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REVIEW ARTICLE

Effect of BCAA supplementation on central fatigue, energy metabolism substrate and muscle damage to the exercise: a systematic review with meta-analysis

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Abstract

Background and aims: Current state of evidence recommends beneficial effects of branched chain amino acids (BCAAs) on exercise performance; however, randomized controlled trials (RCTs) of BCAA supplementation yield discordant results. The objective of this study was to clarify the effects of BCAA supplementation in exercise through meta-analysis of all relevant RCTs.

Methods: A comprehensive search of PubMed, Embase, ISI web of science, and the Cochrane library has been conducted from inception to September 2016. This meta-analysis includes 31 primary trials of the effect of BCAA supplementation on central fatigue, fatigue substances (lactate and ammonia), energy metabolites (glucose and free fatty acids) and, muscle damage substances (LDH and CK). The estimates were either obtained from a fixed-effects model or a random-effects model. The studies' heterogeneity was calculated by Cochrane's test and I^2 index.

Results: BCAA had no effect on central fatigue (SMD −0.31, 95% CI −0.72 to 0.09; $p=0.1$; heterogeneity $I^2=0\%$, $p=0.9$). However, a significant reduction was detected in the lactate levels (WMD −0.16, 95% CI −0.26 to −0.53; $p=0.003$; heterogeneity $I^2=47.9\%$, $p=0.023$). Moreover, BCAA supplementation had beneficial effects on ammonia, glucose, FFA, and CK, but had no effects on LDH.

Conclusion: BCAA supplementation did not have any effect on the feeling of fatigue; however, it led to a favorable effect on fatigue substances, energy metabolites and muscle soreness substances. Therefore, it can be concluded that the ingestion of the BCAA can play a helpful role in the enhancement of the exercise performance.

Keywords BCAA · Exercise fatigue · Exercise damage · Athletic performance

Introduction

In the past 2 decades, numerous studies have shown the advantageous effects of branched chain amino acids (BCAAs) on exercise performance [1]. BCAA as a nutritional supplement may improve serum concentration of fatigue substances (lactate, ammonia and 5-HT), energy metabolites (glucose and free fatty acids) and muscle soreness substances (LDH and CK) [2]. Fatigue during exercise can be attributable to both peripheral and central fatigue factors [3]. Fatigue of central origin translates into impulse conduction which promotes a reduction in the number of active motor units and a decrease in the firing frequency of the motoneurons.

Decrease in blood glucose levels due to liver glycogen depletion is thought to be one factor in the development of central fatigue. Also, serotonin or 5-hydroxytryptamine

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(5-HT) is another factor known to affect the central fatigue. Brain 5-HT increases during exercise which is assumed to be a cause of central fatigue [3, 4]. Increased 5-HT synthesis occurs in response to an increased transport of free tryptophan (f-Trp) across the blood–brain barrier. Furthermore, transport of free tryptophan is influenced by the serum levels of BCAAs. BCAA and f-TRP compete for the same carrier system [4]. Therefore, the f-Trp/BCAA ratio is a key factor that reflects the amount of free tryptophan that is transported to the brain. As a result, ingestion of BCAAs may be able to decrease the uptake of free tryptophan by the brain and also brain 5-HT synthesis and consequently delay central fatigue [3]. Moreover, increasing serum levels of free fatty acids (FFAs) during exercise causes a parallel increase in plasma-free tryptophan unbound to albumin [5, 6].

Earlier studies indicate that BCAA catabolism is increased during exercise [7]. BCAA enters the tricarboxiylic acid (TCA) cycle as a metabolite. When BCAA catabolism is increased, BCAA significantly suppresses the lactate production [8]. The challenge in some studies suggested that the ammonia produced from BCAAs leads to reaction that maintains the energy source of the cells. Therefore, BCAA supplementation during exercise is the key factor that changes the arterial NH_3 production [9–11]. Also, CK and LDH are useful blood measurements that reflect the degree of muscle soreness and damage [12]. CK and LDH control the ATP-PC system and maintain the balance of sugar catabolism and anabolism, respectively [2]. According to some studies, BCAA supplementation reduces serum concentration of LDH and CK [13–15]. There are many RCT studies carried out to investigate the effect of BCAA supplementation on exercise performance, and the results of these investigations are inconsistent. This lack of consistency may be caused by variations in the protocols of exercise and different protocols of BCAA supplementation among trials. In addition, no systematic analysis focused on BCAA supplementation on fatigue substances (lactate and ammonia), energy metabolites (glucose and free fatty acids) and muscle soreness substances (LDH and CK) have been done. Motivated by the controversy about the benefits of BCAA supplementation, the present meta-analysis aimed to evaluate the effects of BCAA supplementation on fatigue, energy metabolism, and muscle damage during exercise.

Methods

Search strategy, study selection, and data extraction

This meta-analysis was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. A comprehensive search of PubMed, Embase, ISI web of science, and the Cochrane library has been conducted from inception to September 2016. The search included English language publications. The phrase branched chain amino acid or BCAA was used in combination with the words fatigue, exhaustion, performance, training, endurance, sport, or exercise in the literature search. Two reviewers (AM and RH) independently reviewed the title and abstract of all relevant studies to identify eligible ones. After excluding the irrelevant studies, the full texts of the qualified studies were assessed to determine if they met the inclusion criteria of the proposed meta-analysis. The reference lists of original and review studies were also searched manually to ensure that further eligible publications were included. This meta-analysis study has been submitted in PROSPERO (ID: CRD42017063873).

Original studies were included with regard to the following inclusion criteria:

1. Methodological design: randomized clinical trial
2. Participants: healthy human females and males, professional athletes and untrained male and female
3. Intervention: BCAA supplementation versus a control feed
4. Outcome: they reported at least one of the results of interest including fatigue, lactate, ammonia, glucose, FFA, CK, and LDH.

The relevant data were extracted: first author's name, publication year, country of trial, sample population in intervention and control groups, characteristics of the subjects (i.e., age, gender), details of the methodological design (i.e., crossover or parallel design), evaluation of quality score of trials, the dosage and protocol of intervention and placebo in trials, exercise intervention, extraction of mean differences, and SD changes of following outcome variables: fatigue, lactate, ammonia, glucose, FFA, CK, and LDH.

Quality assessment

Two reviewers (AM and RH) performed the quality assessment of all studies independently. The Jadad scale was employed to assess the methodological quality of all studies based on methods pertinent to randomization, double blinding, and descriptions of withdrawals [17]. The range of possible score is 0–5. The scores ranging from 0 to 2 were considered as lower scores and the scores ranging from 3 to 5 were considered as higher scores.

