EFFECTS OF BRANCHED-CHAIN AMINO ACIDS ON PLASMA CONCENTRATIONS OF TRYPTOPHAN AND TYROSINE AFTER PHYSICAL ACTIVITY

Review Article
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Artículo de Revisión

EFEITOS DE AMINOÁCIDOS DE CADEIA RAMIFICADA SOBRE A CONCENTRAÇÃO PLASMÁTICA DE TRIPTOFANO E TIROSINA APÓS A ATIVIDADE FÍSICA

EFECTOS DE AMINOÁCIDOS DE CADENA RAMIFICADA EN LAS CONCENTRACIONES PLASMÁTICAS DE TRIPTÓFANO Y TIROSINA TRAS LA ACTIVIDAD FÍSICA

Lei Liu[1]
(Physical Education Professional)
Fu-Gao Jiang[1]
(Physical Education Professional)

1. Krirk University, International College, Bangkok, Thailand.

Correspondence:
Fu-Gao Jiang
Bangkok, Thailand. 10220.
liulei2561@163.com

ABSTRACT

Introduction: Recent papers reveal that the administration of branched-chain amino acids (BCAA) has been widely consumed in sports. It has been determined that exercise modifies amino acid metabolism. In addition, during exercise, BCAAs are used in the muscle as an energy source, and BCAA levels can be reduced with the prolonged sport. Currently, sports may drive the catabolism of BCAAs in humans. In addition, it is believed that administration of BCAA before or during sport may elevate serum and skeletal muscle levels of these amino acids. Objective: Analyze the effects of branched-chain amino acid administration on plasma concentrations of tryptophan and tyrosine after physical activity. Methods: An extensive search in electronic databases (Google Scholar, Cochrane Library Scopus, and Medline) until June 2022 was performed for studies evaluating the effects of BCAA on plasma concentration of tryptophan and tyrosine after muscle injury. The mean and standard deviation of the tryptophan and tyrosine follow-up levels were recorded to calculate the effect size for analysis. Results: BCAA ingestion significantly reduced tryptophan levels: (WMD = -1.14 µmol.L -1, 95% CI: -1.64, -0.65; P = 0.021). Considerable heterogeneity was observed among the articles (Cochran's Q test = 990.80, P = 0.000, I2 = 96.7 %). The impact of BCAA administration on tyrosine levels assessed in 13 trials and analyses indicated a significant decreasing effect on tyrosine levels in the combined mean difference (WMD = -8.77 µmol.L -1, 95% CI: -14.33, -3.21; P = 0.000). Considerable heterogeneity between articles was also observed (Cochran's Q test = 212.84, P = 0.000, I2 = 87.3 %). Conclusion: It is safe to theorize that BCAA stimulates net protein synthesis rates within long recovery phases so that the various essential amino acid levels contain the aromatic amino acids acid decrease in serum. ***Level of evidence II; Therapeutic studies - investigation of treatment outcomes.***

Keywords: Amino Acids, Branched-Chain; Tryptophan; Tyrosine; Physical Exercise.

