between BCAA 169 170 and PLA conditions using a cross-over design (Leahy and Pintauro, 2013, Lin et al., 2017, Matsumoto et al., 2009). Collectively, a score of 'three' was given if all three factors were 171 172 met, a score of 'two' if two factors were met, a score of 'one' if one factor was met, and 'zero' if none of the factors were met. Therefore, a maximum of 17 points was attainable with 173 this modified PEDro scoring tool, with the quality classification as follows: excellent (15-17); 174 good (12-14); fair (9-11); and poor ( $\leq 8$ ) (Doma et al., 2020b). Studies rated as 'poor' were 175 excluded from this systematic review. The participant selection bias was minimised by 176 incorporating studies with all healthy adult participants, irrespective of sex and training 177 background. Any outcome measure (i.e., muscle damage, inflammation, oxidative stress, 178 anti-oxidant status, DOMS and muscle force) that consisted of less than six studies was not 179 deemed appropriate for meta-analysis (Jackson and Turner, 2017). Thus, these excluded 180 outcome measures were reported qualitatively using standard systematic review procedures 181 (Moher et al., 2009). 182

183

184 Statistical methods

The Review Manager software (RevMan, version 5.3, Copenhagen: The Nordic Cochrane
Centre, 2014) was used to conduct the meta-analysis for comparison in outcome measures
between the BCAA and PLA conditions. All outcome measures that were deemed

appropriate for meta-analyses were separately reported at 24 and 48 hours after the muscle-188 damaging protocol to gain an understanding of the time course recovery with the 189 supplementation of BCAA. A weighted average was calculated for outcome measures with 190 similar effect constructs within the same study to report a singular effect estimate (Moeyaert 191 et al., 2017). For example, if a study reported CK, myoglobin and LDH as indirect muscle 192 damage biomarkers, the measure of central tendency and dispersion were averaged, rather 193 194 than being treated as separate effect estimates. This method correctly distributes the weight of studies with multiple outcomes and time points, and standardises the precision estimates of 195 196 the resultant summary effect (Moeyaert et al., 2017). The forest plot was generated as a random effects model to control for inter-study heterogeneity, and the heterogeneity of each 197 study was determined based on the I<sup>2</sup> statistic, with values of 25%, 50% and 75% classified 198 199 as low, moderate and high, respectively. The effect estimate was calculated for each study 200 and imputed in the meta-analysis to combine RCP and cross-over studies using the generic inverse-variance method in RevMan (Higgins et al., 2008). Forest plots were also generated 201 with sub-group analysis to tease out the influence of study design (Higgins and Green, 2011), 202 by calculating the effect estimates and the corresponding variance with separate equations 203 (Uanhoro, 2017) for the randomized, placebo controlled (RCP) and cross-over (COR) designs 204 (Doma et al., 2020b, Deeks et al., 2001). As it is uncommon for studies with cross-over 205 designs to report the variance of the change in mean scores of outcome measures, the 206 207 correlation coefficient required to calculate confidence intervals was set at 0.5, which is a relatively conservative level of association, and is recommended when dealing with missing 208 values (Higgins and Green, 2011, Batson and Burton, 2016). Thus, the forest plots were 209 generated by grouping the studies between the RCP and COR study designs, and SMD, Z-210 scores and associated p-values were calculated separately for each study design, along with 211 the overall summary effect. The effect estimate was reported as standardised mean 212

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213	differences (SMD), with values of 0.2, 0.5 and 0.8 were classified as small, moderate and
214	large, respectively (Cohen, 1988). In addition, a meta-regression was performed to assess
215	whether CK, DOMS and muscle performance measures were moderated by total dosage of
216	BCAA, timing of dosage of BCAA (before, during and/or after the muscle-damaging
217	protocol), the type of muscle-damaging protocol and PEDro scores at 24 hours and 48 hours
218	after the muscle-damaging protocols. This meta-regression was completed using the
219	Statistical Package of Social Sciences (SPSS, v25, IBM Corp., Armonk, NY, USA). The type
220	of muscle-damaging protocol was separated by resistance exercises (e.g., traditional
221	resistance exercise, isokinetic eccentric contractions, transcutaneous neuromuscular
222	stimulation) and endurance exercises (e.g., running, cycling). A sensitivity analysis was
223	conducted for all outcome measures by excluding each study in the meta-analysis to
224	determine the influence that each study had on the overall effect estimate. Furthermore,
225	studies that exhibited PEDro scores of a fair quality, or lower, were excluded in the meta-
226	analysis to ascertain the influence that study quality had on the overall effect estimate.

227

## 228 **Results**

229 Systematic literature search

After removal of duplicate abstracts, a total of 2667 abstracts were screened according to the

inclusion criteria (Figure 1). Upon completion of screening, 2603 abstracts were excluded,

- and the remaining 64 full text articles were screened, leaving 28 articles for inclusion. All
- studies were either conducted as a RCP design with a BCAA or PLA group, or a COR

234 design, with BCAA and PLA conditions.

235 \*\*\*Figure 1 around here\*\*\*

#### 236

#### 237 Participants

Supplementary 2 presents the physical characteristics, sample size and outcome distribution 238 at baseline for the BCAA and PLA conditions for each study. There was a total of 365 239 participants from the RCP studies, with 181 participants in the BCAA condition and 184 240 participants in the PLA condition. The mean  $\pm$  standard deviation for age, height and body 241 242 mass for the BCAA condition were  $25.7 \pm 11.8$  years,  $1.74 \pm 0.05$  m and  $73.1 \pm 7.5$  kg, respectively. For the PLA condition, the age, height and body mass were  $25.4 \pm 11.6$  years, 243  $1.74 \pm 0.03$  m and  $73.9 \pm 8.9$  kg, respectively. Thus, the physical characteristics between the 244 BCAA and PLA conditions were similar for the RCP studies. For the COR studies, there was 245 a total of 114 participants, and the mean  $\pm$  standard deviation for age, height and body mass 246 were  $21.9 \pm 1.5$  years,  $1.70 \pm 0.09$  m and  $65.3 \pm 12.1$  kg, respectively. In addition, no 247 significant differences were identified in the outcome measures between the BCAA and PLA 248 conditions at baseline, except in one study for isokinetic torque (Kephart et al., 2016), 249 250 demonstrating that the outcome measures were relatively standardised between each condition. 251

252

#### 253 Methodological descriptions

The most frequently employed muscle-damaging exercise included multi-joint resistance exercises (13 studies), followed by eccentric contractions (4 studies), cycling (3 studies) and running (2 studies), with isometric neuromuscular stimulation (1 study), drop jumps (1 study) and downhill walking (1 study) as the least common (Supplementary 3). The most common biomarker for indirect muscle damage was CK (20 studies), followed by LDH (9 studies), whilst myoglobin (3 studies) and creatine kinase myocardial band (2 studies) were the least reported. Three studies reported on inflammatory markers, including interleukin-6 (IL-6),

monocyte and granulocyte elastase (GEL), and one study reported on oxidative stress, which 261 was 8-hydroxydeoxyguanosine (OHdG). There were various visual analogue scales (VAS) 262 scales used for DOMS measures, including the 10cm pain scale as the most common (6 263 studies), followed by 100mm pain scale (4 studies), 200mm pain scale (3 studies), and 0-10 264 points pain scale (3 studies), whilst the 6-point pain scale (1 study), 1-10 points pain scale (1 265 study) and 50mm pain scale (1 study) were the least reported. The most common type of 266 267 muscle performance protocol included isometric contractions (7 studies), followed by vertical jump (3 studies), whilst isokinetic contractions (1 study) and leg press (1 study) were the least 268 269 reported.

