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Branched-Chain Amino Acids Supplementation and Post-Exercise Recovery: An Overview of Systematic Reviews

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ABSTRACT

Objective: This overview of systematic reviews (OoSRs) aimed, firstly, to systematically review, summarize, and appraise the findings of published systematic reviews with or without meta-analyses that investigate the effects of branched-chain amino acids (BCAA) on post-exercise recovery of muscle damage biomarkers, muscle soreness, and muscle performance. The secondary objective was to re-analyze and standardize the results of meta-analyses using the random-effects Hartung-Knapp-Sidik-Jonkman (HKSJ) method.

Methods: The methodological quality of the reviews was assessed using A Measurement Tool to Assess Systematic Reviews 2.We searched on five databases (*i.e.,* PubMed, Web of Science, Scopus, SPORTDiscus, ProQuest) for systematic reviews with or without meta-analyses that investigated the effects of BCAA supplementation on the post-exercise recovery of muscle damage biomarkers, muscle soreness, and muscle performance.

Results: Eleven systematic reviews (seven with meta-analyses) of individual studies were included. Evidence suggests BCAA ingestion attenuates creatine kinase (CK) levels (medium effects) and muscle soreness (small effects) immediately post-exercise and accelerates their recovery process, with trivial-to-large effects for CK levels and small-to-large effects for muscle soreness. BCAA supplementation has no effect on lactate dehydrogenase, myoglobin, and muscle performance recovery. The re-analyses with HKSJ method using the original data reported a slight change in results significance, concluding the same evidence as the original results. The major flaws found in the analyzed reviews were the absence of justification for excluding studies, and the lack of provision of sources of funding for primary studies and sources of conflict of interest and/or funding description.

Conclusions: BCAA supplementation is an effective method to reduce post-exercise muscle damage biomarkers, particularly CK levels, and muscle soreness, with no effect on muscle performance. Future systematic reviews with/without meta-analyses, with greater methodological rigor, are needed.

KEY POINTS

- This is the first overview of systematic reviews investigating the impact of BCAA supplementation on muscle damage biomarkers, muscle soreness, and muscle performance post-exercise recovery.
- BCAA supplementation reduces creatine kinase levels and muscle soreness, especially when consuming a high dose of BCAA longitudinally.
- BCAA supplementation has no effect on muscle performance post-exercise recovery.

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Introduction

Branched-chain amino acids (BCAA: leucine, isoleucine, and valine) comprise almost 50% of all EAAs in food and 35% of the total content of essential amino acids (EAAs) in muscle proteins (1, 2). Moreover, BCAA components are catabolized initially in skeletal muscle, while other amino acids are catabolized in the liver (1). BCAA play a crucial role in muscle growth and repair (3) and are commonly supplemented by athletes and bodybuilders to enhance performance and promote muscle hypertrophy (3).

One of the most well-established effects of BCAA supplementation is the ability to enhance muscle protein synthesis (MPS) (4), which is the process by which muscle fibers repair and grow after exercise (4). Therefore, BCAA directly regulate protein turnover in muscle cells, reversing the catabolic and anti-anabolic consequences of exercise-included muscle damage (EIMD) (5). Leucine (6), in particular, is identified as (i) a crucial regulator of mTOR signaling and translation initiation (7) and (ii) a possible promoter in the recovery process of damaged muscle tissues (8). Additionally, BCAA are major precursors of tricarboxylic acid cycle intermediates *via* acetyl-CoA and succinyl-CoA (9). BCAA can also be used as an energy source during endurance exercise (10) and can similarly reduce the muscle damage resulting from intense exercise (11). BCAA supplementation also reduces muscle soreness and inflammation (12), which can reduce recovery time after EIMD. This may be due to BCAA ability to decrease enzyme levels and inflammatory markers associated with muscle damage (12). BCAA supplementation may improve physical performance and recovery between workouts, potentially leading to improved exercise performance (13).

The number of systematic reviews (SRs) with or without meta-analyses on this topic has increased in recent years (8, 14–22). Despite the availability of SRs with/without meta-analyses on the effects of BCAA supplementation in athletes and physically active individuals, the quality and scope of these reviews are inconsistent.

As the next step, we considered an overview of SRs (OoSRs, also called Umbrella Review). The OoSRs is a common type of evidence synthesis defined as a review that uses explicit and systematic methods to search for and identify multiple SRs on a similar topic in order to extract and analyse results across important outcomes (23). We opted for this approach as it provides the most effective method to appraise and present the current body of evidence on the association of BCAA supplementation and muscle damage biomarkers and muscle soreness recovery post-EIMD. This type of work can methodologically evaluate and combine data from various systematic reviews that are relevant to BCAA, giving us a broader scope of understanding (24–26). By doing so, we can also identify gaps in the existing literature, which can guide us in areas where new reviews are urgently needed (27). Finally, an OoSRs on the impact of BCAA on post-exercise muscle recovery, muscle damage biomarkers, and muscle soreness would be a valuable resource for sports scientists, coaches, athletes, and anyone else interested in this topic. It would offer an updated and comprehensive overview of the association between BCAA supplementation and muscle recovery after EIMD, providing useful insights for sports scientists, coaches, clinicians, athletes, and other interested individuals. Following a thorough scoping of the electronic databases (i.e., PROSPERO, Cochrane Database of Systematic Reviews, PubMed, Web of Science, and Scopus), no existing or ongoing OoSRs specifically written in the English language were found on the above-mentioned topic.

Therefore, this study aimed to *(i)* provide a summary of the findings from existing SRs with/without meta-analyses regarding the effects of BCAA supplementation on post-exercise recovery, *(ii)* evaluate the methodological quality of these SRs, and *(iii)* provide recommendations for future research on the consumption of BCAA in individuals engaged in physical activity.

Methods

The present OoSRs was conducted based on the Cochrane Guide for Overviews of Reviews (25) and reported in accordance with the Preferred Reporting Items for Overviews of Systematic Reviews Checklists (PRIOR) (28). Inclusion criteria were chosen using the PICOS model (*Population:* Healthy active individuals (i.e., physically active individuals, competitive athletes), with no restrictions on sex, age, or sports modalities; *Intervention:* BCAA supplementation; *Comparator:* Placebo or control group/condition; *Outcomes:* Any outcome indicative of the post-exercise recovery; and *Study design:* Systematic review with/without meta-analysis) (Table 1).