RESUMO

Introdução: Documentos recentes revelam que a administração de aminoácidos de cadeia ramificada (BCAA) tem sido amplamente consumida nos esportes. Foi determinado que o exercício modifica o metabolismo dos aminoácidos. Além disso, durante o exercício, os BCAA são usados no músculo como fonte de energia e os níveis de BCAA podem ser reduzidos com o esporte prolongado. Atualmente, os esportes podem impulsionar o catabolismo dos BCAA em humanos. Além disso, acredita-se que a administração de BCAA antes ou durante o esporte pode elevar os níveis do soro e do músculo esquelético desses aminoácidos. Objetivo: Analisar os efeitos da administração de aminoácidos de cadeia ramificada sobre a concentração plasmática de triptofano e tirosina após a atividade física. Métodos: Uma extensa pesquisa feita em bancos de dados eletrônicos (Google Scholar, Cochrane Library Scopus e Medline) até junho de 2022 foi executada para estudos de avaliação dos efeitos do BCAA na concentração plasmática de triptofano e tirosina após as lesões musculares. A média e o desvio padrão dos níveis de seguimento de triptofano e tirosina registrados para calcular o tamanho do efeito para análise. Resultados: A ingestão de BCAA teve um efeito redutor considerável nos níveis de triptofano: (WMD = -1,14 µmol.L -1, 95% CI: -1,64, -0,65; P = 0,021). Uma considerável heterogeneidade foi observada entre os artigos (teste Q da Cochran = 990,80, P = 0,000, I2 = 96,7 %). O impacto da administração de BCAA nos níveis de tirosina avaliados em 13 ensaios e análises indicou um significativo efeito decrescente nos níveis de tirosina na diferença média combinada (WMD = -8,77 µmol.L -1, 95% CI: -14,33, -3,21; P = 0,000). Também foi observada uma heterogeneidade considerável entre os artigos (teste Q da Cochran = 212,84, P = 0,000, I2 = 87,3 %). Conclusão: Nesta meta-análise o plasma foi analisado após a conclusão do PA em todos os ensaios; é assim seguro teorizar que o BCAA estimula as taxas de síntese proteica da rede dentro de longas fases de recuperação para que os vários níveis de aminoácidos essenciais, contendo o aminoácido aromático, decresçam no soro. ***Nível de evidência II; Estudos terapêuticos - investigação dos resultados do tratamento.***

Descritores: *Aminoácidos de Cadeia Ramificada; Triptofano; Tirosina; Exercício Físico.*

RESUMEN

Introducción: Trabajos recientes revelan que la administración de aminoácidos de cadena ramificada (BCAA) ha sido ampliamente consumida en el deporte. Se ha determinado que el ejercicio modifica el metabolismo de los aminoácidos. Además, durante el ejercicio, los BCAA se utilizan en el músculo como fuente de energía y los niveles de BCAA pueden reducirse con el deporte prolongado. En la actualidad, el deporte puede impulsar el catabolismo de los BCAA en los seres humanos. Además, se cree que la administración de BCAA antes o durante la práctica deportiva puede elevar los niveles séricos y musculares esqueléticos de estos aminoácidos. Objetivo: Analizar los efectos de la administración de aminoácidos de cadena ramificada sobre las concentraciones plasmáticas de triptófano y tirosina tras la actividad física. Métodos: Se realizó una búsqueda exhaustiva en bases de datos electrónicas (Google Scholar, Cochrane Library Scopus y Medline) hasta junio de 2022 de estudios que evaluaran los efectos de los BCAA en la concentración plasmática de triptófano y tirosina tras una lesión muscular. La media y la desviación estándar de los niveles de seguimiento de triptófano y tirosina se registraron para calcular el tamaño del efecto para el análisis. Resultados: La ingestión de BCAA tuvo un efecto reductor considerable sobre los niveles de triptófano: (DMP = -1,14 µmol.L -1, IC 95%: -1,64, -0,65; P = 0,021). Se observó una heterogeneidad considerable entre los artículos (prueba Q de Cochran = 990,80; P = 0,000; I2 = 96,7 %). El impacto de la administración de BCAA sobre los niveles de tirosina evaluados en 13 ensayos y análisis indicó un efecto de disminución significativo sobre los niveles de tirosina en la diferencia de medias combinada (DMP = -8,77 µmol.L -1, IC 95%: -14,33, -3,21; P = 0,000). También se observó una heterogeneidad considerable entre los artículos (prueba Q de Cochran = 212,84; P = 0,000; I2 = 87,3 %). Conclusión: Es seguro teorizar que los BCAA estimulan las tasas netas de síntesis proteica en las fases de recuperación prolongadas, de modo que los distintos niveles de aminoácidos esenciales que contienen el aminoácido aromático disminuyen en el suero. ***Nivel de evidencia II; Estudios terapéuticos - investigación de los resultados del tratamiento.***