270

271 Methodological quality

The methodological quality according to the PEDro scores ranged from fair to excellent 272 (Supplementary 4). The PEDro items that were identified by all studies included the 273 following: eligibility criteria mentioned; confirmed the amount of BCAA content; all 274 participants received either BCAA or placebo and appropriate statistical analyses were 275 276 conducted to compare data between groups. Most studies addressed the following PEDro items: instructions for participants to refrain from pain medication/supplements and BCAA 277 supplementation prior to and during the study; random allocation of participants into BCAA 278 279 and PLA groups; baseline values were standardized between the BCAA and PLA groups; homogeneity of participants; use of a double-blind method; outcome measures were reported 280 from more than 85% of the participants; and reporting of measure of dispersion (either 281 282 standard deviation, standard error or confidence interval). The least reported PEDro items included the following: allocation of concealment; specificity of resistance training 283 background; and reporting of the bioavailability of the BCAA supplement. 284

285

- 286 Quantitative analysis
- 287 According to the meta-analysis, the muscle damage biomarkers were significantly lower for
- the BCAA condition than the PLA condition 48 hours post-exercise (p = 0.007; Z = 2.68;
- Figure 2B) and approached significance at 24 hours post-exercise (p = 0.06; Z = 1.89), with
- low inter-study heterogeneity ( $I^2 = 54\%$  and 45%, respectively). However, the magnitude of
- differences between conditions were small for both time points (SMD = -0.25 and -0.39,
- respectively). For the DOMS measures, values were significantly lower for the BCAA
- condition than the PLA condition at 24 hours (p = 0.01; Z = 2.47; Figure 3A) and 48 hours (p
- = 0.003; Z = 3.01; Figure 3B), with high inter-study heterogeneity ( $I^2 = 73\%$  and 72%,
- respectively). There were no significant differences in muscle force measures between the
- BCAA and PLA conditions at 24 hours (p = 0.46; Z = 0.74; Figure 4A) and 48 hours (p =
- 297 0.08; Z = 1.76; Figure 4B) post-exercise, with small inter-study heterogeneity ( $I^2 = 0\%$  and
- 298 47%, respectively). In addition, the magnitude of differences between conditions were small
- for both time points (SMD = 0.09 and 0.31, respectively).
- 300 \*\*\*Figure 2 around here\*\*\*
- 301 \*\*\*Figure 3 around here\*\*\*
- 302 \*\*\*Figure 4 around here\*\*\*
- 303
- 304 Meta-regression analysis

According to the meta-regression, the amount of BCAA dosage significantly predicted the muscle damage markers at 24 hours ( $r^2 = 0.24$ ; unstandardised  $\beta = -0.05$ ; p = 0.02) and 48 hours ( $r^2 = 0.32$ ; unstandardised  $\beta = -0.04$ ; p = 0.02) post-exercise. Furthermore, the PEDro

308	score at 24 hours post-exercise significantly predicted the muscle damage markers ( $r^2 = 0.63$ ;
309	unstandardised $\beta = 0.32$ ; p > 0.01), although not at 48 hours post-exercise (r <sup>2</sup> = 0.45;
310	unstandardised $\beta = 0.20$ ; p = 0.07). However, the timing of BCAA ingestion and the type of
311	muscle damage protocol were not significant moderators of the muscle damage markers (p >
312	0.05). For the DOMS measures, the PEDro scores were significant moderators at 24 hours ( $r^2$
313	= 0.0.57; unstandardised $\beta$ = 0.41; p = 0.01) and 48 hours (r <sup>2</sup> = 0.71; unstandardised $\beta$ = 0.58;
314	p < 0.01) post-exercise, although none of the other moderators (dosage, timing of BCAA
315	ingestion and the type of muscle damage protocol) significantly predicted DOMS ( $p > 0.05$ ).
316	In addition, none of the selected moderators predicted muscle force measures ( $p > 0.05$ ).
317	

### 318 Sub-group analysis

For sub-group analyses, the variation in study design (i.e., RCP and COR) appeared to affect all included measures, with significantly greater CK values for PLA than BCAA in studies using the RCP design, although there were no differences in CK between conditions in the studies with COR at 24- and 48-hours post-exercise (Figures 2A and 2B). These trends were reversed for DOMS at 24- and 48-hours post-exercise (Figures 3A and 3B) and muscle force measures at 48 hours post-exercise (Figure 4B).

325

326 Sensitivity analysis

327 The muscle damage markers became significantly lower for the BCAA than the PLA

328 conditions when several studies (Foure et al., 2016, Gervasi et al., 2020, Jackman et al., 2010,

329 Kephart et al., 2016, Waldron et al., 2017, Lin et al., 2017, Sheikholeslami-Vatani and

Ahmadi, 2016, Shimomura et al., 2010) were individually removed at 24-hours post-exercise.

However, the meta-analysis for muscle damage markers remained similar when studies were

individually removed at 48-hours post-exercise. Similarly, the meta-analysis for DOMS 332 remained similar when studies were individually removed at 24- and 48-hours post-exercise, 333 and for muscle performance measures at 24-hours post-exercise. However, the meta-analysis 334 for muscle performance measures was significantly greater for BCAA than PLA when studies 335 by Foure et al. (2016) and Reule et al. (2016) were removed at 48-hours post-exercise. For 336 study quality, the meta-analysis for muscle damage markers were altered when studies with 337 338 'fair' quality were removed, with no differences between the BCAA and PLA conditions at 24- (p = 0.66; Z = 0.44; SMD = -0.05) and 48-hours (p = 0.08; Z = 1.75; SMD = -0.26) post-339 340 exercise. However, results remained similar for DOMS at 24- (p = 0.04; Z = 2.49; SMD = -0.39) and 48-hours (p = 0.008; Z = 2.05; SMD = -0.65) post-exercise. Sensitivity analyses 341 were not conducted for the muscle performance measures as all studies were rated above 342 'fair' quality. 343

344

345 Qualitative analysis

Given that the inflammatory markers were only reported by three studies and oxidative stress 346 347 was reported by one study, these results were not included in the meta-analysis. Furthermore, none of the studies reported anti-oxidant status. Therefore, the findings for inflammatory and 348 oxidative stress markers will be reported qualitatively hereon. With respect to inflammatory 349 350 markers, Jackman et al. (2010) reported no differences in interleukin-6 between the BCAA and PLA conditions at 24 hours following eccentric knee extensor exercises. However, 351 Matsumoto et al. (2009) showed significantly lower granulocyte elastase for the BCAA 352 353 condition than the PLA condition at 24 hours after an intensified training period. Similarly, Kephart et al. (2016) showed significantly lower monocyte percentage for the BCAA 354 condition than PLA condition at 24 hours following barbell back squats. For oxidative stress, 355

Ra et al. (2013a) reported no significant differences between the BCAA and PLA conditions
at 48 hours following eccentric elbow flexor exercises.

358

#### 359 Discussion

The results from the meta-analysis in the current systematic review revealed that BCAA 360 significantly reduced biomarkers of muscle damage and DOMS for up to 48 hours after 361 muscle-damaging exercises when compared to PLA. However, no significant differences 362 were identified between BCAA and PLA conditions for muscle performance measures. 363 Whilst the number of studies to conduct meta-analyses for inflammatory and oxidative stress 364 markers was insufficient, two studies reported significantly lower levels of inflammation for 365 366 the BCAA condition than the PLA condition for up to 24 hours post-exercise, although one study reported comparable measures of inflammation. Furthermore, no significant differences 367 were found in oxidative stress between BCAA and PLA condition according to one study (Ra 368 et al., 2013a). Overall, BCAA supplementation appears to be useful in ameliorating muscle 369 damage and DOMS induced by strenuous exercise, although the inflammatory and oxidative 370 371 stress responses are unclear. Thus, more studies are warranted to confirm the therapeutic effects of BCAA following strenuous exercises. 372

The results from our meta-analysis partly confirms previous meta-analyses that examined indirect measures of muscle damage with the ingestion of BCAA supplementation. For example, our meta-analysis is similar to Rahimi et al. (2017), who reported significantly lower levels of muscle damage for the BCAA condition than the PLA condition at 24 hours following muscle-damaging exercises based on six studies. However, our meta-analysis does not align with Rahimi et al. (2017) at 48 hours after muscle-damaging exercises, as they reported no differences in muscle damage between BCAA and PLA conditions. The

discrepancy in these findings may be attributed to Rahimi et al. (2017) only including two 380 studies, whereas we included 15 studies, thus allowing for greater statistical power (Jackson 381 and Turner, 2017). Hormoznejad et al. (2019) also showed that BCAA significantly lowered 382 levels of muscle damage than PLA following muscle-damaging exercises based on eight 383 studies. However, comparing our findings to that of Hormoznejad et al. (2019) is difficult, 384 given that they combined post-exercise time points from less than 24 hours, to several days 385 386 after muscle-damaging exercises, which limits the scope of time course recovery with BCAA. In addition, our meta-regression identified a novel dose-response relationship between BCAA 387 388 and muscle-damage markers at 24- and 48-hours post-exercise. Thus, it appears that BCAA minimizes the level of muscle damage markers, and this level of attenuation may be 389 augmented by ingesting a greater amount of BCAA. 390

With respect to DOMS, our meta-analyses were not in line with the meta-analysis by Rahimi 391 et al. (2017), who showed no significant differences between BCAA and PLA conditions at 392 24 and 48 hours after muscle-damaging exercises. Similar to the muscle damage markers, 393 Rahimi et al. (2017) only included three studies at 24 hours post-exercise and four studies at 394 48 hours post-exercise, which may have limited their statistical power. In fact, Fedewa et al. 395 (2019) reported significantly lower levels of DOMS with BCAA than PLA for up to 48 hours 396 post-exercise based on eight studies in their meta-analysis, and our meta-analysis supports 397 398 these findings with 18 studies at 24 hours post-exercise and 14 studies at 48 hours postexercise. Collectively, BCAA appears to be an ergogenic supplement to reduce the level of 399 EIMD following muscle-damaging exercises from 24- to 48-hours post-exercise, with our 400 meta-analysis confirming this effect with almost three fold the number of studies included 401 than previous meta-analyses. 402