Data analysis

Mean and standard deviation (SD) of the pre- and postintervention were obtained from the original studies. Graph

digitizer was used to obtain data from graphs when original data values were not available [18]. In any study that standard error of the mean (SEM) was reported, SD was calculated as $SD = SEM \times \sqrt{n}$, where n equals group sample size. Mean differences and SD changes have been used to assess the treatment effects. The following formula has proved to be a reliable measure for the calculation of SD change:

$$\text{SD change} = \sqrt{[(SD_{pre})^2 + (SD_{post})^2 - 2 \times \text{Corr}(pre, post) \times SD_{pre} \times SD_{post}]}.$$

Also, the correlation coefficients of the studies were obtained. If the correlation coefficient was not mentioned in a study, a correlation of 0.5 was assumed. The data analyses were conducted with a fixed-effects model, unless a study with heterogeneity random-effects model was used [19]. Forest plots were generated to show the mean effect size with 95% confidence interval (CI). The weighted mean difference (WMD) was calculated with 95% CI when all of the studies had measured the outcome variable on the same measurement scale. Since different measurement scales were used across studies, the standard mean difference (SMD) was calculated with 95% CI. The heterogeneity among studies was measured by Cochrane's test (Q test) and I^2 index. Percentages of around 25% ($I^2 = 25$), 50% ($I^2 = 50$), and 75% ($I^2 = 75$) would mean low, medium, and high heterogeneity, respectively. Furthermore, subgroup analyses were performed to explore the source of heterogeneity and assess the possible effects of BCAA supplementation on study outcomes. Subgroup analyses were performed according to the duration of BCAA supplementation [< 1 days (short-term) or > 1 days (long-term)]. Additionally, sensitivity analysis was performed using one-study removed (leave-one-out) approach. Risk of publication bias in meta-analysis was assessed by both the visual funnel plot and Egger's test [21]. All analyses were performed using STATA (version 12; college station, TX, USA). $p < 0.05$ was considered as significant.

Results

Summary of the included studies

The flow diagram for selection of trials is summarized in Fig. 1. A total of 120 articles were identified from database searching. In addition, nine articles were identified from the reference lists of the relevant studies. After removing 33 duplicate articles, 96 articles were left for selection assessment. After assessing the titles and abstracts, 51 full text articles were initially selected. After further evaluation, 20 articles were excluded for the following reasons; reporting insufficient data (9 articles) [41–49], using duplicate data (2 articles) [50, 51], using BCAA infusion (1 article) [52], using leucine alone (4 articles) [53–56], and combining BCAAs with another amino acid supplement (4 articles) [57–60]. Finally, 31 articles were adopted for inclusion in this meta-analysis. A total of 576 subjects, 378 subjects received BCAA supplements and 379 subjects received a control feed. Mean age of the participants recruited in this study was 25.62 ± 5.5. Characteristics of eligible studies are listed in Table 1. Of the 31 eligible studies, 26 studies were performed on men only, 2 studies were performed on women only [14, 29] and 3 studies were performed on both males and females [13, 25, 38]. Methodological design of 12 studies was parallel and 19 studies were crossover. The variation in the dosage and mixture of BCAAs (leucine, isoleucine and valine) was observed between trials. Moreover, included trials in this meta-analysis reported different lengths of time that BCAA supplementation was applied. The protocols of BCAA supplementation were different across included studies. Therefore, subgroup classification was performed based on the duration of BCAA supplementation. According to the subgroup classification, 20 studies assumed to be short-term BCAA supplementation and 11 studies assumed to be long-term BCAA supplementation. Summary of the trials included in current meta-analysis is presented in Table 2.

The extracted data from trials were pooled in this meta-analysis. The main focus of this review was placed on the following outcome variables: fatigue, lactate, ammonia, glucose, FFA, CK, and LDH. The forest plots of all the outcome variables are presented in Figs. 2, 3, 4, 5, 6, 7 and 8.

Effect of BCAA supplementation on fatigue and fatigue substances (lactate and ammonia)

The central fatigue was evaluated via different scales across studies. Portier et al. [6] employed an analog visual scale with the crew members. Also, this traditional scale has been validated (Lagarde and Batejat) [61]. Chevrount et al. [23] and Mittelman et al. [25] used profile of mood states (POMS) scale consisting of depression, tension, anger, confusion vigor, and fatigue. Struder et al. [28] used EZ-scale comprising drive, confidence, mood, and fatigue. Blomstrand et al. [22] used a category-ratio scale CR-10 (Borg) [62]. To remove the effects of different measurement scales used in the trials, the standardized mean differences (SMD) were calculated. Five trials had recorded central fatigue, pooled results of which are presented in Fig. 2. The Fig. 2 shows results with low heterogeneity; the confidence interval around I^2 contains near 0% value and can hold the homogeneity and