***Descriptores*:** *Aminoácidos de Cadena Ramificada; Triptófano; Tirosina; Ejercicio Físico.*

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INTRODUCTION

The branched-chain amino acids (BCAAs) include leucine, isoleucine, and valine account for 35 percent of the indispensable amino acids existed in skeletal muscle proteins.[1] It has been indicated that branched-chain amino acids specially leucine has significant role in protein metabolism by elevating the rate of protein synthesis and reducing the rate of protein break down.[2,3] Plasma levels of free amino acids demonstrate equilibrium between exogenous uptake and produced metabolites in protein metabolism.[4]

Recently, BCAA supplementation have been widely consumed in sports.[5] It has been determined that physical activity (PA) affects the metabolism of amino acids.[6] Also, during PA, the branched-chain amino acid (BCAA) are used in muscle as source of energy and BCAA levels can reduce with extended sport.[7] Actually, sports can boost BCAAs catabolism in human.[6] Also, administration of BCAA pre or during sport can elevated both the serum and skeletal muscle levels of these amino acids.[8]

BCAA has effects similar to insulin on glucose, leading to decrease in glucose concentration. BCAA that are supplemented pre PA may be oxidized via human muscles and applied as energy within the PA, diminishing the requirement of liver for increasing grades of glycogenosis. Within endurance PA, pyruvates molecule which are the results of glucose metabolisms are altered to lactate, a metabolite which can cause metabolic acidosis.[9,10] Elevated dosages of lactate make glucoses metabolism to cease until decrease more pH decline. BCAA administration has been revealed to reduce lactate concentrations in the skeletal muscles, permitting glucoses metabolisms to carry on.[11] This outcomes in decreased rate of glycogenosis in the liver and less serum concentrations of glucose consequently. Although, articles performed regarding chronic effect of BCAA on glucoses concentrations have revealed that stable BCAA administration don't have a considerable effects on bloods glucoses concentration without PA.[12] Also past assays have revealed that BCAA decrease concentrations of circulating free fatty-acids (FFA) in the blood.[13] FFA challenge for binding's site with tryptophan on albumins and where concentrations of FFA in the bloodstream are reduced, concentrations of free tryptophan reduce as more are bind with albumins. Within PA, concentrations of free tryptophan pass into the brain are elevated, leading to augment in 5 hydroxytryptamines (5-HT, aka serotonins), a molecules for the fatigues feeling. Within their decrease in FFA concentrations in the bloodstream, BCAA may assist to decrease the concentrations of free tryptophan pass into brain, and assist to decrease the feeling of fatigues as PA outcomes.[14] Decrease in tryptophan absorption in the brain cause decrement in serotonins clearance and synthesis.[15] Decrease in serotonin may be as high as 95 percent; low serotonin concentrations reduce fatigue sensations, but cause to lack of focus, aggressive treatment, poor impulse control and downscale planning.[16]

As well as, consumption of either a mixture of BCAA or leucine alone in human can reduce the blood and the skeletal muscle levels of several amino acids, including the aromatic amino acids such as tryptophan and tyrosine.[17] Also, it is offered that these alteration can created by a reduction in the rate of protein break down in skeletal muscle. Therefore, the elevated rate of use of BCAA by skeletal muscle can lead to a reduction in its blood level. So, there is a growth in the level ratio of free tryptophan/BCAA in the blood.[18] In addition, in previous studies, it is offered that during extended PA the elevated catabolism of BCAA and the shift of tryptophan from albumin by the augmenting fatty acid level result in an enhance in the tryptophan/BCAA ratio.[19] Previous studies showed that BCAA consumption before PA can lead to a reduction in serum aromatic amino acids such as tryptophan and tyrosine levels.[2,20] Total related papers have been recorded and to the data quality allows and the BCAA effect on tryptophan and tyrosine post of PA have been evaluated in more detailed than in the past studies. The present meta-analysis evaluated plasma amino acids, including tryptophan and tyrosine plasma levels, amongst healthy adult subjects of both genders, considering reported trials. Current meta-analysis prepares an extensive literature analysis with regards the hypothesis that BCAA administration can reduces tryptophan and tyrosine levels.