The anabolic and anti-catabolic properties of BCAA have been suggested as potentialmodulators that ameliorate the level of EIMD. For example, the ingestion of BCAA,

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particularly from leucine, enhances protein synthesis, whilst concomitantly decreasing 405 catabolic effects (Anthony et al., 2002). The ergogenic effects of BCAA supplementation for 406 recovery has been supported at a sub-cellular level, by upregulating both mammalian target 407 of rapamycin and ribosomal protein S6 kinase beta-1 following resistance exercises, which 408 are key enzymes that orchestrates protein synthesis (Blomstrand et al., 2006). These 409 processes have been speculated to minimize the level of cytoskeletal damage in the muscle, 410 411 thereby limiting intramuscular leakage, such as CK, and sustaining the integrity of membrane-bound proteins. Furthermore, exogenous BCAA may attenuate the decrease of 412 413 amino acid in the free muscle pool during exercise, which limits the initiation of muscle protein breakdown, and accelerate recovery (Greer et al., 2007). Interestingly, several studies 414 included in our systematic review reported increases in leucine, isoleucine and valine post-415 exercise (Foure et al., 2016, Gervasi et al., 2020, Lin et al., 2017, Ra et al., 2018, 416 Sheikholeslami-Vatani and Ahmadi, 2016, Shimomura et al., 2010), demonstrating the 417 bioavailability of these amino acids with BCAA ingestion. 418 The EIMD response is considered biphasic, with the mechanical stress of the muscle-419 damaging exercise inducing a primary response, and a subsequent increase in inflammation 420 and oxidative stress for several days post-exercise known as the secondary response (Hyldahl 421 and Hubal, 2014). It has been speculated that the supplementation of BCAA may 422 downregulate the secondary muscle damage response by increasing the bioavailability of 423 amino acids (Howatson et al., 2012). Specifically, it has been suggested that BCAA can 424 enhance glutamine synthesis via transamination of glutamate, which then influences the 425 transcription of nuclear factor of activated beta cells, thereby attenuating local inflammation 426 (for more information, see Nicastro et al. (2012)). Indeed, Matsumoto et al. (2009) reported 427 significantly lower levels of GEL for the BCAA condition than PLA condition, indicating a 428 suppression in elevated inflammatory responses with BCAA supplementation during periods 429

of EIMD. In addition, Kephart et al. (2016) reported significantly lower monocyte
percentages for the BCAA condition than PLA condition, which are commonly known to
differentiate into macrophages, and if increased, may further initiate an inflammatory
response. Whilst there are findings supporting the anti-inflammatory role of BCAA following
strenuous activity, much more research is needed to understand the pro- and antiinflammatory effects of BCAA following strenuous activity.

The exercise-induced inflammatory response may also incur further skeletal muscle damage 436 to previously damaged muscle fibers, and their neighboring non-damaged counterparts, by 437 producing reactive oxygen species, which increases oxidative stress (Aoi et al., 2004). As far 438 as we are aware, Ra et al. (2013a) are the only group of researchers who examined the effect 439 of BCAA supplementation as a recovery intervention on oxidative stress following muscle-440 damaging exercises. Interestingly, comparable measures of 8-OHdG were found between 441 BCAA and PLA conditions, indicating that the supplementation of BCAA had no influence 442 on the level of oxidative stress. However, given the variety of oxidative biomarkers available, 443 and the multiple ways in which BCAA supplementation and muscle-damaging protocols 444 could be conducted, it is difficult to determine whether BCAA reduces the level of oxidative 445 stress from one study. Furthermore, BCAA supplementation has been reported to reduce 8-446 OHdG levels for patients with liver cirrhosis, demonstrating that BCAA may reduce DNA 447 damage in the muscle due to oxidative stress within a clinical context. Thus, similar to 448 inflammatory responses, further research is warranted to examine the effects of BCAA on 449 oxidative stress levels during periods of EIMD. 450

The current meta-analysis also demonstrated significantly lower levels of DOMS for the BCAA condition than the PLA condition for up to 48 hours following muscle-damaging exercises. It is hypothesized that the damage to the intermediate filaments of the myofibres activates groups III and IV afferent nociceptors, resulting in muscular pain (Ebbeling and Clarkson, 1989). This process is supported by our meta-analysis with muscle damage
biomarkers, suggesting that the lower levels of DOMS may have been attributed to
suppressing muscular structural damage. In addition, inflammation of the perimysium or
epimysium has been suggested to cause muscular pain (Proske and Morgan, 2001). Although
the evidence of reduced inflammation with BCAA has only been reported by two studies
(Matsumoto et al., 2009, Kephart et al., 2016), it is plausible that the anti-inflammatory
properties of BCAA may contribute to a reduction in DOMS.

Whilst improvement in DOMS was apparent in our meta-analysis, BCAA supplementation 462 was not favorable for any muscle performance measure. This is surprising, given that 463 reduction in DOMS has been speculated to suppress neural inhibition during periods of 464 EIMD, and accelerate restoration of muscle reflex sensitivity and performance (Nicol et al., 465 2003). Whilst the meta-regression suggested that dosage, timing of BCAA ingestion, the type 466 of muscle-damaging protocol and the PEDro rating did not moderate muscle performance, 467 468 the number of included studies were far less than the CK measure, possibly limiting statistical power. Thus, the lack of any effect of BCAA on muscle performance measures may still be 469 attributed to distinct muscle-damaging exercises employed, particularly between endurance-470 oriented exercises (e.g., running, cycling), traditional resistance exercises and eccentrically-471 biased endurance exercises (e.g., downhill running). Furthermore, the type of muscle groups 472 being assessed, the performance parameters selected (e.g., isometric contractions vs vertical 473 jump height), and the fewer number of studies included when compared to muscle damage 474 and DOMS measures may have also attributed to the limited effect of BCAA on muscle 475 performance measure. However, this finding is plausible since previous reports have 476 confirmed the different time course of muscle damage and performance measures in previous 477 studies with muscle damaging exercises (Chen et al., 2020, Nosaka et al., 2006). 478

Based on the critical appraisal of studies included in this systematic review, several 479 recommendations can be provided for future research. Firstly, only eight studies reported on 480 the bioavailability of leucine, isoleucine and valine, thus more studies should consider 481 including these biomarkers to distinguish the ergogenic effects of BCAA from PLA. 482 Reporting the ergogenic effects of leucine, isoleucine and valine separately will demonstrate 483 the role that each amino acid has in assisting with the recovery process following strenuous 484 485 exercises. This may particularly be evident for leucine, given that this amino acid has been considered to exhibit the greatest anabolic potential for proteostasis (Mero, 1999). Secondly, 486 487 very few studies have examined the inflammatory and oxidative stress responses during periods of EIMD with the ingestion of BCAA. Monitoring these biomarkers will confirm 488 whether BCAA constitutes of anti-inflammatory and anti-oxidant properties, and expand our 489 knowledge on the potential mechanisms contributing to the amelioration of EIMD. Third, 490 only three studies concealed allocation of participants into BCAA and PLA conditions, and 491 future studies should account for this approach to limit selection bias. There are also studies 492 that reported greater ergogenic effects of BCAA when combined with taurine (Ra et al., 493 2013b), although there is an insufficient number of studies to confirm this with a meta-494 analysis at present. Furthermore, although there are other commercially available 495 supplements that are known to enhance recovery dynamics during periods of EIMD, such as 496 plant-based extracts (Doma et al., 2020a, Doma et al., 2020b, Hill et al., 2021, Doma et al., 497 2021), the ergogenic effects of these combinations are not clear and warrant more research. 498 Fourth, the majority of studies to date have examined the ergogenic effects of BCAA in adult, 499 healthy populations. However, conditions with elevated levels of muscle damage, 500 inflammation and oxidative stress are also apparent in elite athletes due to strenuous training, 501 and older individuals with common clinical conditions, such as, but not limited to, 502 osteoarthritis, cardiovascular diseases and diabetes. Thus, future research is encouraged to 503

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determine whether BCAA may ameliorate the signs and symptoms of these population
groups in their respective, contextual applications. Finally, the meta-regression identified that
the PEDro score was a significant moderator for the magnitude of differences between
BCAA and PLA conditions for CK. Therefore, future studies examining effects of oral
supplementation on EIMD markers should consider addressing the modified PEDro items
employed in the current systematic review to optimize study quality.