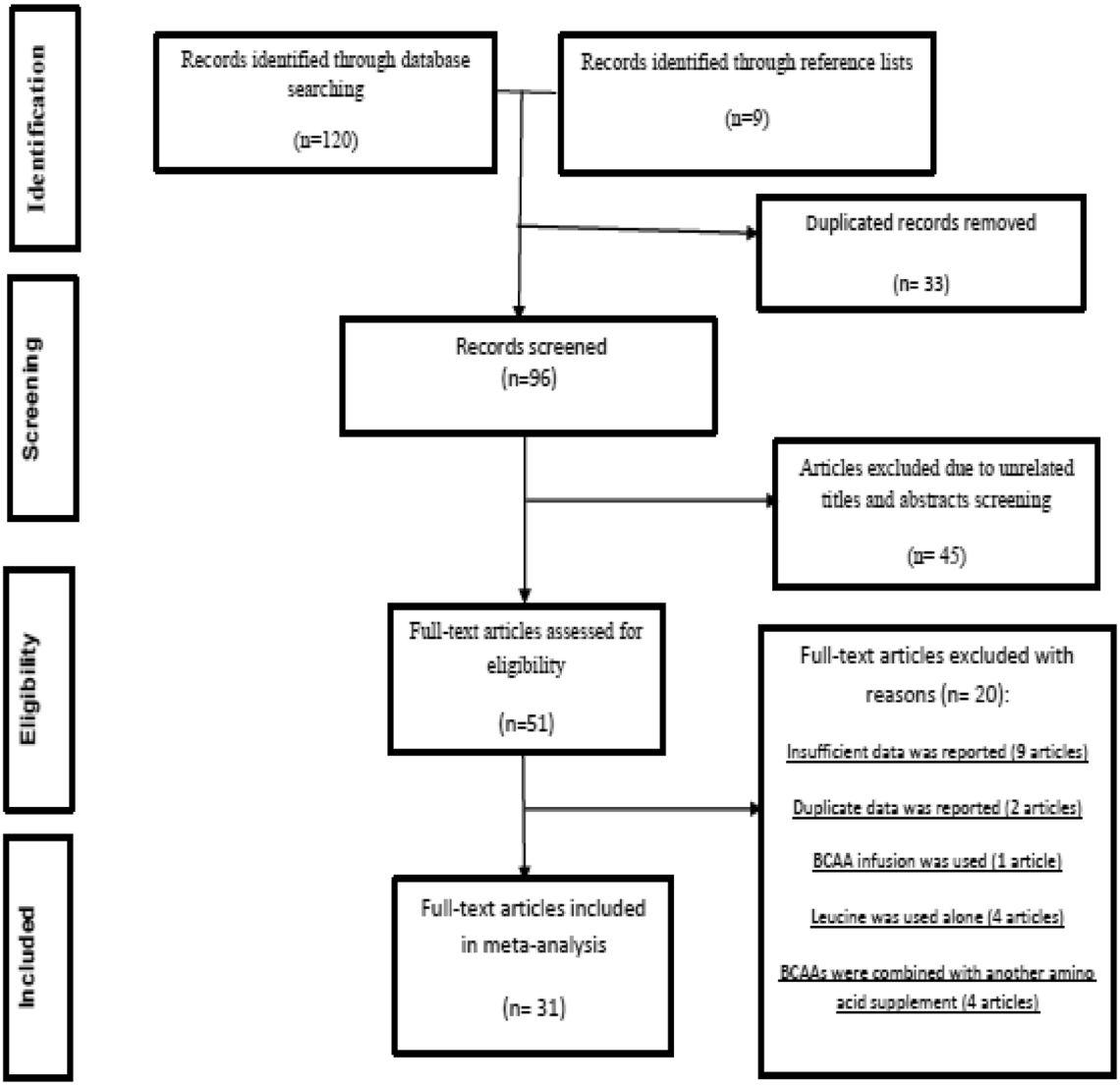

Fig. 1 Flow diagram of study selection process

the hypothesis of the meta-analysis. A good relationship favoring BCAA that had no effect on central fatigue (SMD −0.31, 95% CI −0.72 to 0.09; $p=0.1$; heterogeneity $I^2=0\%$, $p=0.9$). The levels of lactate were also analyzed. Fixed-effects model showed that the BCAA supplementation had a reduction effect on lactate Levels (WMD −0.16, 95% CI −0.26 to −0.53; $p=0.003$; heterogeneity $I^2=47.9\%$, $p=0.02$). Pooled results from these studies are presented in Fig. 3. Regarding the ammonia, the heterogeneity was observed by fixed-effects model among trials. Therefore, random-effects model was calculated (Table 2) which showed a statistically significant positive effect (WMD 19.52, 95% CI 6.84–32.2; $p=0.003$). Pooled results from these studies are presented in Fig. 4. Also, there was an insufficient number of trials in the subgroup classification which researchers performed calculation of the subgroup meta-analysis to explore the source of heterogeneity.

Effect of BCAA supplementation on energy metabolite substance (glucose and free fatty acids)

Concerning the glucose, random-effects model was calculated because of the heterogeneity that was observed (Table 2). Also, subgroup analysis was performed to explore the source of heterogeneity. Subgroup analysis of short-term BCAA supplementation showed a significant reduction effect on glucose levels (WMD −0.41, 95% CI −0.53 to

Table 1 Characteristics of the included studies

Author	Study type	Participants	Mean age	Exercise intervention	Total dosage (g)	Supplementation protocol	Supplementation duration	Relevant outcome variables
Blomstrand et al. [22]	Crossover	8 8 male	25 ± 7.4	Cycling	6.6	6.6 g/day	80 min (short)	Glucose, lactate, ammonia, FFA, fatigue
Koba et al. [12]	Crossover	8 8 male	20.4 ± 1.2	Run	23	6 g/day + 5 g in exercise day	4 days (long)	Ammonia, CK, LDH
Matsumoto et al. [8]	Crossover	8 8 male	21 ± 2	Cycling	40	6 g/day + 4 g in exercise day	7 days (long)	Glucose, lactate
Cheuvront et al. [23]	Crossover	7 7 male	21 ± 2	Cycling and run	NA	NA	90 min (short)	Glucose, lactate, FFA
Greer et al. [5]	Crossover	9 9 male	21.6 ± 3.2	Cycling	48.6	48.6 g/day	90 min (short)	Glucose, fatigue
Coombes et al. [1]	Parallel	16 16 male	21.3 ± 1.1	Cycling	188	12 g/day + 20 g in exercise day	14 days (long)	CK, LDH
Wisnik et al. [24]	Crossover	10 10 male	25 ± 3.16	Soccer	7	7 g BCAA	90 min (short)	Glucose, lactate, FFA
Portier et al. [6]	Parallel	12 12 male	35.2 ± 11.7	Sailing	72.5	48.3 g/day	1.5 days (long)	Fatigue
Mittleman et al. [25]	Crossover	16 8 male 8 female	24.2 ± 4.75	Cycling	~12.6	~12.6 g	180 min (short)	Glucose, ammonia, FFA, fatigue
Gualano et al. [26]	Crossover	7 7 male	24 ± 2	Exhaustive exercise test	~63	~21 g/day	3 days (long)	Glucose, fatigue
Matsumoto et al. [13]	Crossover	12 6 male 6 female	20 ± 1	Run	60	20 g/day	3 days (long)	Fatigue, CK, LDH
Blomstrand 1 et al. [27]	Parallel	25 25 male	40.4 ± 5.98	Run	7.5	7.5 g	170 min (short)	Glucose, FFA
Blomstrand 2 et al. [27]	Parallel	193 193 male	38.6 ± 7.92	Run	16	16 g	230 min (short)	Glucose, FFA
Struder et al. [28]	Crossover	10 10 male	25.5 ± 2.1	Cycle ergometer test	21	21 g	90 min (short)	Glucose, lactate, ammonia, FFA, fatigue
Shimomura et al. [29]	Crossover	12 12 female	22.2 ± 1.6	Squat exercise	5.5	5.5 g	4.6 min (short)	Glucose, lactate, ammonia, FFA, CK
Kim et al. [2]	Parallel	26 26 male	23 ± 2.4	Cycling	~5.34	~5.34 g	30 min (short)	Glucose, ammonia, FFA, CK
MacLean et al. [10]	Parallel	5 5 male	26.6 ± 2.89	Dynamic knee extensor exercise	~22	~22 g	90 min (short)	Ammonia
MacLean et al. [9]	Crossover	5 5 male	24.4 ± 4.23	Dynamic knee extensor exercise	~5.6	~5.6 g	60 min (short)	Lactate, FFA
MacLean et al. [11]	Crossover	7 7 male	27.7 ± 7.65	Cycling	~6	~6 g	60 min (short)	Glucose, lactate, ammonia, FFA

Table 1 (continued)