METHODS

Strategy of Search

This meta-analysis carried out according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21] From inception to June 2022 a electronic searching conducted applying diverse database consists of Scopus, ISI Web of Science, PubMed and a search in Google Scholar. These keywords and their complex used, including: "branched chain amino acid", "plasma amino acids", "sports", "amino acids"," exercise", "physical activity" and "amino acids, branched--chain". "controlled trial", "tyrosine", "tryptophan" and "cross-over design". References section of the whole papers checked for more suitable studies.

Criteria of Eligibility

Papers should have involved human subjects supplemented with BCAA administration pre PA or pre and post PA. Papers meeting the following criteria selected for screening: 1) the study designs was randomized in a supplementation group (BCAA) and a placebo group; 2) at least one result measures of plasma tryptophan and tyrosine; 3) BCAA used pre or post PA and repeat the administration procedure on subsequent days' post PA and 4) participants might be men, women or both and of any athletic training situation. There were no limitations placed on the PA type or placebo applied. Papers using multiple administrations, such as BCAA in mixture with another nutrient not investigated.

Selection of studies

Two independent authors selected studies for inclusion. The title and abstract of papers achieved in the searching strategies checked. All studies classified as related with either of the authors retrieved. According to the data based on information, we applied standardized forms to select the studies eligible for inclusion in review. Contradiction between authors resolved by consensus or third reviewer.

Data extraction

Two independent reviewers conducted the data extraction by a customized sheet and solved difference with consensus. This applied to extract related information on methodological designs, eligibility criteria, intervention (including features of the BCAA administration protocol), and comparison and result measures.

Measures of treatment effect

Mean difference and standard deviations calculated on continuous outcomes for every study. For continuous outcomes which pooled on different scale, standardized means differences applied. We had designed to preferentially extract information according to change from pre-intervention (means changes score); although, most of papers recorded follow-ups score. In the models that there were no heterogeneity evidences of effects (P>0.1), a fixed-effects models applied for meta-analysis. In situation that there were statistically heterogenic evidences, we screened the results by random-effect modes.

NutriGrade

For evaluating the whole quality of meta-analysis regard to the BCAA supplementation efficacy on tryptophan and tyrosine, we applied the NutriGrade rating system.[22] NutriGrade applies a rating system (0 to 10) to determine the meta-analysis quality performed in the nutrition field. NutriGrade provides these items: 1) bias risk (3 scores), 2) precision (1 score), 3) heterogeneity (1 score), 4) directness (1 score), 5) publication bias (1 score), 6) funding bias (1 score) and study design (2 scores). For evidence validity assessment, NutriGrade provides 4 categories: 1) high (≥8 scores); 2) moderate (6–7.9 scores); 3) low (4–5.9 scores) and 4) very low (≤ 3.9 scores).[22]

RESULTS AND DISCUSSION

Searching outcomes

Computerized search found 148 related articles. After remove of duplicate articles, a wide checking of papers title and abstract was performed on 138 articles. Fourteen articles left after screening the eligibility of the inclusion and exclusion criteria. Finally, 7 articles included in meta-analysis, consist of 17 and 13 effect sizes for tryptophan and tyrosine concentration, that assessed 107 and 97 subjects respectively. These participants covering numbers who dropout in several trials. Subjects age were 21 to 41 years old and in one study participants were men[8,18,19,23] and in a study that only females took part[24] (n = 12).