Search strategy, study selection, and data extraction

The systematic literature search was conducted using five online databases (PubMed, Web of Science, Scopus, SPORTDiscus, and ProQuest) from database inception to January 13th, 2023. The full research strategy and keywords were presented in the online Supplementary Table S1. References of all included papers were manually screened for additional relevant reviews. Google Scholar was searched on June 25th, 2023, for potential published reviews.

Duplicated articles were removed using the Endnote software (version 20). All articles were screened by title, abstract, and full text using the PICOS inclusion criteria. The following data were extracted and presented in Table S3: (i) authors and year of publication, (ii) the number of studies, (iii) the pooled sample size, (iv) analysis, (v) outcomes measure, (vi) results, and (vii) the certainty of evidence. The

Table 1. PICOS model used in this overview of systematic reviews.

Parameter	Inclusion criteria
Population	Healthy active individuals, with no restrictions on sex, age, or sports modalities.
Intervention	BCAAs supplementation (Acute or Chronic supplementation)
Comparator	Placebo or control group/condition
Outcomes	Muscle performance, muscle damage biomarkers (i.e., CK, LDH, myoglobin), muscle soreness (i.e., VAS)
Study design	Systematic review and meta-analysis.

BCAAs: Branched-chain amino acids; MVC: CK: Creatine kinase; LDH: Lactate dehydrogenase; VAS: Visual analogue scale.

selection process and data extraction were conducted by two authors independently. After each step, the spreadsheets' accuracy was double-checked by the authors, and any disagreements were solved by discussion between the two authors.

Methodological quality assessment

The methodological quality of the SRs was assessed using the AMSTAR2 (A MeaSurement Tool to Assess Systematic Reviews) (29) with 16-item. Seven items are considered critical, and three items concern meta-analytical methods and are not applicable for SRs without accompanying meta-analysis (Table S4). The AMSTAR2 rates SRs as critically low (more than one critical weakness, with or without noncritical weaknesses), low (one critical weakness, with or without noncritical weaknesses), moderate (no critical weakness, with more than one non-critical weakness), or high quality (neither critical nor non-critical weaknesses) (29). AMSTAR2 was conducted independently by two authors, with any disagreements solved by discussion between the two authors.

GRADE criteria can be applied to SRs (30). However, as this approach was originally designed for empirical studies, there is a lack of pertinent guidance on how this is best performed (31, 32). Therefore, GRADE assessments were not performed for the included reviews.

Overlap of included studies

The degree of overlap was quantified using the corrected covered area (CCA) method (33). The CCA is calculated by dividing the frequency of repeated occurrences of index studies (first occurrence of a primary study) in other reviews (of the same domain) by the product of the number of index studies and the number of reviews, minus the number of reviews. The CCA is represented as a percentage between 0 and 100%. A CCA of 0–5% is considered a slight overlap, 6–10% moderate overlap, 11–15% high overlap, and more than 15% very high overlap (33). To visualize pairs of overlapping SRs in each domain, a heatmap was generated using the "ccaR" package in the R programming language (https://github.com/thdiakon/ccaR) (34, 35). Additional information regarding the heatmap is illustrated in Figures S1–S3.

Data synthesis

For the SRs using narrative synthesis, we quantified the number of studies specific to outcomes demonstrating statistically significant favorable differences. These differences were defined as those reported by the SRs. For each meta-analysis, the pooled number of participants, estimate effect (i.e., standardized mean difference (SMD) or mean difference (MD)), and lower and upper 95% confidence interval (95% CI) for each outcome were extracted from the individual studies, for each outcome at each time point. For unstandardized estimate effects (i.e., MD), we recalculated the SMDs and their standard error (SE) using MD, lower and upper 95% CI, and sample size values of each individual study using Comprehensive Meta-Analyses software (version 3, Biostat, Englewood, USA) (36). All re-analyses were processed using R programming language (version 4.2.1) with the "Metafor" package (version 3.8.1) (37). In order to standardize all SMDs (of the original pooling method) with the same pooling method, we re-analyzed the SMDs utilizing a random-effects model using restricted maximum likelihood (REML) estimator with the Hartung-Knapp-Sidik-Jonkman (HKSJ) method (38). The 95% prediction interval (95% PI) for each outcome was calculated (39) using R programming language (version 4.2.1) SMDs were classified as <0.20 trivial, 0.20–0.50 small, 0.50–0.80 medium, and ≥0.80 large effects (40). The statistical significance level was set at $p < 0.05$ for all analyses. The level of certainty (or confidence) in the evidence collected was presented in Table S6 outlining the findings, using a color-coding system of red, orange, and green to aid visual interpretation (41).

Results

Study selection

A total of 65 articles were identified *via* online databases. A total of 36 duplicates were removed. After screening 29 articles based on title and abstract, 17 were excluded. After a careful review of full-text articles, two reviews were excluded, and nine reviews were included. The list of excluded studies is presented in Table S2. An additional search on Google scholar identified one review, resulting in a total of 10 reviews included in this OoSRs. Three studies used narrative synthesis, three studies used meta-analysis, and four studies used both narrative synthesis and meta-analysis (Figure 1). The agreement between reviewers during study selection was high at the title and abstract screening stage (% of agreement = 98%), the full text review stage (% of agreement = 100%), and the Google Scholar search (% of agreement = 100%).

Studies characteristics

A summary of the included reviews is presented in Table S3. The included reviews were published between 2017–2022. The number of included original studies ranged from 5–23 (11 on average), and the sample sizes were between 93 and 479 participants. These reviews investigated the effect of BCAA supplementation on post-exercise recovery of muscle damage biomarkers (8, 14, 16–19, 21, 22), muscle soreness (8, 14, 15, 17, 19, 21), and muscle performance (8, 14, 18, 22). For data extraction, the agreement among authors was 97%.