Author	Study type	Participants	Mean age	Exercise intervention	Total dosage (g)	Supplementation protocol	Supplementation duration	Relevant outcome variables
Howatson et al. [30]	Parallel	12 12 male	23 ± 2	Drop jump	260	20 g/day + 20 g in exercise day	12 days (long)	CK
Blomstrand et al. [31]	Cross over	7 7 male	25 ± 2.64	Cycling	~8.2	~8.2 g	180 min (short)	Glucose, lactate, ammonia, FFA
Bigard et al. [32]	Parallel	24 24 male	33 (25–42)	Ski mountaineering	22.4	22.4 g/day	0.5 day (short)	Glucose, lactate, ammonia, FFA
Greer et al. [33]	Crossover	9 9 male	21.6 ± 3.2	Cycling	50	50 g/day	90 min (short)	CK, LDH
Watson et al. [34]	Crossover	8 8 male	28.5 ± 8.2	Cycling	NA	NA	90 min (short)	Glucose, lactate, ammonia, FFA, fatigue
Tang et al. [35]	Parallel	19 19 male	20.5(19–22)	Crawl stroke competition	168	12 g /day	14 days (long)	Glucose, lactate
Carli et al. [36]	Crossover	14 14 male	33.78 ± 1	Run	10.28	10.28 g	150 min (short)	Glucose
De Palo et al. [37]	Parallel	11 11 male	32.8 ± 6.9	Cycle ergometer performance	~441	~14.38 g/day + 9.64 g in exercise day	31 days (long)	Lactate
Apro et al. [38]	Crossover	9 4 male 5 female	25 ± 4.62	Heavy resistance	~5.11	~5.11 g	115 min (short)	Lactate
Fouré et al. [39]	Parallel	26 26 male	22.5 ± 1.5	Neuromuscular electrostimulation exercise	~7	~1 g/day + 3 g in exercise day	5 days (long)	CK
Sheikholeslami-Vatani et al. [14]	Crossover	10 10 female	22 ± 1.5	Heavy resistance	4.5	4.5 g	70 min (short)	CK, LDH
De Palo et al. [40]	Parallel	14 14 male	21 ± 1	Cycling	~402	~13.4 g/day	30 days (long)	FFA

CK creatine kinase, *LDH* lactate dehydrogenase, *FFA* free fatty acids, *NA* not available

Table 2 Summary of the meta-analysis and subgroup meta-analysis of trials included in this review

Trials	No. of trials	Effect size			Study heterogeneity	
		WMD	95% CI	*p* value	I^2, %	*p* value
Fatigue						
All trials	5	−0.31	−0.72, 0.09	0.1	0	0.94
Lactate (mmol/L)						
All trials	14	−0.16	−0.26, −0.05	0.003	47.9	0.023
Ammonia (μmol/L)						
All trials	11	19.52	6.84, 32.2	0.003	77.4	<0.001
Glucose (mmol/L)						
All trials	18	−0.23	−0.45, −0.02	0.03	67.7	<0.001
Short-term BCAA supplementation trials	15	−0.41	−0.53, −0.29	<0.001	49.9	0.01
Long-term BCAA supplementation trials	3	−0.01	−0.23, 0.2	0.9	86	0.001
FFA (mmol/L)						
All trials	14	−0.059	−0.11, −0.005	0.03	24.3	0.19
LDH (IU/L)						
All trials	5	−10.2	−40.1, 19.75	0.5	78.9	0.001
CK (IU/L)						
All trials	8	−15.3	−29.7, −1	0.03	59.5	0.01
Short-term BCAA supplementation trials	4	−1.96	−6, 2.07	0.34	60.7	0.05
Longer-term BCAA supplementation trials	4	−34.69	−55.9, −13.4	0.001	0	0.83

Subgroup analyses were performed according to the duration of BCAA supplementation [< 1 days (short) or > 1 days (long)]

WMD weighted mean difference, *CI* confidence interval, *CK* creatine kinase, *LDH* lactate dehydrogenase, *FFA* free fatty acids, *NA* not available

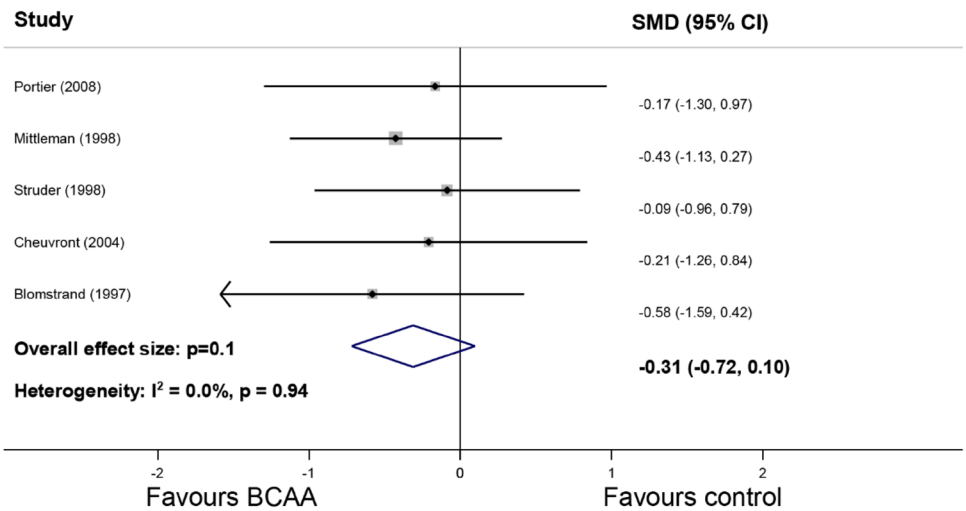

Fig. 2 Meta-analysis of trials testing the effect of BCAA on central fatigue

−0.29; $p < 0.001$). However, in the subgroup of long-term BCAA supplementation, no effect on glucose levels was found (WMD −0.01, 95% CI −0.23 to 0.2). Therefore, the reduction effects of BCAA supplementation are related to trials with a short-term of BCAA supplementation. Additionally, duration of trials is the source of heterogeneity. Pooled results from these studies are presented in two subgroups in Fig. 5. Regarding the free fatty acids, a beneficial effect was observed (WMD −0.059, 95% CI −0.112 to −0.005; $p = 0.03$; heterogeneity $I^2 = 24.3\%$, $p = 0.19$). Pooled result from these studies is presented in Fig. 6.