With respect to the sub-group analysis, although study design appeared to exhibit a notable 510 influence on the overall effect estimate, the trends were dependent on the type of outcome 511 measure. For example, the RCP studies demonstrated greater benefits of BCAA than the 512 COR studies at 24- and 48-hours post exercise for muscle damage markers, suggesting that if 513 participants are separated into BCAA and PLA groups in future studies, the potential carry-514 over effects may be nullified. However, this trend was reversed for DOMS and muscle 515 performance measures, with greater benefits of BCAA in the COR studies, exemplifying the 516 517 advantage of repeated measures design by minimizing inter-individual variability. Thus, our findings do not allow for an appropriate consensus on the optimal study design for studies 518 examining the effectiveness of BCAA on recovery dynamics due to differences between 519 outcome measures. Nonetheless, the PEDro scores significantly predicted the overall effect 520 estimate according to our meta-regression, indicating that future studies should consider the 521 522 PEDro items, including the additional items included in this systematic review. For example, studies employing an RCP design should make every effort to homogenize the sample 523 between the BCAA and PLA groups (e.g., resistance training background, supplement and 524 dietary history and sex). Studies with a COR design should ensure that the BCAA and PLA 525 conditions are separated by at least two weeks to minimize potential carry-over responses of 526 BCAA or EIMD. Furthermore, the participants should be instructed to refrain from ingesting 527

dietary supplements and medication that are known to ameliorate the signs and symptoms of 528 EIMD during the course of the study, irrespective of the study design. 529 In conclusion, our systematic review and meta-analysis identified significant reductions in 530 muscle damage markers at 48 hours after muscle-damaging exercises and DOMS for up to 48 531 hours after muscle-damaging exercises, but not for muscle performance measures. The lack 532 of any differences in muscle performance for the meta-analysis may be attributed limited 533 statistical power when compared to biomarkers, such as CK, and DOMS. However, given 534 that muscle performance has been considered as the primary, indirect muscle damage 535 measure (Warren et al., 1999), studies from hereon are encouraged to focus on ascertaining 536 the ergogenic effects of BCAA as a recovery intervention for muscle function during periods 537 of EIMD in diverse populations. 538

539

540	Figure captions
541	
542	Figure 1. PRISMA flow chart
543	
544 545	<b>Figure 2.</b> Forest plot for indirect muscle damage markers. A: at 24-hours after the muscle damaging exercise; B: at 48-hours after the muscle damaging exercise.
546 547	BCAA – branched chain amino acid; PLA – placebo; SUPP – supplementary; RCP – randomized, controlled placebo trial
548	
549 550	<b>Figure 3.</b> Forest plot for delayed onset of muscle soreness. A: at 24-hours after the muscle damaging exercise; B: at 48-hours after the muscle damaging exercise.
551 552	BCAA – branched chain amino acid; PLA – placebo; RCP – randomized, controlled placebo trial
553	
554 555	<b>Figure 4.</b> Forest plot for muscle force. A: at 24-hours after the muscle damaging exercise; B: at 48-hours after the muscle damaging exercise.
556 557	BCAA – branched chain amino acid; PLA – placebo; SUPP – supplementary; RCP – randomized, controlled placebo trial

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792	



Figure 1

161x163mm (600 x 600 DPI)

A				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 RCP					
Amirsasan et al 2011 (SUPP 1)	-1.68	0.55	3.6%	-1.68 [-2.76, -0.60]	
Amirsasan et al 2011 (SUPP 2)	-0.43	0.47	4.3%	-0.43 [-1.35, 0.49]	
Coobmes et al 2000	-3.29	0.82	2.1%	-3.29 [-4.90, -1.68]	
Foure et al 2016	0.34	0.39	5.2%	0.34 [-0.42, 1.10]	
Gervasi et al 2020	0.46	0.36	5.5%	0.46 [-0.25, 1.17]	+ <b>-</b> -
Howatson et al 2012	-0.89	0.62	3.1%	-0.89 [-2.11, 0.33]	
Jackman et al 2010	0.04	0.42	4.8%	0.04 [-0.78, 0.86]	
Kephart et al 2016	0.03	0.37	5.4%	0.03 [-0.70, 0.76]	
Mohamad-Panahi et al 2013 (SUPP 1)	-0.23	0.45	4.5%	-0.23 [-1.11, 0.65]	
Mohamad-Panahi et al 2013 (SUPP 2)	-0.51	0.46	4.4%	-0.51 [-1.41, 0.39]	
Osmond et al 2019	-1.15	0.57	3.5%	-1.15 [-2.27, -0.03]	
Ra et al 2013	-0.26	0.47	4.3%	-0.26 [-1.18, 0.66]	
Ra et al 2018 (POST)	-0.38	0.64	3.0%	-0.38 [-1.63, 0.87]	
Ra et al 2018 (PRE)	-0.52	0.65	2.9%	-0.52 [-1.79, 0.75]	
Reule et al 2017	-0.16	0.31	6.1%	-0.16 [-0.77, 0.45]	
VanDusseldorp et al 2018	-0.07	0.45	4.5%	-0.07 [-0.95, 0.81]	
Waldron et al 2017	0.69	0.52	3.9%	0.69 [-0.33, 1.71]	
Subtotal (95% CI)			71.0%	-0.33 [-0.67, 0.00]	•
Heterogeneity: Tau <sup>2</sup> = 0.26; Chi <sup>2</sup> = 35.45;	df = 16 (P = 0.003); I <sup>2</sup> =	55%			
Test for overall effect: Z = 1.94 (P = 0.05)					
1.1.2 Cross-over					
Greer et al 2007	-1.32	0.58	3.4%	-1.32 [-2.46, -0.18]	
Lin et al 2017	0.05	0.3	6.3%	0.05 [-0.54, 0.64]	-
Matsumoto et al 2009	-0.36	0.3	6.3%	-0.36 [-0.95, 0.23]	
Sheikholelami-Vatani et al 2016	0.28	0.26	6.8%	0.28 [-0.23, 0.79]	
Shimomura et al 2010	0.25	0.3	6.3%	0.25 [-0.34, 0.84]	<u>+</u>
Subtotal (95% CI)			29.0%	-0.08 [-0.49, 0.34]	•
Heterogeneity: Tau <sup>2</sup> = 0.11; Chi <sup>2</sup> = 8.50,	df = 4 (P = 0.07); I <sup>2</sup> = 539	6			
Test for overall effect: Z = 0.36 (P = 0.72)					
Total (95% CI)			100.0%	-0.25 [-0.52, 0.01]	•
Heterogeneity: Tau <sup>2</sup> = 0.20; Chi <sup>2</sup> = 45.45;	df = 21 (P = 0.002); I <sup>2</sup> =	54%		-	
Test for overall effect: Z = 1.89 (P = 0.06)					Favours (BCAA) Favours (PLA)
Test for subgroup differences: Chi <sup>2</sup> = 0.8	9, df = 1 (P = 0.35), l <sup>2</sup> = 0	0%			i avoars (borer) i avoars (FEA)

#### В

D				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.2.1 RCP					
Amirsasan et al 2011 (SUPP 1)	-0.74	0.48	5.6%	-0.74 [-1.68, 0.20]	
Amirsasan et al 2011 (SUPP 2)	-0.34	0.46	5.9%	-0.34 [-1.24, 0.56]	
Foure et al 2016	0.15	0.39	7.0%	0.15 [-0.61, 0.91]	
Howatson et al 2012	-0.48	0.59	4.3%	-0.48 [-1.64, 0.68]	
Jackman et al 2010	0.05	0.42	6.5%	0.05 [-0.77, 0.87]	
Kephart et al 2016	0.03	0.37	7.4%	0.03 [-0.70, 0.76]	
Mohamad-Panahi et al 2013 (SUPP 1)	-1.85	0.45	6.1%	-1.85 [-2.73, -0.97]	
Mohamad-Panahi et al 2013 (SUPP 2)	-0.27	0.45	6.1%	-0.27 [-1.15, 0.61]	
Osmond et al 2019	-0.7	0.54	4.9%	-0.70 [-1.76, 0.36]	
Ra et al 2013	-0.2	0.47	5.8%	-0.20 [-1.12, 0.72]	
Ra et al 2018 (POST)	-0.61	0.65	3.8%	-0.61 [-1.88, 0.66]	
Ra et al 2018 (PRE)	-0.53	0.65	3.8%	-0.53 [-1.80, 0.74]	
Reule et al 2017	-0.23	0.31	8.6%	-0.23 [-0.84, 0.38]	
VanDusseldorp et al 2018	-1.28	0.5	5.4%	-1.28 [-2.26, -0.30]	
Waldron et al 2017	0.8	0.52	5.1%	0.80 [-0.22, 1.82]	
Subtotal (95% CI)			86.2%	-0.38 [-0.70, -0.07]	◆
Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 24.71,	df = 14 (P = 0.04); I <sup>2</sup> = 4	3%			
Test for overall effect: Z = 2.40 (P = 0.02)					
1.2.2 Cross-over					
Greer et al 2007	-1.29	0.55	4.8%	-1.29 [-2.37, -0.21]	
Shimomura et al 2010	-0.02	0.29	9.0%	-0.02 [-0.59, 0.55]	
Subtotal (95% CI)			13.8%	-0.57 [-1.80, 0.66]	
Heterogeneity: Tau <sup>2</sup> = 0.61; Chi <sup>2</sup> = 4.17, o	if = 1 (P = 0.04); I <sup>2</sup> = 76%	6			
Test for overall effect: Z = 0.90 (P = 0.37)					
Total (95% CI)			100.0%	-0.39 [-0.68, -0.10]	◆
Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 28.93,	df = 16 (P = 0.02); l <sup>2</sup> = 4	5%		-	
Test for overall effect: Z = 2.66 (P = 0.008	3)				-2 -1 0 1 2
Test for subgroup differences: Chi <sup>2</sup> = 0.08	, df = 1 (P = 0.78), l <sup>2</sup> = 0	%			Favours (DCAA) Favours (PLA)