The methodological quality assessment

The AMSTAR2 of the included reviews is summarized in Table S4, reporting low and critically low in four and six reviews, respectively. The failure to supply a list of excluded studies (Item 7) is a common critical flaw in all reviews. Five reviews performed the registration of the review protocol in

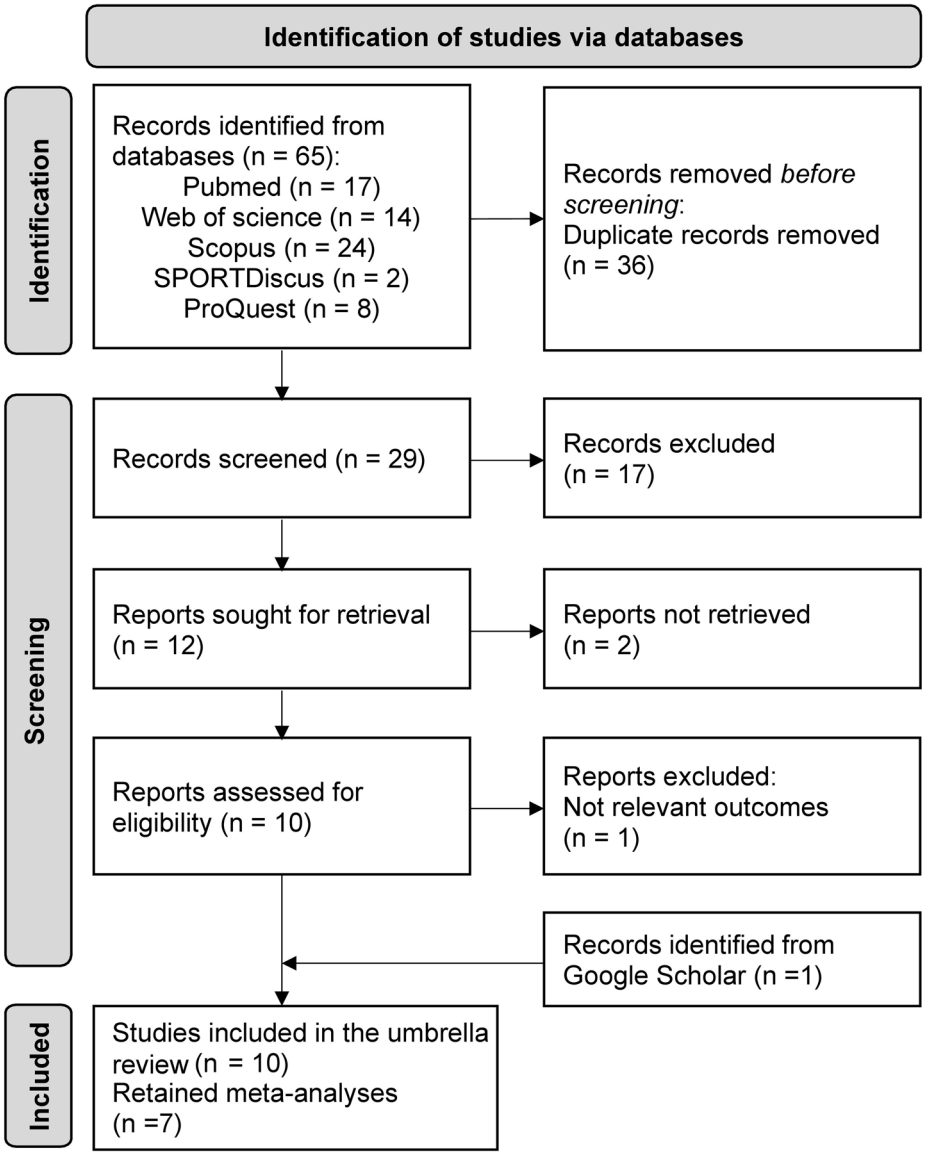

Figure 1. PRISMA flowchart of searching strategy and studies selection.

PROSPERO database or other engines (Item 2). All reviews used a comprehensive literature search strategy at least in one database (Item 4). One systematic review did not assess the risk of bias in the included studies (Item 9). The risk of bias in primary studies was not accounted for when interpreting/discussing the results in two SRs (Item 13). Except for one systematic review and meta-analysis, the research questions and inclusion criteria include the components of PICO (Item 1) in the remaining reviews. Four reviews provided an explanation related to the choice of study design for inclusion in the review (Item 3). One systematic review and one systematic review and meta-analysis did not perform the study selection and data extraction in duplicate (Items 5 and 6). All reviews described the primary studies in detail (Item 8). However, all reviews did not report sources of funding for primary studies (Item 10) and sources of conflict of interest and/or describe any funding (Item 16). Four reviews did not provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the reviews (Item 14). Three SRs could not be assessed using items 11, 12, and 15, due to the absence of meta-analyses. All meta-analyses used the appropriate method for the statistical combination of results (Item 11). Three meta-analyses did not assess the potential impact of risk of bias for included studies (Item 12), and two meta-analyses assessed publication bias and discussed its impact on the results (Item 15). Overall, agreement among reviewers for all items was 97.8%.

Certainty of evidence

The certainty of evidence was not conducted in any of the included SRs with/without meta-analyses of our OoSRs.

Overlap of the included studies

The results of the overlap of the included SRs are presented in Table S5. The overlap was very high in the reviews relating to (i) muscle damage biomarkers (CCA = 23.8%), (ii)

muscle soreness (CCA = 22.3%), and (iii) muscle performance (CCA = 33.3%). The CCAs by pair of reviews for all comparisons are presented in Figures S1–S3.

Results of narrative synthesis

The effects of BCAA supplementation on muscle damage biomarkers, muscle soreness, and muscle performance recovery post-exercise were systematically reviewed in five (8, 16, 18, 19, 22), five (8, 18–20, 22), and three (8, 18, 22) reviews, respectively. Fifteen of 28, 17 of 30, and 7 of 16 studies reported positive effects of BCAA ingestion on post-exercise recovery muscle damage biomarkers, muscle soreness, and muscle performance, respectively.