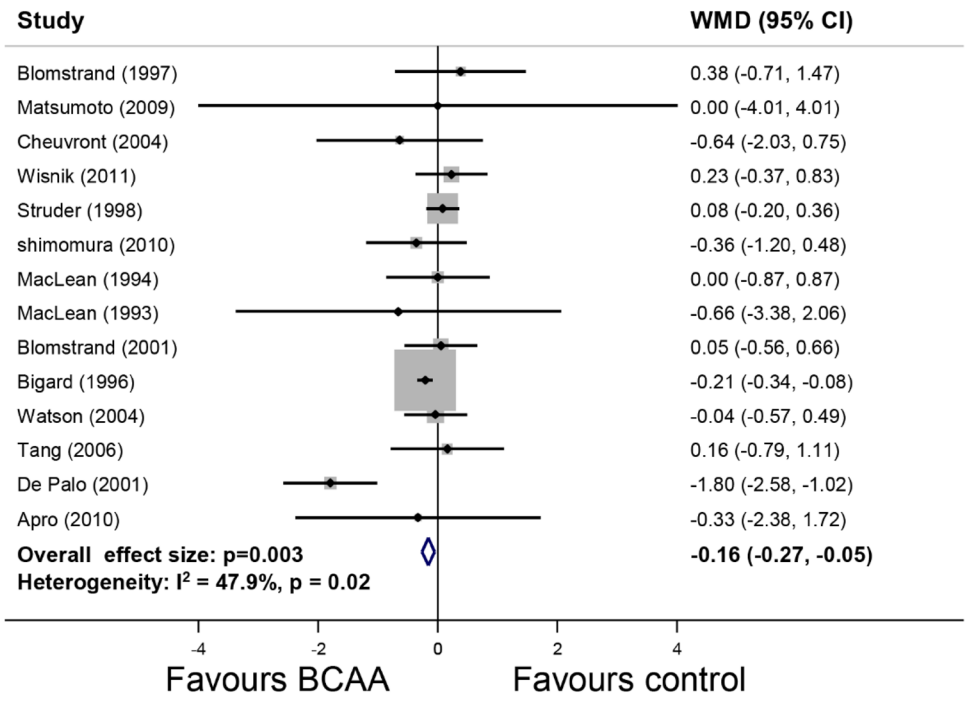

Fig. 3 Meta-analysis of trials testing the effect of BCAA on lactate

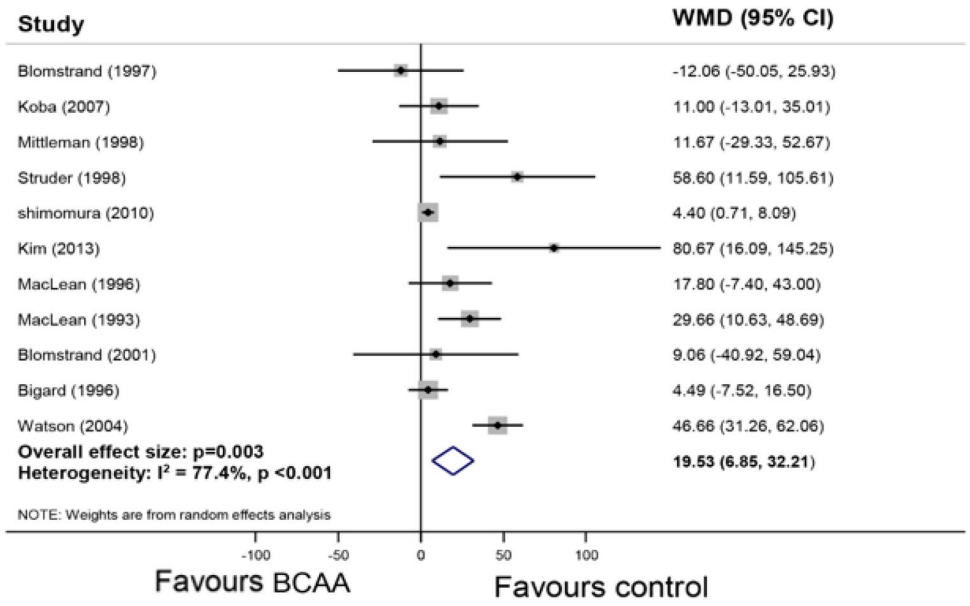

Fig. 4 Meta-analysis of trials testing the effect of BCAA on ammonia

Effect of BCAA supplementation on muscle soreness substances (LDH and CK)

Five trials had recorded levels of LDH. Pooled results from these studies are shown in Fig. 7. Random-effects model exhibited that the BCAA supplementation did not significantly improve LDH levels (WMD − 10.2, 95% CI − 40.1 to 19.75; $p = 0.5$; heterogeneity $I^2 = 78.9\%$, $p = 0.001$). Also, there was an insufficient number of trials in the subgroup classification for subgroup analysis. The levels of CK were also analyzed. Concerning the heterogeneity between trials, random-effects model was calculated (Table 2). Also, subgroup analysis was performed. In the subgroup of the short duration of BCAA supplementation, no effect on CK levels was found (WMD − 1.96, 95% CI − 6 to 2.07; $p = 0.34$), but a significant reduction was seen in the long duration subgroup (WMD − 34.69, 95% CI − 55.9 to − 13.4; $p = 0.001$). Therefore, the reduction effects of BCAA supplementation are only related to trials with a long duration of BCAA supplementation.