#### Figure 2

196x273mm (600 x 600 DPI)

A				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.1.1 RCP					
Estoche et al 2019	-0.3	0.42	5.6%	-0.30 [-1.12, 0.52]	
Foure et al 2016	0.22	0.39	5.8%	0.22 [-0.54, 0.98]	
Howatson et al 2012	-1.59	0.69	3.9%	-1.59 [-2.94, -0.24]	
Jackman et al 2010	-1.46	0.47	5.3%	-1.46 [-2.38, -0.54]	
Compart et al 2016	1.97	0.45	5.4%	1.97 [1.09, 2.85]	
Denoted 2013	-1.83	0.04	4.2%	-1.83 [-3.08, -0.38]	
Ra et al 2018 (POST)	-0.22	0.47	4.2%	-0.11 [-1.34 1.12]	
Ra et al 2018 (PRE)	0.25	0.64	4.2%	0.25 [-1.00, 1.50]	
Reule et al 2017	0.02	0.31	6.4%	0.02 [-0.59, 0.63]	+
VanDusseldorp et al 2018	-0.85	0.47	5.3%	-0.85 [-1.77, 0.07]	
Waldron et al 2017	-0.37	0.51	5.0%	-0.37 [-1.37, 0.63]	
Subtotal (95% CI)			60.4%	-0.31 [-0.86, 0.24]	•
Heterogeneity: Tau <sup>2</sup> = 0.70; Chi <sup>2</sup> = Test for overall effect: Z = 1.10 (P	= 45.24, df = 11 (P < 0.00 = 0.27)	001);	² = 76%		
2.1.2 Cross-over	0.00	0.00	0.0%		
Gee et al 2016 Green et al 2007	-0.39	0.32	0.3%	-0.39 [-1.02, 0.24]	
Leaby et al 2007	-1.54	0.04	4.8%	-1.34 [-2.00, -0.48]	
Lin et al 2017	-0.45	0.20	6.5%	0.04 [-0.55, 0.63]	+
Shimomura et al 2006 (Female)	-0.33	0.67	4.0%	-0.33 [-1.64, 0.98]	
Shimomura et al 2006 (Male)	-2.04	0.5	5.1%	-2.04 [-3.02, -1.06]	
Shimomura et al 2010	-0.86	0.35	6.1%	-0.86 [-1.55, -0.17]	
Subtotal (95% CI)			39.6%	-0.72 [-1.20, -0.24]	•
Heterogeneity: Tau <sup>2</sup> = 0.26; Chi <sup>2</sup> = Test for overall effect: Z = 2.93 (P	= 17.36, df = 6 (P = 0.008 = 0.003)	5);   <sup>2</sup> =	65%		
Total (95% CI)			100.0%	-0 47 [-0 85 -0 10]	
Heterogeneity: $Tau^2 = 0.48$ : Chi <sup>2</sup> =	:66 65 df = 18 (P < 0.00	001)	<sup>2</sup> = 73%		
Test for overall effect: 7 = 2 47 (P	= 0.01)		1070		-4 -2 0 2 4
	- 0.011				
Test for subgroup differences: Chi	<sup>2</sup> = 1.19, df = 1 (P = 0.28	i), l² =	15.9%		Favours [BCAA] Favours [PLA]
Test for subgroup differences: Chi	<sup>2</sup> = 1.19, df = 1 (P = 0.28	i), l² =	15.9%		Favours [BCAA] Favours [PLA]
Test for subgroup differences: Chi	<sup>2</sup> = 1.19, df = 1 (P = 0.28	i),  ² =	15.9%	Std. Mean Difference	Favours [BCAA] Favours [PLA]
Test for subgroup differences: Chi B Study or Subgroup	2 <sup>2</sup> = 1.19, df = 1 (P = 0.28 Std. Mean Difference	i), l² = SE	15.9% Weight	Std. Mean Difference IV, Random, 95% Cl	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
Test for subgroup differences: Chi B Study or Subgroup 2.2.1 RCP	2 <sup>2</sup> = 1.19, df = 1 (P = 0.28 Std. Mean Difference	s), l² =	15.9% Weight	Std. Mean Difference IV, Random, 95% Cl	Favours (BCAA) Favours [PLA] Std. Mean Difference IV, Random, 95% Cl
Test for subaroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019	Std. Mean Difference	s), l <sup>2</sup> = SE 0.43	15.9% Weight 7.1%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78]	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
Test for subgroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016	2 = 1.19, df = 1 (P = 0.28 Std. Mean Difference 0.94 0.1	0.43 0.39	15.9% Weight 7.1% 7.4%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86]	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
Test for subgroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Leafmore et al 2012	Std. Mean Difference 0.94 0.1 0.1 0.1 0.1 0.1 0.1	0.43 0.63 0.52	15.9% Weight 7.1% 7.4% 5.5%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17]	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019	<sup>2</sup> = 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -17	0.43 0.39 0.63 0.53	Weight 7.1% 7.4% 5.5% 6.2% 5.5%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 (-3.21, -1.13] -1 70 [-23, -0.47]	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
Test for subaroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2010 Jackman et al 2010 Osmond et al 2019 Ra et al 2013	<sup>2</sup> = 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -1.7 -0.34	0.43 0.39 0.63 0.53 0.63 0.48	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.5% 6.6%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60]	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
Test for subgroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2018 (POST)	Std. Mean Difference Std. Mean Difference 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22	0.43 0.39 0.63 0.53 0.63 0.48 0.64	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.5% 6.6% 5.4%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03]	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2018 (PRST) Ra et al 2018 (PRE)	<sup>2</sup> = 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38	0.43 0.39 0.63 0.63 0.63 0.64 0.64	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.5% 5.5% 5.4% 5.4%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.33, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63]	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2013 Ra et al 2018 (PRE) Reule et al 2017	<sup>2</sup> = 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -0.34 -0.22 0.38 0.02	0.43 0.39 0.63 0.63 0.63 0.64 0.64 0.64 0.31	Weight 7.1% 7.4% 5.5% 6.2% 5.5% 6.6% 5.4% 5.4% 8.0%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.29, 0.17] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63]	Favours (BCAA) Favours (PLA) Std. Mean Difference IV, Random, 95% Cl
Test for subaroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2010 Jackman et al 2010 Osmond et al 2019 Ra et al 2013 Ra et al 2018 (POST) Ra et al 2017 VanDusseldorp et al 2018	<sup>2</sup> = 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59	<ul> <li>SE</li> <li>0.43</li> <li>0.39</li> <li>0.63</li> <li>0.63</li> <li>0.64</li> <li>0.64</li> <li>0.64</li> <li>0.31</li> <li>0.52</li> </ul>	Weight 7.1% 7.4% 5.5% 6.2% 5.5% 6.6% 5.4% 5.4% 8.0% 6.3%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.76] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.39, 0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57]	Favours [BCAA] Favours [PLA]
B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2013 Ra et al 2013 Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (PCST) Ra et al 2018 (	<sup>2</sup> 3 = 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -0.34 -0.22 0.38 0.02 -1.59 -0.5	0.43 0.63 0.63 0.63 0.63 0.64 0.64 0.64 0.64 0.52 0.51	Weight 7.1% 7.4% 5.5% 6.2% 5.5% 6.6% 5.4% 5.4% 8.0% 6.3% 6.3%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.67, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50]	Favours (BCAA) Favours (PLA)