Results of meta-analyses

The effects of BCAA supplementation on muscle damage biomarkers (i.e., CK and LDH levels), muscle soreness, and muscle performance across various time points varied from <24 to 96 h post-exercise, and are displayed in Table S5 and Figures 2 and 3. Positive effects were reported on CK levels at <24 (16, 17, 21), 24 (17, 19, 21), and 48 h (17) post-exercise. However, two SRs and meta-analyses revealed no effects on CK levels at <24 (19), 48 (19, 21), and 72 h (19) post-exercise. Furthermore, no effects were reported on LDH levels at <24 (16, 21), 24 (17, 19, 21), and 48 h (17, 19, 21) post-exercise. Doma et al. (14) averaged all muscle damage biomarkers and analyzed them as one parameter. The authors reported a positive effect at 48 h, but not at 24 h post-exercise (14). Additionally, positive effects on muscle soreness at <24 (17), 24 (14, 19, 20), 48 (14, 19), and 72 h (19, 20) post-exercise were reported. Likewise, Fedewa et al. (15) reported a significant overall effect on muscle soreness and positive effects from 24 to 96 h post-exercise. Nevertheless, no effects were identified for muscle soreness at <24 (19, 21), 24 (17, 21), 48 (17, 20,21), 72 (21), and 96 h (19–21) post-exercise. Only Doma et al. (14) examined the effects of BCAA supplementation on muscle performance recovery and revealed a non-significant effect vs. the placebo/control intervention. None of the included SRs and meta-analyses reported the 95% PI.

Results of subgroup meta-analyses

Three meta-analyses performed subgroup analyses for muscle damage biomarkers, muscle soreness, and muscle performance (Table S2). Hormoznejad et al. (16) investigated the effect of supplementation period on CK levels and reported a favorable effect of long-term vs. short-term supplementation trials. Doma et al. (14) analyzed the effect of the study design on muscle damage biomarkers, muscle soreness, and muscle performance. The authors reported favorable effects in randomized controlled placebo compared to crossover trials in muscle damage biomarkers (14). Studies with a crossover study design revealed better improvement than the randomized controlled placebo trial for muscle soreness and muscle performance (14). One meta-analysis (20) investigated the effects of fitness levels, supplementation period,

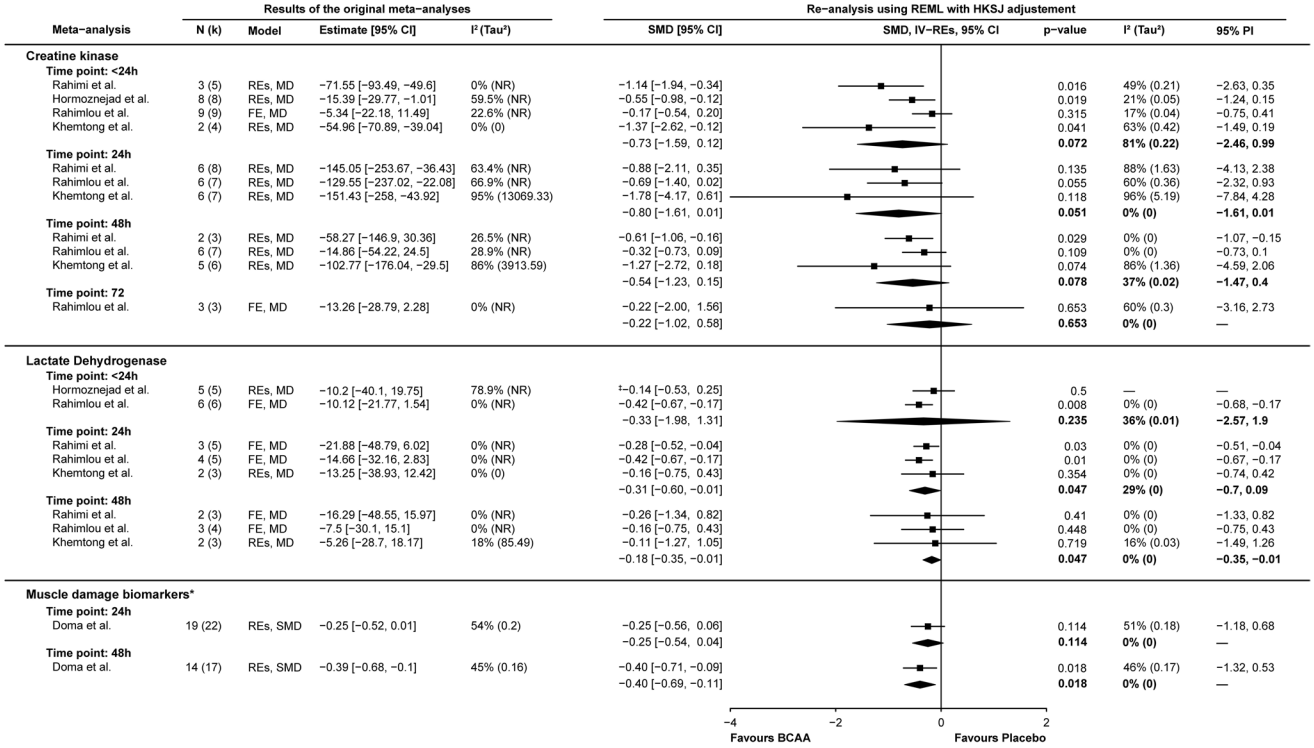

Figure 2. Summary of the original results of meta-analyses and the re-analyzed results of the estimate effects for muscle damage biomarkers. N: Number of studies; k: Number of effects; MD: Mean difference; SMD: Standardized mean difference; CI: Confidence interval; PI: Prediction interval; REML: Restricted maximum likelihood; HKSJ: Hartung-Knapp-Sidik-Jonkman method; REs: Random-effects model; FE: Fixed-effect model; NR: Not reported; Bold values: Significant effect for BCAA supplementation, * = All muscle damage biomarkers were averaged in each individual study and analyzed as one outcome, ‡ = Overall SMD recalculated from the overall MD with CMA software.