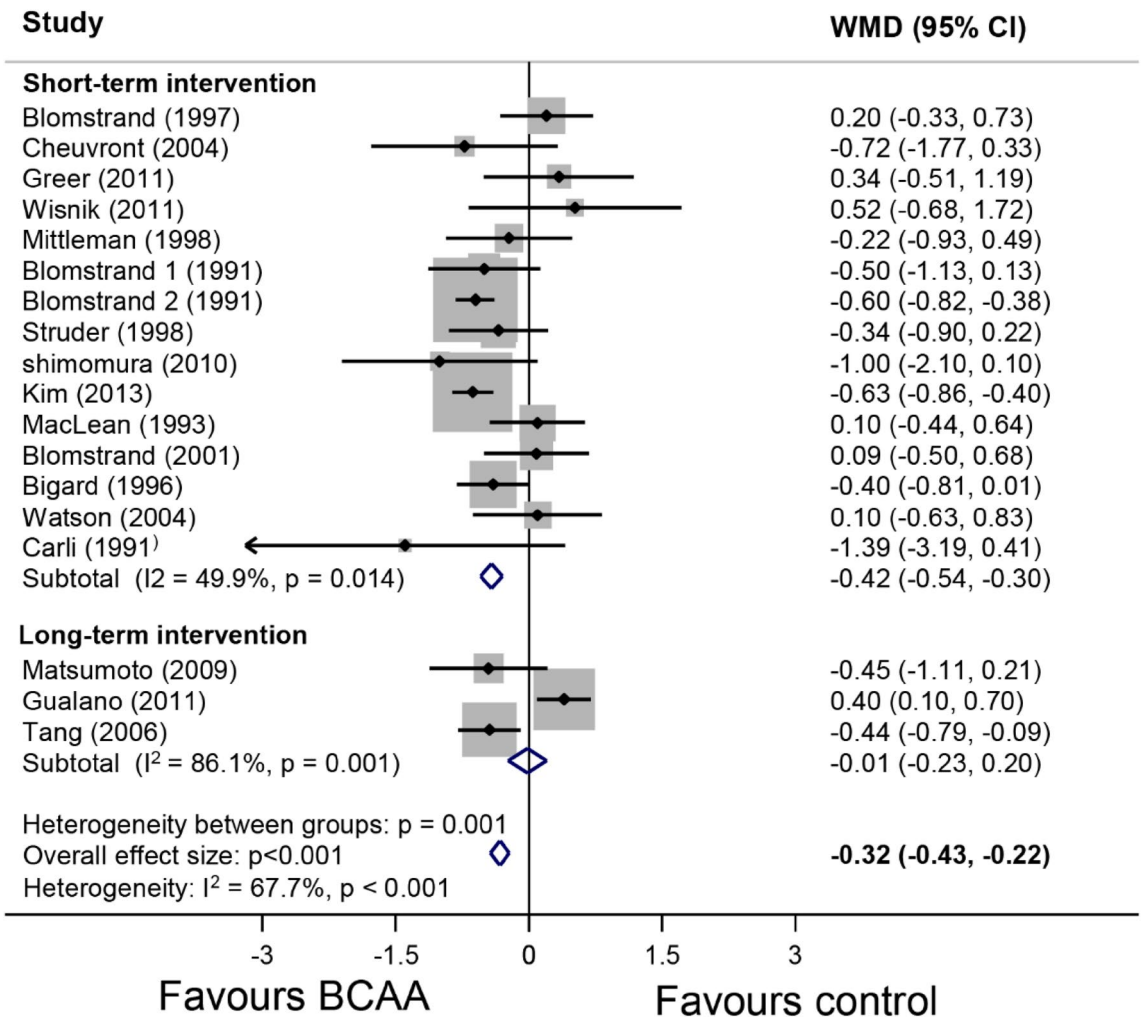

Fig. 5 Subgroup meta-analyses of the effect of BCAA on glucose

Sensitivity analysis and risk of publication bias

After leaving out the studies (leave-one-out approach), results did not show significant changes (data not shown). Funnel plot for lactate as important fatigue substance was generated to evaluate the risk of publication bias (Fig. 9). The Eggers test was not observed to be significant for any of outcome variables.

Discussion

In this meta-analysis, the effect of BCAA supplementation on central fatigue, fatigue substances (lactate and ammonia), energy metabolites (glucose and free fatty acids), and muscle soreness substances (LDH and CK) was evaluated. The results of this meta-analysis suggest that BCAA supplementation had a beneficial effect on lactate, FFA, glucose, ammonia, and CK; however, no beneficial effects of BCAAs on central fatigue and LDH were observed. The assessment of publication bias and the sensitivity analysis revealed solid evidence that supports BCAAs as a potentially effective nutritional supplement for sport fatigue.

Branched chain amino acids (BCAA; leucine, isoleucine, and valine) are the most oxidized types of amino acids that are catabolized in the skeletal muscle and augment muscle regeneration by suppressing endogenous post-exercise muscle protein degradation [2, 49]. Insufficient essential post-exercise amino acids may delay stimulating skeletal muscle protein synthesis. Therefore, the popularity of protein and amino acid supplementation for athletes is growing [7, 49]. Nutritional strategies were designed to decrease 5-HT-mediated fatigue. Carbohydrate sports drinks are frequently used for people who practice sports. The increased ratio of free tryptophan (f-Trp) was shown by consumption of carbohydrate sports drinks; whereas, BCAA supplementation decreases the ratio of free tryptophan (f-Trp) compared to sports drinks [23].