B Study or Subgroup differences: Chi Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2018 (PRST) Ra et al 2018 (PRST) Ra et al 2018 (PRE) Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% C1) Hetersprenzity: Taula – 0.63: Chila	<sup>2</sup> 3-1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -0.34 -0.22 0.38 0.02 -1.59 -0.5 -0.551 df = 10 (P < 0.00)	5), I <sup>2</sup> = 5E 0.43 0.39 0.63 0.63 0.63 0.64 0.64 0.64 0.52 0.51 0.52 0.51	15.9% Weight 7.1% 7.4% 5.5% 6.6% 5.5% 6.6% 5.4% 8.0% 6.3% 6.3% 6.4% 6.4%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.33, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04]	Favours (BCAA) Favours (PLA)
B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2010 Jackman et al 2010 Osmond et al 2019 Ra et al 2013 Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (POST) Helerogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> = Test for overall effect: Z = 1.81 (P	<sup>2</sup> 3 5 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 = 36.51, df = 10 (P < 0.00 = 0.07)	SE 0.43 0.39 0.63 0.63 0.63 0.64 0.64 0.64 0.64 0.52 0.51	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.5% 6.6% 5.4% 8.0% 6.3% 6.3% 6.4% 69.9% = 73%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04]	Favours (BCAA) Favours (PLA)
B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2011 Ra et al 2013 Ra et al 2013 Ra et al 2013 Ra et al 2017 VanDusseldorp et al 2017 VanDusseldorp et al 2017 VanDusseldorp et al 2017 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> = Test for overall effect: Z = 1.81 (P 2.2.2 Cross-over	= 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 = 36.51, df = 10 (P < 0.00 = 0.07)	SE 0.43 0.39 0.63 0.63 0.63 0.64 0.64 0.64 0.51 0.51	15.9% Weight 7.1% 5.5% 6.2% 5.5% 6.6% 5.4% 5.4% 5.4% 6.3% 6.3% 6.4% 69.9% = 73%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04]	Favours (BCAA) Favours (PLA)
B Study or Subgroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2018 (PRE) Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> = Test for overall effect: Z = 1.81 (P 2.2.2 Cross-over Greer et al 2007 Lachu et al 2013	= 1.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 = 36.51, df = 10 (P < 0.00 = 0.07)	SE 0.43 0.63 0.63 0.63 0.63 0.64 0.64 0.64 0.51 0.51 0.51 0.1; l <sup>2</sup>	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.4% 6.6% 5.4% 6.6% 6.6% 6.3% 6.3% 6.3% 69.9% 5.4% 5.4%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.33, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.67, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.90 [-0.93, 0.23]	Favours (BCAA) Favours (PLA)
B     Study or Subgroup       2.2.1 RCP       Estoche et al 2019       Foure et al 2016       Howatson et al 2012       Jackman et al 2010       Osmond et al 2019       Ra et al 2013       Ra et al 2018 (PRE)       Reule et al 2017       VanDusseldorp et al 2018       Waldron et al 2017       Subtotal (95% CI)       Heterogeneity: Tau² = 0.63; Chi² =       Test for overall effect: Z = 1.81 (P       2.2.2 Cross-over       Greer et al 2007       Leahy et al 2013       Shimomura et al 2016 (Fermelo)	Std. Mean Difference 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 : 36.51, df = 10 (P < 0.00 = 0.07) -1.04 -0.3 -0.3	SE 0.43 0.39 0.63 0.63 0.64 0.64 0.64 0.64 0.64 0.64 0.64 0.64 1.52 0.51 001); l <sup>2</sup>	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.4% 6.6% 5.4% 6.6% 6.3% 6.3% 6.3% 6.3% 6.3% 6.8% 7.9%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.30 [-0.93, 0.33] 4 68 [8 03, -1.33]	Favours (BCAA) Favours (PLA)
Study or Subgroup       2.2.1 RCP       Estoche et al 2019       Foure et al 2016       Howatson et al 2012       Jackman et al 2010       Osmond et al 2019       Ra et al 2013       Ra et al 2018 (POST)       Ra et al 2018 (POST)       Ra et al 2017       VanDusseldorp et al 2017       Subtotat (95% CI)       Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> =       Test for overall effect: Z = 1.81 (P       2.2.2 Cross-over       Greer et al 2007       Leahy et al 2013       Shimomura et al 2006 (Female)	Std. Mean Difference 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 -36.51, df = 10 (P < 0.00 = 0.07) -1.04 -0.3 -4.68 -2.24	SE           0.43         0.39           0.63         0.63           0.63         0.63           0.64         0.64           0.61         0.52           0.51         0.51           001); I <sup>2</sup> Image: Comparison of the second	15.9% Weight 7.1% 7.4% 5.5% 6.6% 5.4% 8.0% 6.4% 6.4% 6.4% 69.9% = 73% 6.8% 7.9% 1.5% 5.9%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, 0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.67, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.30 [-0.93, 0.33] -4.68 [-8.03, -1.33] -2.24 [-3.8, -1 10]	Favours (BCAA) Favours (PLA)
B Study or Subgroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2013 Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (PCST) Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> = Test for overall effect: Z = 1.81 (P 2.2.2 Cross-over Greer et al 2007 Leahy et al 2013 Shimomura et al 2006 (Female) Shimomura et al 2006	Std. Mean Difference 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 = 36.51, df = 10 (P < 0.00 = 0.07)	SE           0.43         0.39           0.63         0.63           0.63         0.63           0.64         0.64           0.51         0.52           0.51         0.51           0.46         0.32           1.71         0.58           0.31         0.54	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.4% 5.4% 6.3% 6.3% 6.3% 6.3% 6.3% 5.9% 8.0%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.67, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.30 [-0.93, 0.33] -4.68 [-8.03, -1.33] -2.24 [-3.38, -1.10] -0.45 [-1.66, 0.16]	Favours (BCAA) Favours (PLA)
B Study or Subgroup differences: Chi Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2018 (PRE) Reule et al 2019 Ra et al 2018 (PRE) Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> = Test for overall effect: Z = 1.81 (P 2.2.2 Cross-over Greer et al 2007 Leahy et al 2013 Shimomura et al 2006 (Female) Shimomura et al 2006 (Female)	Std. Mean Difference 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 = 36.51, df = 10 (P < 0.00 = 0.07) -1.04 -0.3 -1.04 -0.3 -1.04 -0.3 -1.04 -0.3 -0.5	i),   <sup>2</sup> = SE 0.43 0.63 0.63 0.63 0.64 0.64 0.64 0.64 0.61 0.52 0.51 0.61 0.62 1.71 0.58 0.31	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.5% 6.6% 5.4% 5.4% 5.4% 6.3% 6.3% 6.3% 6.3% 6.3% 6.3% 6.3% 6.3	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.03 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.30 [-0.93, 0.33] -4.68 [-8.03, -1.33] -2.24 [-3.38, -1.10] -0.45 [-1.06, 0.16] -1.10 [-1.92, -0.28]	Favours (BCAA) Favours (PLA)