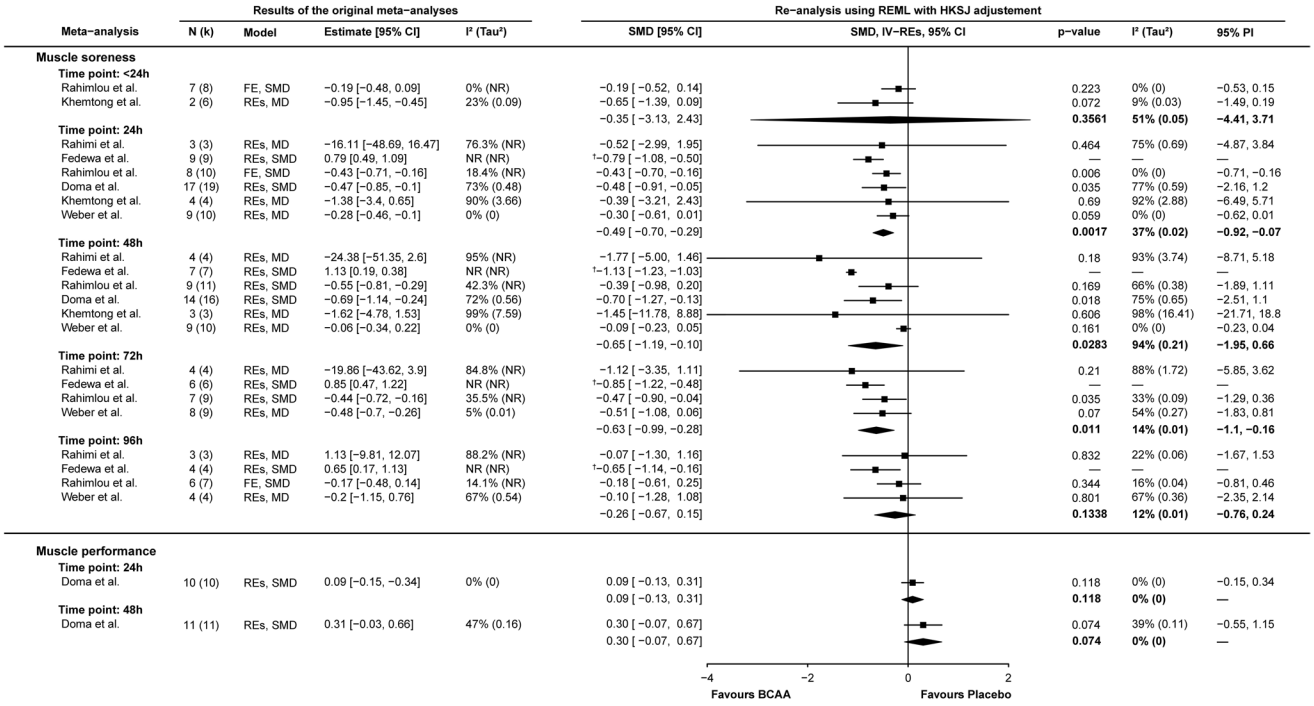

Figure 3. Summary of the original results of meta-analyses and the re-analyzed results of the estimate effects for muscle soreness and muscle performance. N: Number of studies; k: Number of effects; CI: Confidence interval; PI: Prediction interval; REML: Restricted maximum likelihood; HKSJ: Hartung-Knapp-Sidik-Jonkman method; REs; Random-effects model; FE: Fixed-effect model; MD: Mean difference; SMD: Standardized mean difference; NR: Not reported, † = Original SMDs were converted into negative effect to fit our analysis.

BCAA dosage, and exercise severity on muscle soreness. The authors revealed favorable findings for trained vs. untrained individuals, long-term vs. acute and short-term supplementation, higher vs. lower dose at 24 h and lower vs. higher dose at 72 h, and for moderate vs. light and severe exercises at 24 h and for light vs. moderate and severe exercises at 72 h (20).

Re-analysis of meta-analyses

The re-analyzed estimate effect (SMD (95% CI)) using the original pooling method, *p*value, I^2, tau^2, and 95% PI of meta-analyses are displayed in Table S5. The standardizing of estimate effects to SMDs slightly varies the significance for CK levels (17) at 24h and LDH levels (19) at <24 and 24h post-exercise.

The re-analyzed estimate effect (SMD (95% CI)) using the REML estimator with HKSJ method, *p*value, I^2, tau^2, and 95% PI of meta-analyses are displayed in Table S5 and Figures 2 and 3. Our data re-analysis indicated medium-to-large effects of BCAA supplementation on CK levels at <24 (16, 17, 21) and 48 h (14, 21) post-exercise. However, non-significant small-to-large overall effects were reported at all time points. Likewise, small effects were reported on LDH levels at <24 (19) and 24 h (19, 21). Significant trivial-to-small overall effect of BCAA supplementation on muscle damage biomarkers at 24 and 48 h post-exercise. Doma et al. (14) reported a small effect on muscle damage biomarkers at 48 h, but not at 24 h post-exercise. Moreover, small-to-large effects were reported on muscle soreness at 24 (14, 19), 48 (14), and 72 h (19) post-exercise, with significant small-to-moderate overall effects at 24, 48, and 72 h post-exercise. However, numerous meta-analyses reported no effects of BCAA supplementation on CK (19) and LDH (16, 17) levels and muscle soreness (17, 20, 21) respectively, at all-time points. Furthermore, no effects of BCAA supplementation were found on muscle performance at all time points (14).

Summary of evidence

A summary of evidence regarding the effectiveness of BCAA supplementation on various biomarkers of muscle damage, muscle soreness, and muscle performance is provided in Table S7. This summary shows BCAA supplementation has positive effects marked by a reduction of muscle soreness and CK levels, non-significant effects on LDH levels, and muscle performance.

Discussion

Main findings

The current OoSRs aimed to provide a systematic overview of the effects of BCAA supplementation on post-exercise recovery of muscle damage biomarkers, muscle soreness, and muscle performance. The main finding of this OoSRs of 10 SRs with/without meta-analyses is that BCAA supplementation has small-to-large effects on muscle damage biomarkers (i.e., CK levels), large effects on muscle soreness, and no effects on muscle performance. The effects of BCAA supplementation on post-exercise recovery of muscle damage biomarkers, muscle soreness, and muscle performance were

substantiated by the moderate quality of evidence resulting from critically low-to-low quality reviews.