Figure 1 and Table 1 presented reasons for studies exclusion and selection process. In summary, the papers published 1991 to 2015. The participant's number who finished the assays was 52 participants in intervention and 55 in control group for tryptophan levels and 47 participants in intervention and 50 in control group for tyrosine levels. The BCAA duration of supplementation was between one day to 21 days. Cross over designation used in all studies except one study[18] that applied randomized cross-over design. The BCAA effect on tryptophan and tyrosine was examined in all studies together except in one study that examined tryptophan only.[23]

For both amino acids, most of the studies evaluated some follow-up time (immediately, 5, 10, 15, 30 and 60 minutes and 1, 2, 24, 48 and 72 hours after PA for tryptophan and tyrosine levels). We extracted outcomes recorded minutes and hours after PA and latter days. All 7 trials had a follow-up time immediately post PA; Eight trials reported below 1 hour follow-up times; Two trials presented 1 hour follow-up times and five trials reported more than 1 day follow-up times post PA. Moreover, paricipants in all studies were trained except in one study that paricipants had untrained status.[23]

Results of quality assessments

The bias evaluation quality presented in Table 2. Briefly, participant's random allocation was reported in whole articles. However, seven studies reported the random sequence generation method.[18,25] One study reported allocation concealment.[25] All studies reported low bias risk according to incomplete outcome and elective outcome report. Also, all articles had high and unclear bias risk for participants and personnel blinding except two articles that reported low risk about of participants and personnel blinding and assessment of outcome.[7,25] At last, most of articles had medium bias risk and one article had low bias risk.[25]

Findings from BCAA supplementation effects on plasma amino acids

BCAA supplementation effects on tryptophan levels

According to analysis on 17 trials, BCAA administration had significant decreasing effect on tryptophan levels overall: (WMD = -1.14 μmol.L^{-1}, 95% CI: -1.64, -0.65; P = 0.021). Considerable heterogeneity observed amongst the articles (Cochran's Q test= 990.80, P = 0.000, I^2 = 96.7 %) (Figure 2). For evaluating if the effect of BCAA administration on tryptophan levels is contradictory based on subgroup analysis, meta-analysis performed by supplementation duration (≤1 week or >1 week), gender type (male and female) and BCAA dosage (≤10 g/day or >10 g/day) (Table 3). Subgroup analyses indicated that BCAA administration have a significant decreasing effect on tryptophan levels in trials with both dose of ≤10 g/day or >10 g/day, trials with female participant and trials with both ≤1 week or >1 week duration.

BCAA supplementation effects on tyrosine levels

BCAA administration impact on tyrosine levels evaluated in 13 trials and analysis indicated a significant decreasing effect on tyrosine levels