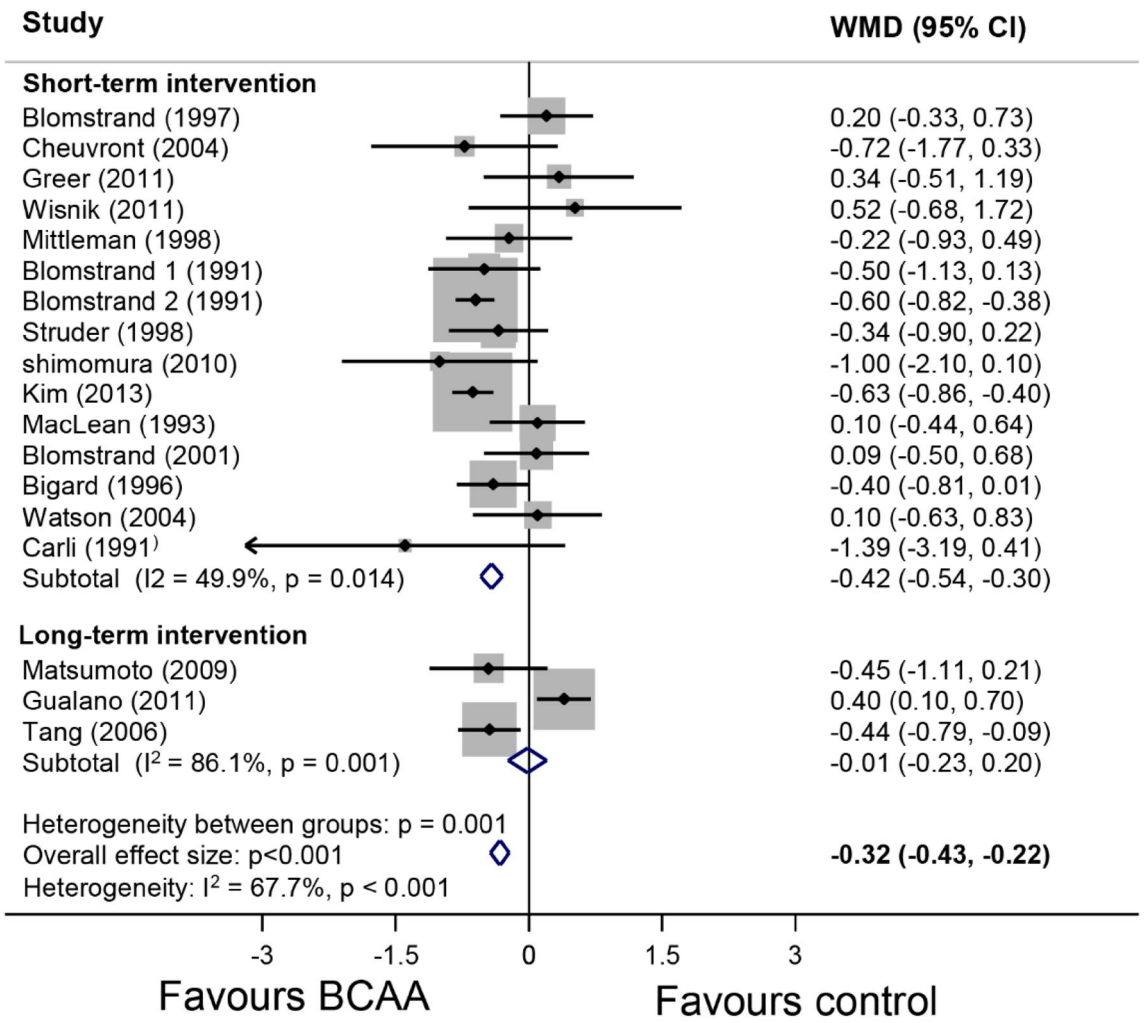

Fig. 6 Meta-analysis of trials testing the effect of BCAA on FFA

Fatigue during exercise is related to both peripheral and central fatigue factors. Several biochemical factors were identified as causes of peripheral fatigue including depletion of phosphocreatine, depletion of muscle glycogen, and accumulation of protons. However, the factors related to central fatigue are less known [3]. In this meta-analysis, five studies can be pooled and assessed to analyze central fatigue. These studies evaluated central fatigue with different scales. Therefore, the standardized mean differences (SMD) were calculated. BCAAs resulted in no improvement in fatigue sensation compared to control group. Several studies that evaluated the effect of BCAAs on sport fatigue were excluded. These studies reported different scales which they did not have suitable condition for pooling, for example, Gualano et al. [26] and Watson et al. [34] used exercise time to exhaustion, Dudgeon et al [49] used repetition to fatigue and Matsumoto et al [13] used a visual analog scale (VAS) for assessment of peripheral fatigue.

This meta-analysis measured the lactate and ammonia levels, with an aim to determine the effect of BCAA supplementation on fatigue substances. Lactate is considered to reflect the anaerobic glucose metabolism during exercise. Lactate is the most important barometer known to affect the limitation factors of muscle activity and muscle fatigue [8]. This meta-analysis confirms that BCAAs had a positive influence on lactate levels. Several studies suggested that the high ammonia can be highly toxic to the brain, and can deteriorate muscle function [2, 6, 28, 63–65]. BCAA supplementation can lead to suppression of endogenous skeletal muscle protein breakdown, and can lead to detoxification of ammonia to glutamine (GLN) in skeletal muscle [10, 11]. The results of this meta-analysis demonstrate a beneficial effect of BCAA supplementation on ammonia levels. Although BCAA had no decreasing effect on serum levels of ammonia in the BCAA group, it prevented increasing ammonia in this group.