Interpretation of the results

In three SRs (8, 18, 22) and five SRs with meta-analyses (14, 16, 17, 19, 21) included in this OoSRs, CK, LDH, and myoglobin levels were used as muscle damage biomarkers. Furthermore, the consumption of BCAA has positive effects on recovery by decreasing CK levels, with an evident effect at <24, 24, and 48 h post-exercise, but not on LDH levels. Previous meta-analyses showed the most significant effects of BCAA supplementation on muscle damage biomarkers appear at <24 (17, 21), 24 (17, 19, 21), and 48 h (14, 17, 21) post-exercise. One meta-analysis evaluated the effect of BCAA supplementation after EIMD (i.e., resistance exercises) on muscle damage biomarkers and recovery in trained males (17). The main finding of this OoSRs reported BCAA supplementation accelerated CK recovery at <24, 24, and 48 h post-exercise (SMD = −0.73, −0.8, and −0.54, respectively). These results agree with previous studies of high methodological quality (42, 43) using only BCAA supplementation independent of additional ingredients. In this context, Greer et al. (42) investigated the effects of a single dose of 5 g of BCAA in healthy untrained men after 90 min of aerobic exercise at 55% Vo2max; they reported a significant increase in CK levels at 4, 24, and 48 h post-exercise for the placebo condition, with high levels compared to the BCAA conditions. CK levels for both BCAA and placebo conditions failed to return to baseline values 48 h post-exercise, but the BCAA condition exhibited a favorable positive effect. Regarding protocols involving damaging eccentric/concentric squat exercises, VanDusseldorp et al. (43) involved resistance-trained participants who supplemented with 0.22 g/kg/day for 8 days, reporting a significant increase in CK levels for both BCAA and placebo conditions at 24 h post-exercise. Furthermore, individuals supplemented with BCAA presented faster recovery at 48 h post-exercise, with non-significantly lower CK values at 72 h post-exercise for BCAA compared to placebo. Thus, it seems BCAA effects only appear in the first 48 h after EIMD, and its efficacy diminishes 72 h post-exercise. Contrarywise, Shimomura et al. (44) revealed no effects of BCAA supplementation on CK levels' recovery post-resistance training exercise in female participants. The lack of significance in this study might be due to the supplementation strategy used, where Shimomura et al. (44) administered a single dose of 5.5 g of BCAA before exercise. This amount appears relatively small compared to other studies. Furthermore, the dosage of BCAA was not standardized to participants' body mass. It should be acknowledged that the higher bioavailability of nitrogen sources and the maintenance of membrane integrity in the subsequent phase of muscle damage following eccentric exercise have been suggested as mechanisms explaining the attenuation of CK release (17, 45, 46). None of the included reviews revealed attenuation of LDH and myoglobin levels with BCAA supplementation. One meta-analysis averaged the estimate effects of muscle damage biomarkers into a single estimate effect and reported a significant effect only at 48 h post-exercise (14). Averaging the effect sizes method (AV) was suggested by Moeyaert et al. (47) to handle multiple dependent estimate effects within studies by combining estimate effects within studies before combining results over studies as Doma et al. (14). Although this method is simple to use, many limitations have been reported, including the constricted scope of research questions that can be addressed (47). Specifically, in studies where multiple outcomes are averaged, predictors of outcome characteristics cannot be included in the meta-analysis to explore within-study heterogeneity (47). Additionally, when AV is used, the standard errors are overestimated, leading to wider 95% CIs and an increase in type-2 error estimates (47). Otherwise, Greer et al. (42) reported lower LDH levels at 4 h post-exercise for BCAA compared to placebo. As LDH levels do not exhibit a post-exercise increase as significant as CK, it is possible a higher exercise intensity or a longer exercise duration would have generated more pronounced distinctions between experimental and placebo conditions. Regarding myoglobin levels, the results of Kephart et al. (48) and Shimomura et al. (44) were in accordance with those of our study, revealing no difference between BCAA supplementation or placebo. It is worth noting CK is considered a more sensitive marker for exercise-induced muscle damage compared to LDH and myoglobin due to its tissue specificity and responsiveness to muscle injury (49). CK is primarily found in muscle cells, so its elevation in the bloodstream is a direct indicator of muscle damage. In contrast, LDH is present in various tissues throughout the body, and while it can increase with muscle damage, it lacks the specificity offered by CK (49). Myoglobin, while highly sensitive to muscle damage, can also originate from damaged heart tissue, reducing its specificity to skeletal muscle. Therefore, CK's sensitivity and muscle-specific nature make it a preferred marker for assessing exercise-induced muscle damage, while LDH and myoglobin, though still valuable, are considered less sensitive and specific in this context (49).

Three SRs (8, 18, 22) and six meta-analyses (14, 15, 17, 19–21) evaluated the effect of BCAA supplementation on muscle soreness using a visual analogue scale. The authors concluded a favorable effect of BCAA supplementation on muscle soreness (8, 14, 15, 17–22) reporting positive effects in 50% of four individual studies included in SRs (8, 18, 22) and trivial-to-large effects in meta-analyses (14, 15, 17, 19–21). Regarding high-quality individual studies investigating effects of BCAA on muscle soreness, previous studies (42–45) found muscle soreness post-exercise could be attenuated with BCAA supplementation. Furthermore, BCAA consumption decreased muscle soreness at 24 h (42, 44, 45), 48 h (43–45), and 72 h (43) post-exercise. Moreover, Greer et al. (42) showed less muscle soreness in the BCAA condition at 24 h with no difference between conditions 48 h post-exercise. This may be explained by the small amount of BCAA consumed, as it was a single 5 g dose ingested only once before exercise. However, several studies reported favorable effects for BCAA at 24 and 48 h post-exercise (44, 45), where each study used a different damaging protocol (e.g., eccentric/eccentric squat with body weight (44) and Drop jump (45)). The choice of exercise type in each study

could possibly account for the varying results observed 48 h post-exercise, highlighting the significance of exercise intensity. Indeed, VanDusseldorp et al. (43) reported positive effects of BCAA in muscle soreness reduction only at 48 and 72 h post-exercise. These studies used a long supplementation period of 7 days with 20 g/day of BCAA for Howatson et al. (45) and 8 days with 0.22 mg/kg/day for VanDusseldorp et al. (43). Using a long supplementation period demonstrated more lasting effects of BCAA on muscle soreness. This finding was explained by the increase of β-Hydroxy β-methyl butyric (3HMB) levels during exercise, which may have been linked to the beneficial effects of BCAA supplementation on muscle soreness (50). Additionally, previous studies suggest oxidative stress and exercise-induced free radicals, as well as inflammation in connective tissue components, may be involved (50, 51), potentially sensitizing nociceptors (52). BCAA supplementation may reduce oxidative stress and free radical levels in athletes (53). It is noteworthy that the effect of glutamine (Gln) could also explain the influence of BCAA on muscle soreness (5, 54). In this context, it has been reported BCAA could enhance Gln synthesis *via* transamination of glutamate (5, 54). Nevertheless, the mechanism producing muscle soreness is still unclear. However, few SRs (18, 22) evaluated the impact of BCAA supplementation on the rating of perceived exertion. The authors showed that BCAA ingestion reduced the rating of perceived exertion. Unfortunately, explanations related to the effects of BCAA on rating of perceived exertion were not provided in these reviews. Future studies focusing on mechanism(s) related to the effects of BCAA on muscle soreness and the rating of perceived exertion are needed.