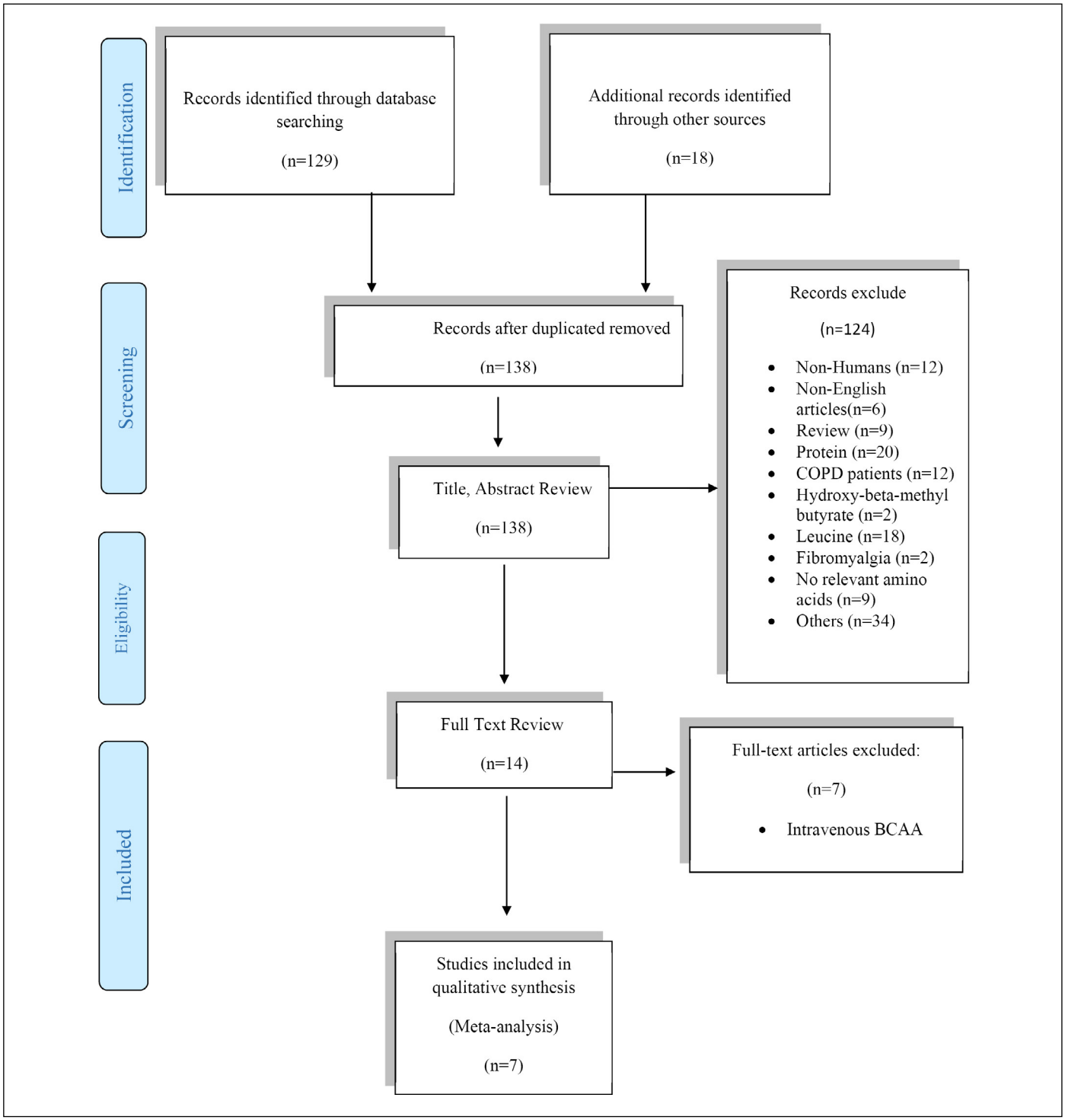

Figure 1. Features of included articles.

Table 1. Characteristics of the related papers.

Author (year)	Study design characteristics						Average age (y)	Sample size		Exercise type	Amino acids Assessment
	Design	Country	Training status	Bcaa dose (g/d)	Duration (D)	Gender		Bcaa	Placebo		
Graham et al. (1995)	CP	USA	T	0.5	1	M	24	5	5	aerobic	trp
Wagenmakers et al. (1995)	CP	USA	T	6	21	M	23	10	10	resistance	Trp, Tyr
Wagenmakers et al. (1995)	CP	USA	T	18	21	M	23	10	10	resistance	Trp, Tyr
Shimomura et al. (2009)	CP	Japan	U	5.5	3	F	22	6	6	resistance	Trp, Tyr
Blomstrand et al. (1991)	RP	Sweden	T	7.5	1	M	39	11	14	resistance	Trp, Tyr
Blomstrand et al. (1991)	RP	Sweden	T	16	1	M	41	13	13	resistance	Trp, Tyr
Blomstrand et al. (1996)	CP	Sweden	T	7	21	M	25	7	7	resistance	Trp, Tyr
Fouré et al. (2015)	RP	France	U	7	6	M	22	13	13	resistance	Tyr
Matsomuto et al. (2009) #	CP	Japan	U	2	6	M	21	8	8	aerobic	-

Tyr = Tyrosine; Trp = Tryptophan; RP = randomized controlled trial; CP = cross-over studies; M = male; F = Female; D=Days; Y=years; T=trained; U= untrained. # excluded from meta-analysis.

Table 2. Cochrane Risk of Bias Assessment.