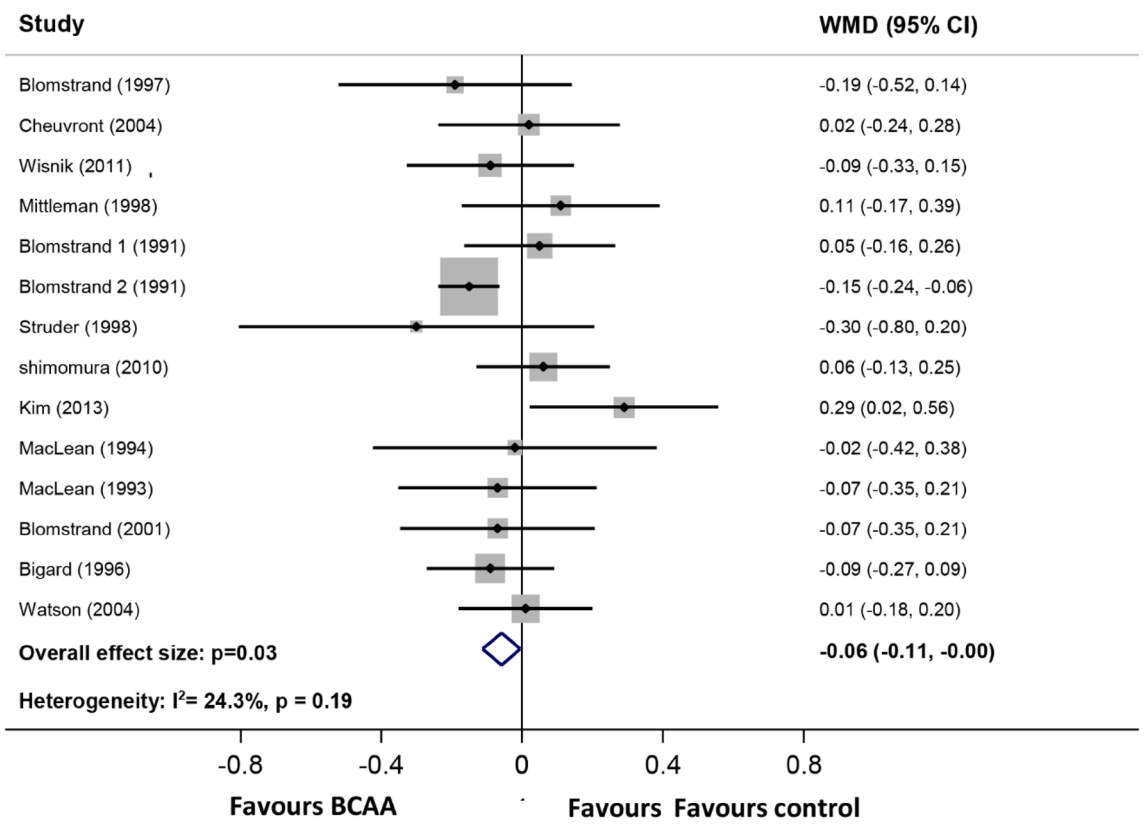

Fig. 7 Meta-analysis of trials testing the effect of BCAA on LDH

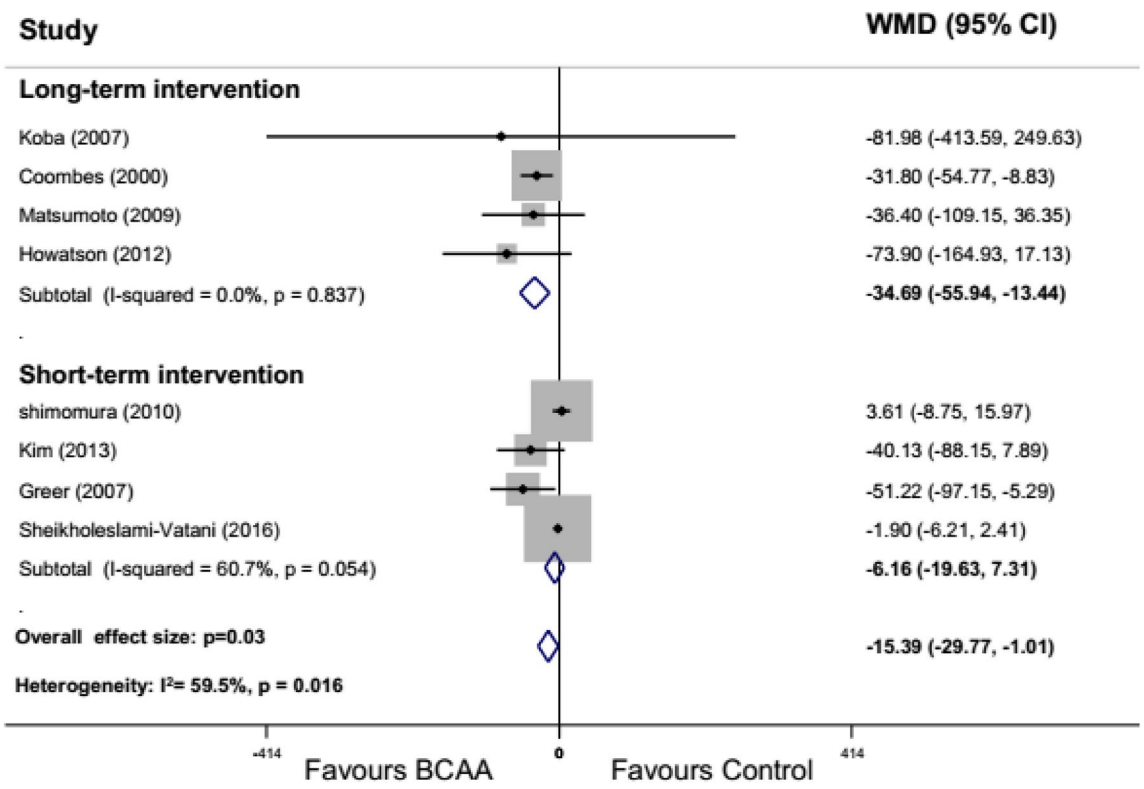

Fig. 8 Subgroup meta-analyses of the effect of BCAA on CK

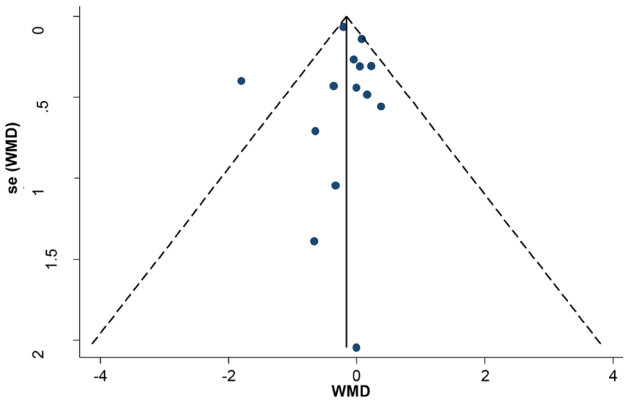

Fig. 9 Funnel plot of trials included in the meta-analysis on the effect of BCAA on lactate

The liver's activity of releasing glucose and mobilizing stored glycogen increases during exercise. However, ingestion of BCAA helps to supply additional energy. BCAA is taken up by the muscles and is oxidized. As a result, glucose release from the liver is reduced, and consequently, the glucose level in the blood is decreased. The evidence indicated that ingestion of BCAA can prevent exercise performance from deteriorating which is caused by depletion of the liver glycogen stores [2, 66]. The result of this meta-analysis indicated that short-term BCAA supplementation had a reduction effect on glucose levels. However, long-term BCAA ingestion did not decrease the levels of glucose. Pooled results from these studies confirmed the beneficial effect of BCAA supplementation on glucose levels. In addition, this review confirms that BCAA supplementation had a beneficial effect on FFA levels. Decreasing levels of FFA during exercise are presumably the result of the insulinogenic effect of ingestion of the BCAA mixture [34]. Additionally, increasing levels of FFA during exercise can increase the amount of free tryptophan that enters the brain [5]. The current evidence confirms that BCAA supplementation before exercise can decrease the FFA levels and consequently can reduce sensation of fatigue.

This review did not demonstrate any beneficial effect of BCAA supplementation on LDH levels. LDH as an indicator of muscle soreness plays an important role in production of lactate in muscle cells. The levels of LDH and CK play an important role in providing skeletal muscle energy metabolism for muscle activity. CK and LDH serve as global markers for muscle damage [13]. This review confirms that BCAA supplementation had a positive influence on CK levels. Meanwhile, the beneficial effect of BCAA supplementation is related to trials with a long-term BCAA supplementation. The result of this meta-analysis suggested that ingestion of BCAA following chronic supplementation can decrease serum levels of CK. Of the eligible publications that were included, a limited number of studies were performed on women. A significant gender effect is demonstrated in serum levels of CK [67]. Furthermore, the response of LDH and CK relies on where the site of muscle cell damage happened [68].

This is the first systematic review and meta-analyses that specifically evaluated the effect of BCAA supplementation on sport fatigue. This meta-analysis has certain limitations. This study is limited to English language trials. Also, a limited number of studies included in this meta-analysis were performed on women, and most studies were performed on men. Included studies in this review measured each outcome variable at multiple follow-up times, for example, before exercise and immediately (15 min, 30 min, 1 h, 2 h, 3 h, 24 h, 72 h and 96 h) after exercise for both intervention and control groups. Because of different follow-up times for each outcome variable among trials, this review focused on outcome variables reported before and immediately after exercise. In addition, the variation in dosage and mixture of BCAAs (leucine, isoleucine, and valine), different repetition per day of BCAA and different BCAA manufacturers were observed among trials. Also, included studies in this review reported acute or chronic BCAA supplementation. The protocols of BCAA supplementation were different among studies. BCAAs were applied before exercise and continued during and after exercise or not continued during and after exercise. These factors may contribute to the incompatibility between findings. Subgroup analysis was performed. However, available data were insufficient to perform subgroup meta-analysis for several outcome variables. In this review, high heterogeneity and inconclusive findings were observed. However, the effect of heterogeneity was minimized by selecting a random-effects model and the source of heterogeneity was found by subgroup analysis in possible.

Conclusion

This meta-analysis suggests that BCAA supplementation had no statistically significant effect on the feeling of fatigue; however, it leads to a beneficial effect on fatigue substances, which subsequently leads to a favorable effect on some muscle damage substances and some energy metabolites. Therefore, the ingestion of the BCAA ingestion can play a beneficial role in enhancement of the exercise performance. Further well-designed randomized controlled trials may be necessary to improve our knowledge regarding of BCAA ingestion on exercise performance.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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