Three SRs (8, 18, 22) and one meta-analysis (14) investigated the effects of BCAA intake on muscle performance recovery. These reviews focused on the evaluation of maximal voluntary contraction force, counter-movement jump, seated shot-put throw, and jump squat peak power. Positive effects in 53% of 15 individual studies included in SRs and non-significant trivial-to-small for placebo/control (SMD = 0.09 and 0.31 at 24 and 48h, respectively) in meta-analysis (14) were reported. Our OoSRs' results were in accordance with several high-quality individual studies examining the effect of BCAA intake, reporting non-favorable effects on MP recovery in different populations (trained in collective sport (45), resistance trained (43, 48, 55), and untrained participants (44)). However, the relationship between the concentration of muscle damage biomarkers and the loss in muscle performance has been observed (56, 57). When muscle damage biomarkers, such as CK and LDH levels are elevated, it is an indication the muscle fibers have experienced microtears or other damage (58). This can lead to muscle performance decrease, including reduced strength and endurance (58). The magnitude of the decrease in muscle performance is related to the level of the biomarkers in circulation (58).

Subgroup analyses in the original meta-analyses reported positive effects of BCAA supplementation on CK levels (16) and muscle soreness (20) for long-term supplementation periods compared to short ones. Additionally, a systematic review demonstrated that a long supplementation period (> 10 days) of BCAA has beneficial effects on muscle damage markers and muscle soreness (8). It should be acknowledged that several primary studies used longer supplementation periods and showed positive effects of BCAA supplementation on CK levels (43, 45, 46, 59) and DOMS (45, 46, 60). The effectiveness of the study design was significant for randomized controlled placebo compared to crossover trial in muscle damage biomarkers and for crossover compared to randomized controlled placebo trial for muscle soreness and muscle performance (14). The crossover design is more stable and more powerful than the parallel design to detect the difference between interventions (61). Also, the crossover design is used to minimize inter-individual variability (14). The effects of fitness levels, supplementation period, BCAA dosage, and exercise severity were reported as significant moderators on muscle soreness (20). The positive results observed in trained individuals compared to untrained individuals (20) could potentially be attributed to a better muscle adaptation in athletes compared to sedentary individuals, including increased mobilization and activation of anti-inflammatory cells (specifically, T regulatory cells) (62, 63). However, based on current data, it is difficult to make formal recommendations regarding the dosage of BCAA. Favorable effects on muscle soreness for high doses were observed at 24 h and for the low doses at 72 h (20). It is worth noting that several primary studies reported beneficial outcomes in terms of preventing EIMD for doses >200 mg/kg/day (45, 64–66). Most SRs and meta-analyses, except one meta-analysis (17), reviewed and meta-analyzed primary studies involving both male and female participants. However, the change of female hormones (i.e., estrogen) during menstruation has been shown to affect the exercise-induced response in plasma muscle damage indicators (67).

Furthermore, the effects of BCAA on post-exercise recovery, for muscle damage biomarkers or MP, especially muscle soreness, varies based on several factors such as gender, fitness level of participants, nutritional background, and especially the type of EIMD. Regarding the type of EIMD, most of the individual studies in the included SRs with/without meta-analyses performed eccentric exercises; a few studies used aerobic exercises, two studies were conducted during a marathon race (68, 69), and one study used a 5 day training program with daily supplementation (70). Regarding studies involving competition, non-significant effects of BCAA on muscle soreness were reported. However, Koba et al. (70) reported lower muscle soreness in BCAA compared to placebo, but this study used a 5 day supplementation period. Therefore, studies incorporating eccentric exercises (43, 44) presented diverse outcomes in terms of muscle damage biomarkers and muscle soreness recovery. The variations in exercise intensity and volume from one study to another may potentially impact both the muscle-damaging process and the subsequent recovery process.

Interpretation of the re-analyzed results

In the present OoSRs, most of the included meta-analytical reviews used the mean difference as an estimate effect to

report the clinical effects of BCAA supplementation. Therefore, we re-analyzed and standardized the estimate effects of SMD using the same pooling method used in the original meta-analyses. The results' significance changed in two meta-analyses (17, 19), as well as their heterogeneity (i.e., I^2). The SMD helps to describe the magnitude of the estimate effect compared to MD. Additionally, no meta-analysis used the HKSJ method to compute the estimate effect. The HKJS method is suggested as the most accurate for the synthesis of primary studies, especially in random-effects meta-analyses with a small number of studies and in the presence of non-trivial heterogeneity (38). The HKSJ method allows for the ability to compute wider 95% CIs around the estimate effects (38). We computed the 95% PIs around each estimate effect, and we observed that the width was considerably wider than the 95% CI computed in our re-analyses using the HKSJ method in most of estimate effects. However, 95% PIs around estimate effects with a null (i.e., 0%) heterogeneity were the same as 95% CIs (adjusted with HKSJ method). The 95% PIs extended outside the limit of no difference and included values that were favorable to the placebo/control intervention in all meta-analyses, except of Rahimi et al. (21) (CK levels at 48 h and LDH levels at 24 h) and Rahimlou et al. (19) (LDH levels at <24 and 24 h and muscle soreness at 24 h).

Our re-analyses results are in line with numerous original meta-analyses results in different outcomes at different time points. Nonetheless, using the HKSJ method for the CI adjustment changed the significance of the results. For example, the authors of original meta-analyses reported significant effects of BCAA supplementation on CK levels at 24 h (17, 19, 21) and muscle soreness at <24 (17), 24 (20), 48 (19), and 72 h (20) post-exercise, when using MD Rahimlou et al. (19) used SMD for muscle soreness as the estimate effect without applying the HKSJ method. However, the re-analysis of the same data did reveal a non-significant effect. Additionally, two meta-analyses reported non-significant effect of BCAA supplementation on CK (21) and LDH levels (19, 21). The authors of the original meta-analyses used MD as an estimate effect without applying the HKSJ method (16, 17, 19–21). The re-analyses of the same data did not support the original results and revealed significant effects of BCAA supplementation on CK and LDH levels in the previous meta-analyses (19, 21).