Test for subaroup differences: Chi B Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2010 Jackman et al 2010 Osmond et al 2019 Ra et al 2013 Ra et al 2018 (POST) Ra et al 2018 (POST) Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> = Test for overall effect: Z = 1.81 (P 2.2.2 Cross-over Greer et al 2007 Leahy et al 2013 Shimomura et al 2006 (Female) Shimomura et al 2006 (Semale) Shimomura et al 2006 Shimomura et al 2007 Shimomura et al 2006 Shimomura et al 2006 Shimomura et al 2007 Shimomura et al 2007 Shimomura et al 2007 Shimomura et al 2006 Shimomura et al 2007 Shimomura et al 2007 Shimomura et al 2007 Shimomura et al 2006 Shimomura et al 2006 Shimomura et al 2007 Shimomura et al 2007 Shimomura et al 2007 Shimomura et al 2007 Shimomura et al 200	■ 3.19, df = 1 (P = 0.28 <u>Std. Mean Difference</u> 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 = 36.51, df = 10 (P < 0.00 = 0.07) -1.04 -0.3 -4.68 -2.24 -0.45 = 15.19, df = 4 (P = 0.004 = 0.008)	<pre>)),  <sup>2</sup> = SE 0.43 0.39 0.63 0.63 0.63 0.64 0.64 0.64 0.64 0.51 0.51 0.51 0.51 0.51 0.52 0.51 0.51 0.52 0.51 0.53 0.53 0.53 0.63 0.64 0.64 0.52 0.51 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.53 0.53 0.53 0.64 0.54 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.51 0.52 0.53 0.53 0.53 0.54 0.55 0.55 0.51 0.52 0.51 0.52 0.53 0.53 0.53 0.52 0.51 0.52 0.51 0.52 0.5</pre>	15.9% Weight 7.1% 5.5% 6.2% 5.5% 6.6% 5.4% 6.8% 6.9.9% 6.8% 6.9.9% 1.5% 5.9% 8.0% 30.1%	Std. Mean Difference IV, Random, 95% CI 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.39, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.30 [-0.93, 0.33] -4.68 [-8.03, -1.33] -2.24 [-3.38, -1.10] -0.45 [-1.06, 0.16] -1.10 [-1.92, -0.28]	Favours (BCAA) Favours (PLA)
B         Study or Subgroup         2.2.1 RCP         Estoche et al 2019         Foure et al 2016         Howatson et al 2012         Jackman et al 2010         Osmond et al 2019         Ra et al 2018 (POST)         Ra et al 2018 (POST)         Ra et al 2018 (PRE)         Ruel et al 2017         VanDusseldorp et al 2018         Waldron et al 2017         Subtotal (95% CI)         Heterogeneity: Tau² = 0.63; Chi² =         Test for overall effect: Z = 1.81 (P         2.2.2 Cross-over         Greer et al 2007         Leahy et al 2013         Shimomura et al 2006 (Female)         Shimomura et al 2006 (Semale)         Shimomura et al 2010         Subtotal (95% CI)         Heterogeneity: Tau² = 0.56; Chi² =         Test for overall effect: Z = 2.64 (P	Std. Mean Difference 0.94 0.1 0.1 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 36.51, df = 10 (P < 0.00 = 0.07) -1.04 -0.3 -0.5 -1.04 -0.3 -0.5	)),   <sup>2</sup> = <u>SE</u> 0.43 0.63 0.63 0.63 0.64 0.64 0.64 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.51 0.53 0.63 0.63 0.64 0.64 0.51 0.51 0.51 0.54 0.54 0.54 0.55	15.9% Weight 7.1% 5.5% 6.6% 5.4% 8.0% 6.3% 8.0% 6.4% 69.9% = 73% 6.8% 7.9% 1.5% 5.9% 8.00% 6.4% 6.9.9%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.038 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.30 [-0.93, 0.33] -4.68 [-8.03, -1.33] -2.24 [-3.38, -1.10] -0.45 [-1.06, 0.16] -1.10 [-1.92, -0.28]	Favours (BCAA) Favours (PLA)
B         Study or Subgroup         2.2.1 RCP         Estoche et al 2019         Foure et al 2016         Howatson et al 2012         Jackman et al 2016         Howatson et al 2019         Ra et al 2018         Ra et al 2018 (POST)         Ra et al 2018 (POST)         Ra et al 2018 (PCST)         Ruel et al 2017         Subtotal (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.66; Chi <sup>2</sup> =         Shimomura et al 2006 (Female)         Shimomura et al 2010         Subtotal (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.66; Chi <sup>2</sup> =         Test for overall effect: Z = 2.64 (P         Total (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.67; Chi <sup>2</sup> =	Std. Mean Difference 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 -36.51, df = 10 (P < 0.00 = 0.07) -1.04 -0.3 -4.68 -2.24 -0.45 = 15.19, df = 4 (P = 0.004 = 0.008)	<pre>)),  <sup>2</sup> = <u>SE</u> 0.43 0.39 0.63 0.53 0.63 0.63 0.64 0.64 0.64 0.31 0.52 0.51 0.1);  <sup>2</sup> = 0.46 0.32 1.71 0.31 0.31</pre>	15.9% Weight 7.1% 5.5% 6.2% 5.5% 6.6% 5.4% 8.0% 6.4% 6.9.9% 1.5% 6.8% 6.4% 6.9.9% 1.5% 6.4% 6.9.9% 1.5	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.30 [-0.93, 0.33] -4.68 [-8.03, -1.33] -2.24 [-3.38, -1.10] -0.45 [-1.06, 0.16] -1.10 [-1.92, -0.28] -0.69 [-1.14, -0.24]	Favours (BCAA) Favours (PLA)
Test for subaroup differences: Chi Test for subaroup differences: Chi Study or Subgroup 2.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Osmond et al 2019 Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (POST) Ra et al 2018 (PCST) Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.63; Chi <sup>2</sup> = Test for overall effect: Z = 1.81 (P 2.2.2 Cross-over Greer et al 2007 Leahy et al 2013 Shimomura et al 2006 (Female) Shimomura et al 2006 (Kemale) Shimomura et al 2006 (Kemale) Shimomura et al 2006 (Male) Shimomura et al 2006 (Male) Shimomura et al 2006 (Male) Shimomura et al 2010 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.56; Chi <sup>2</sup> = Test for overall effect: Z = 2.64 (P	Std. Mean Difference 0.94 0.1 -1.06 -2.17 -1.7 -0.34 -0.22 0.38 0.02 -1.59 -0.5 -36.51, df = 10 (P < 0.00 = 0.07) -1.04 -0.3 -4.68 -2.24 -0.45 = 15.19, df = 4 (P = 0.004 = 0.008) = 0.003	<pre>)),  * = SE 0.43 0.39 0.63 0.53 0.63 0.64 0.64 0.64 0.64 0.64 0.64 0.64 0.64</pre>	15.9% Weight 7.1% 7.4% 5.5% 6.2% 5.5% 6.2% 5.4% 5.4% 5.4% 6.3% 6.3% 6.3% 6.3% 6.3% 6.3% 6.3% 6.3% 6.2% 7.4% 100.0% 2 = 72%	Std. Mean Difference IV, Random, 95% Cl 0.94 [0.10, 1.78] 0.10 [-0.66, 0.86] -1.06 [-2.29, 0.17] -2.17 [-3.21, -1.13] -1.70 [-2.93, -0.47] -0.34 [-1.28, 0.60] -0.22 [-1.47, 1.03] 0.38 [-0.87, 1.63] 0.02 [-0.59, 0.63] -1.59 [-2.61, -0.57] -0.50 [-1.50, 0.50] -0.52 [-1.08, 0.04] -1.04 [-1.94, -0.14] -0.30 [-0.93, 0.33] -4.68 [-8.03, -1.33] -2.24 [-3.38, -1.10] -0.45 [-1.06, 0.16] -1.10 [-1.92, -0.28] -0.69 [-1.14, -0.24]	Favours (BCAA) Favours (PLA)