Study	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall Risk of Bias
Graham et al. (1995)	U	U	U	U	L	L	L	Medium
Wagenmakers et al. (1995)	U	U	U	U	L	L	L	Medium
Wagenmakers et al. (1995)	U	U	U	U	U	L	L	Medium
Shimomura et al. (2009)	U	U	U	U	U	L	L	Medium
Blomstrand et al. (1991)	U	U	U	H	L	L	L	Medium
Blomstrand et al. (1991)	L	U	U	U	L	L	L	Medium
Blomstrand et al. (1996)	U	U	U	U	U	L	L	Medium
Fouré et al. (2015)	L	L	L	L	L	L	L	Low
Matsomuto et al. (2009) #	U	U	U	L	L	L	L	Medium

L, low risk of bias; H, high risk of bias; M, medium risk of bias; U, unclear risk of bias.

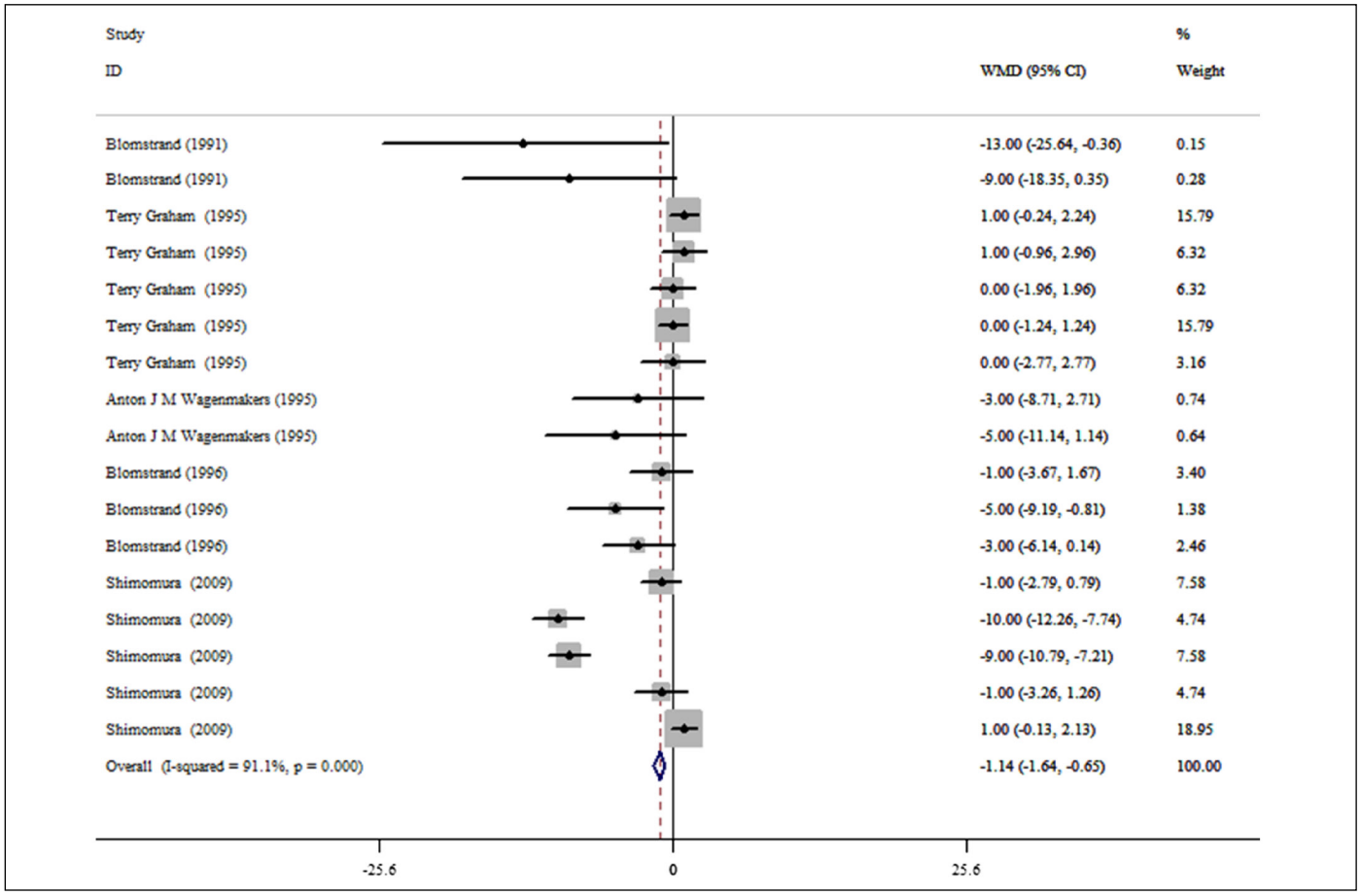

Figure 2. Forest plot of the effect of BCAA administration on tryptophan. WMD = weighted mean difference; CI = confidence interval.

Table 3. Subgroup Analysis to Assess the Effect of BCAA on Tryptophan and Tyrosine concentration.

Subgrouped by	No. of trials	Effect size[1]	95% CI	P Value	I^2 (%)	p for heterogeneity
Tryptophan						
Dose of BCAA						
≤10 g/day	11	0.467	-0.249 1.182	0.011	93.5	<0.001
>10 g/day	2	-3.907	-6.923 -0.890	0.018	0.0	0.483
Duration						
≤1 week	12	-2.301	-4.541 -0.061	0.044	93.7	<0.001
>1 week	5	-2.681	-4.356 -0.684	0.002	0.0	0.509
Gender						
Male	12	-0.836	-2.013 0.341	0.164	54.5	0.012
Female	5	-2.520	-8.512 0.572	0.047	97.0	<0.001
Tyrosine						
Dose of BCAA						
≤10 g/day	11	-8.73	-14.71 -2.66	0.005	97.8	<0.001
>10 g/day	2	-9.00	-14.32 -3.20	0.005	0.0	1
Duration						
≤1 week	8	-10.324	-21.659 1.011	0.074	98.2	<0.001
>1 week	5	-8.744	-16.268 -1.220	0.023	95.6	<0.001
Gender						
Male	8	-9.575	-17.748 -1.402	0.022	93.4	<0.001
Female	5	-7.632	-16.390 1.125	0.088	98.8	<0.001

[1]Calculated by random effects model. CI = confidence interval.