Methodological considerations

While OoSRs can provide valuable insights into the existing evidence base, there are several limitations to consider when interpreting the findings.

First, this OoSRs compared the findings of SRs with meta-analyses to those without meta-analyses. Findings based solely on qualitative synthesis (i.e., SR without meta-analysis) may differ from those derived through a quantitative summary of the evidence (i.e., SR with meta-analysis). The latter approach enables a more precise estimate of the overall treatment effect compared to qualitative synthesis alone. Therefore, conclusions drawn from SRs with and without meta-analyses should be interpreted with caution.

Second, the lack of assessment of the level of bias present within SRs using ROBIS (Risk of Bias in Systematic Reviews) tool (71) is another methodological weakness. Although AMSTAR-2 was utilized in the present OoSRs to assess the methodological quality of the included SRs, the inclusion of the ROBIS tool in future OoSRs would contribute to a more comprehensive assessment of the included SRs. It is worth noting that ROBIS assessments should ideally be conducted by experienced systematic reviewers/methodologists, ensuring the validity and reliability of the risk of bias assessment process (72).

Third, OoSRs may be subject to publication bias, where SRs with/without meta-analyses with positive results are more likely to be published and indexed in databases. This can lead to bias in the results of OoSRs toward positive findings and, therefore, a possible overestimation of the association of RO with the outcomes of interest. In the present OoSRs, we included only published SRs with/without meta-analyses. Future OoSRs might comprehensively search for unpublished SRs, such as those available in preprint servers or registries.

Fourth, the findings of an OoSRs are based on evidence that may not capture newly published primary studies, which may create a time lag (73). The most recent included primary study was published in 2019, suggesting that conclusions drawn from SRs may be outdated or incomplete. Nevertheless, there is an ongoing debate about whether authors should search for primary studies to fill "gaps" in the SR evidence or to ensure the updating of the overview of reviews (74).

Fifth, all reviews, particularly for sleep and physical performance parameters, demonstrated overlapping. This latter may lead to double-counting of the evidence (75). Therefore, performing studies with greater methodological rigor (e.g., detailed description of the studies methods, the use of a gold standard method of assessment such as polysomnography for sleep, larger sample size), rather than just performing additional SRs, is warranted. This could improve the methodological quality of SRs and subsequently, of future OoSRs.

Sixth, overall quality of the OoSR was largely influenced by the low methodological quality of the included SRs. Using the AMSTAR-2 tool, the methodological quality of the reviews was found to be generally low or critically low. A common critical weakness was the lack of justification for excluding articles, indicating noncompliance with PRISMA 2020 guidelines (76). However, it should be noted that some of the included reviews (8, 16, 19, 21) were published before the PRISMA 2020 statement, where this justification was not mandatory. Another critical weakness is that the authors did not register protocols in specific databases. Protocols of SRs with/without meta-analyses should be registered in requisite databases/engines (77). If such protocols are registered and publicly available, they may help reduce the risk of duplicate reviews by independent research groups (77). Additionally, the protocol should be precise to aid in limiting the publication of SRs with meta-analyses reporting biased results

and discordant conclusions (78). As such, Sandau et al. (78) advised the conclusions of SRs with meta-analyses with absent or imprecise protocols should be interpreted with caution. The lack of transparency in reporting funding sources for primary studies in the SRs was also identified as a weakness, although this issue did not seem relevant to BCAA supplementation-based studies, as we are not aware of any industry-related BCAA supplementation and sport that might impact the literature.

Seventh, the current body of evidence pertaining to the investigated parameters is derived from observational studies, which lack randomization and observer blinding. Furthermore, none of the included SRs assessed the certainty of evidence using methodologies such as GRADE (Grading of Recommendations Assessment, Development, and Evaluation) (79), despite it being a mandatory requirement when adhering to PRISMA 2020 (76). This methodological issue makes it challenging to assess the confidence in the findings and determine the strength of recommendations based on the available evidence.

Eighth, future studies should consider applying techniques such as funnel plots or Egger's test to examine publication bias and avoid possible skewness of the overall meta-analytic outcomes. Moreover, further cohort studies and randomized controlled trials are needed to further validate the relationships among athletes, as well as other populations. In the case of small number of studies, future meta-analyses should conduct statistical analyses with the HKSJ method, which should be more appropriate for pooled ES estimation especially with small sample sizes ($n < 5$). Additionally, it is crucial for future research reviews to thoroughly explore the practical implications of their findings in a clinical context. This means taking the time to clearly and straightforwardly explain how the research outcomes can directly benefit or influence clinical practices. This will enhance the practical applicability of such reviews for sports and medical practitioners.

Finally, as mentioned in Ammar et al. (80) in terms of selecting muscle damage biomarkers, it is important to acknowledge exercise is demonstrated to induce muscle damage, inflammation, and oxidative changes in various biological components (81–86). Additionally, it has been recommended to employ at least two or more biomarkers to accurately assess muscle inflammatory damage (87–89). Therefore, future studies should consider the use of multiple relevant biomarkers, such as CK and LDH to assess muscle damage, high-sensitivity C-reactive protein, and IL-6 to detect inflammation (80). This approach will help confirm the potential effects of BCAA supplementation in mitigating exercise-induced muscle damage or inflammation.

The above-mentioned limitations weaken arguments for causality; this should be considered when making decisions regarding BCAA supplementation and post-EIMD recovery.

Conclusion

BCAA supplementation is an effective strategy to reduce post-exercise muscle damage biomarkers (i.e., CK levels) and muscle soreness. The magnitude of the effectiveness of BCAA supplementation is generally greater in reducing post-exercise CK levels and muscle soreness than in reducing post-exercise LDH. BCAA supplementation has no effect on post-exercise muscle performance recovery. Future SRs with/without meta-analyses should have higher methodological rigor. This includes providing a list of excluded studies and registering protocols in a specific database. Therefore, coaches and athletes should take the following into consideration: (i) if athletes train four times a week, BCAA supplementation may aid in recovery between training sessions due to the positive effects of BCAA at both less than 24 h and 24 h post-exercise. However, if they train only three times a week, supplementation is not suggested, (ii) supplementation of BCAA, both in low and high doses, for an extended period, could be an effective strategy for recovering from muscle damage induced by EIMD, (iii) and consuming BCAA before exercise or a training session has more beneficial effects on muscle damage biomarkers, as well as on muscle soreness.

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