#### Figure 3

196x263mm (600 x 600 DPI)

А				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
3.1.1 RCP					
Estoche et al 2019	0.1	0.41	9.5%	0.10 [-0.70, 0.90]	
Foure et al 2016	-0.08	0.39	10.5%	-0.08 [-0.84, 0.68]	
Howatson et al 2012	0.42	0.59	4.6%	0.42 [-0.74, 1.58]	
Jackman et al 2010	0.02	0.41	9.5%	0.02 [-0.78, 0.82]	
Osmond et al 2019	-0.8	0.54	5.5%	-0.80 [-1.86, 0.26]	
Reule et al 2017	-0.16	0.31	16.6%	-0.16 [-0.77, 0.45]	
VanDusseldorp et al 2018	0.09	0.45	7.9%	0.09 [-0.79, 0.97]	
Waldron et al 2017 Subtotal (95% CI)	0.87	0.53	5.7% 69.6%	0.87 [-0.17, 1.91] 0.01 [-0.28, 0.31]	•
Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 5.80, df = 7 (P = 0	.56); F	<sup>2</sup> = 0%	• / •	T
Test for overall effect: Z = 0.	08 (P = 0.94)	,.			
3.1.2 Cross-over					
Gee et al 2016	0.26	0.34	13.8%	0.26 [-0.41, 0.93]	
Greer et al 2007	0.3	0.31	16.6%	0.30 [-0.31, 0.91]	
Subtotal (95% CI)	ou in		30.4%	0.28 [-0.17, 0.73]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Test for overall effect: Z = 1.	Chi <sup>2</sup> = 0.01, df = 1 (P = 0 23 (P = 0.22)	1.93); F	2 = 0%		
Total (95% CI)			100.0%	0.09 [-0.15, 0.34]	•
Heterogeneity: Tau <sup>2</sup> = 0.00:	Chi <sup>2</sup> = 6.77, df = 9 (P = 0	.66); I	<sup>2</sup> = 0%		
Test for overall effect: Z = 0.	74 (P = 0.46)	,			
Test for subaroup difference	s: Chi <sup>2</sup> = 0.97. df = 1 (P :	= 0.33	). I <sup>2</sup> = 0%		Favours [BCAA] Favours [PLA]
В				Otd Maan Difference	Otd Mann Difference
B Study of Subgroup	Std Maan Difference	9E	Woight	Std. Mean Difference	Std. Mean Difference
B Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% Cl
B Study or Subgroup 3.2.1 RCP	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estore et al 2019 Estore et al 2019	Std. Mean Difference	SE 0.41	9.6%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Hourdsnot et al 2012	Std. Mean Difference -0.11 -0.17 0.19	SE 0.41 0.39	9.6%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.32]	Std. Mean Difference IV, Random, 95% Cl
B Study or Subgroup 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 lackman et al 2010	Std. Mean Difference -0.11 -0.17 0.19 0.16	SE 0.41 0.39 0.58 0.41	9.6% 10.1% 6.3%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.65]	Std. Mean Difference IV, Random, 95% Cl
B Study or Subgroup 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kophet et al 2016	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2	SE 0.41 0.39 0.58 0.41 0.37	9.6% 10.1% 6.3% 9.6%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.29 [-0.53, 0.93]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2019	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2 2.47	SE 0.41 0.39 0.58 0.41 0.37 0.73	9.6% 10.1% 6.3% 9.6% 10.6%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [10 (4.3 99]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2016 Osmond et al 2019 Beule et al 2017	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21	SE 0.41 0.39 0.58 0.41 0.37 0.73 0.31	9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2016 Osmond et al 2019 Reule et al 2017 VanDusseldorn et al 2018	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21	SE 0.41 0.39 0.58 0.41 0.37 0.73 0.31 0.45	9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3% 8 7%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Osmond et al 2019 Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017	<u>Std. Mean Difference</u> -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.18	SE 0.41 0.39 0.58 0.41 0.37 0.73 0.31 0.45 0.5	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3% 8.7% 7.7%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2019 Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI)	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.21	SE 0.41 0.39 0.58 0.41 0.37 0.73 0.31 0.45 0.5	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3% 8.7% 7.7% 79.3%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.10;	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.18 Chi <sup>2</sup> = 12.48, df = 8 (P =	SE 0.41 0.39 0.58 0.41 0.37 0.73 0.31 0.45 0.5 0.13);	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3% 8.7% 7.7% 79.3%   <sup>2</sup> = 36%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2010 Osmond et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.10; Test for overall effect: Z = 0.	<u>Std. Mean Difference</u> -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.21 0.21 0.21 0.21 0.21 0.21	SE 0.41 0.39 0.58 0.41 0.37 0.73 0.31 0.45 0.5 0.13);	Weight           9.6%           10.1%           6.3%           9.6%           10.6%           4.5%           12.3%           8.7%           7.7%           79.3%            ² = 36%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51]	Std. Mean Difference IV, Random, 95% CI
B <u>study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2019 Reule et al 2019 Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.10; Test for overall effect: Z = 0.	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.18 Chi <sup>p</sup> = 12.48, df = 8 (P = 87 (P = 0.38)	SE 0.41 0.39 0.58 0.41 0.37 0.73 0.31 0.45 0.5 0.13);	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3% 8.7% 7.7% 79.3%   <sup>2</sup> = 36%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51]	Std. Mean Difference IV, Random, 95% Cl
B <u>Study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2019 Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.10; Test for overall effect: Z = 0. 3.2.2 Cross-over Greer et al 2007	<u>Std. Mean Difference</u> -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.21 0.18 Chi <sup>2</sup> = 12.48, df = 8 (P = 87 (P = 0.38) 0.59	SE 0.41 0.39 0.58 0.41 0.37 0.73 0.31 0.45 0.5 0.13); 0.37	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 12.3% 8.7% 7.7% 79.3%  ² = 36% 10.6%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51] 0.59 [-0.14, 1.32]	Std. Mean Difference IV, Random, 95% Cl
B <u>study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2019 Reule et al 2019 Reule et al 2019 Rubarto et al 2018 Waldron et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.10; Test for overall effect: Z = 0. 3.2.2 Cross-over Greer et al 2007 Shimomura et al 2010 Subtotal (95% CI)	<u>Std. Mean Difference</u> -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.18 Chi <sup>p</sup> = 12.48, df = 8 (P = 87 (P = 0.38) 0.59 1.09	SE 0.41 0.39 0.58 0.37 0.73 0.31 0.45 0.5 0.13); 0.37 0.39	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3% 8.7% 79.3% 12 = 36% 10.6% 10.1% 20.7%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.221 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51] 0.59 [-0.14, 1.32] 1.09 [0.33, 1.85] 0.83 [0.30, 1.35]	Std. Mean Difference IV, Random, 95% CI
B <u>study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.10; Test for overall effect: Z = 0. 3.2.2 Cross-over Greer et al 2007 Shimomura et al 2010 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00:	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.18 Chi <sup>2</sup> = 12.48, df = 8 (P = 87 (P = 0.38) 0.59 1.09 Chi <sup>2</sup> = 0.87, df = 1 (P = 0)	SE 0.41 0.39 0.58 0.37 0.37 0.5 0.13); 0.37 0.39 0.37; 0.39	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3% 8.7% 7.7% 79.3% I <sup>2</sup> = 36% 10.6% 10.1% 20.7% <sup>2</sup> = 0%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51] 0.59 [-0.14, 1.32] 1.09 [0.33, 1.85] 0.83 [0.30, 1.35]	Std. Mean Difference IV, Random, 95% Cl
B <u>study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.10; Test for overall effect: Z = 0. 3.2.2 Cross-over Greer et al 2010 Shimomura et al 2010 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00; Test for overall effect: Z = 3.	$\begin{array}{c} \text{Std. Mean Difference} \\ & -0.11 \\ & -0.17 \\ & 0.19 \\ 0.16 \\ & 0.2 \\ 2.47 \\ & -0.21 \\ & 0.21 \\ & 0.21 \\ & 0.21 \\ & 0.25 \\ & 0.27 \\ & 0.21 \\$	SE 0.41 0.39 0.58 0.41 0.37 0.31 0.45 0.5 0.13); 0.37 0.39 0.35); F	Weight           9.6%           10.1%           6.3%           9.6%           10.6%           4.5%           79.3%           12 = 36%           10.6%           10.1%           20.7%           2 = 0%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.67, 1.09] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51] 0.59 [-0.14, 1.32] 1.09 [0.33, 1.85] 0.83 [0.30, 1.35]	Std. Mean Difference IV, Random, 95% CI
B <u>study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2019 Reule et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.10; Test for overall effect: Z = 0. 3.2.2 Cross-over Greer et al 2007 Shimomura et al 2010 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00; Test for overall effect: Z = 3. Total (95% CI)	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	SE 0.41 0.39 0.58 0.41 0.37 0.31 0.45 0.5 0.13); 0.45 0.45 0.45 0.45 0.45 0.5 0.13); F	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 4.5% 12.3% 8.7% 79.3% I <sup>2</sup> = 36% 10.6% 10.1% 20.7% <sup>2</sup> = 0%	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51] 0.59 [-0.14, 1.32] 1.09 [0.33, 1.85] 0.83 [0.30, 1.35] 0.31 [-0.03, 0.66]	Std. Mean Difference IV, Random, 95% CI
B <u>study or Subgroup</u> 3.2.1 RCP Estoche et al 2019 Foure et al 2016 Howatson et al 2012 Jackman et al 2010 Kephart et al 2010 Kephart et al 2017 VanDusseldorp et al 2018 Waldron et al 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00; Test for overall effect: Z = 3. Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.01; Test for overall effect: Z = 3. Total (95% CI)	Std. Mean Difference -0.11 -0.17 0.19 0.16 0.2 2.47 -0.21 0.21 0.21 0.18 Chi <sup>2</sup> = 12.48, df = 8 (P = 87 (P = 0.38) 0.59 1.09 Chi <sup>2</sup> = 0.87, df = 1 (P = 0 08 (P = 0.08) Chi <sup>2</sup> = 18.96, df = 10 (P = 7 76 (P = 0.08)	SE 0.41 0.39 0.58 0.47 0.73 0.37 0.5 0.13); 0.39 0.39 .35); F	Weight 9.6% 10.1% 6.3% 9.6% 10.6% 12.3% 8.7% 7.3% 79.3% 12 = 36% 10.6% 10.1% 20.7% 2 = 0% 100.0% ; 1 <sup>2</sup> = 479	Std. Mean Difference IV, Random, 95% CI -0.11 [-0.91, 0.69] -0.17 [-0.93, 0.59] 0.19 [-0.95, 1.33] 0.16 [-0.64, 0.96] 0.20 [-0.53, 0.93] 2.47 [1.04, 3.90] -0.21 [-0.82, 0.40] 0.21 [-0.67, 1.09] 0.18 [-0.80, 1.16] 0.16 [-0.20, 0.51] 0.59 [-0.14, 1.32] 1.09 [0.33, 1.85] 0.83 [0.30, 1.35] 0.31 [-0.03, 0.66] 6	Std. Mean Difference IV, Random, 95% CI

#### Figure 4

196x219mm (300 x 300 DPI)