in pooled mean difference (WMD = -8.77 μmol.L^{-1}, 95% CI: -14.33, -3.21; P = 0.000) (Figure 3). Also considerable heterogeneity observed amongst the articles (Cochran's Q test = 212.84, P = 0.000, I^2 = 87.3 %)**.** For evaluating if the BCAA administration effect on tyrosine levels is contrary according to subgroup analysis, meta-analysis performed meta-analysis performed by supplementation duration (≤1 week or >1 week), gender type (male and female) and BCAA dosage (≤10 g/day or >10 g/day) (Table 3). Subgroup analyses indicated that BCAA administration have a significant decreasing effect on tyrosine levels in trials with both dose of ≤10 g/day or >10 g/day, trials with male participant and trials with >1 week duration.

Sensitivity analysis

No alteration observed in the meta-analysis outcomes with removal of any the studies from the analysis, on plasma tyrosine levels according to sensitivity analysis while, the outcomes on tryptophan levels were sensitive to omitting 1 study.[18] Funnel plots were symmetric for tryptophan levels (Figure 4), and the Begg's test outcomes didn't specify publication bias evidence in articles that investigate the BCAA consumption effect in tryptophan concentration (Begg's test, P = 0.123) and in tyrosine (Begg's test, P = 0.617).

NutriGrade

Total quality points of outcomes, that assessed by the NutriGrade scoring system, were 6.1 for tryptophan (indicating medium confidence in effect estimate, that shows future RCTs with appropriate designation required for our results affirmation), and 5.3 for tyrosine (indicating low confidence in the effect estimate, that shows further assays will suggest considerable documents on the confidence in effect estimate and probably convert the estimation effects).

CONCLUSION

The present work is the first systematic review and meta-analysis, assess the efficiency of BCAAs on athletic tyrosine and tryptophan levels post of PA. The present evidences based data suggested that BCAAs is better than applying rest or recovery without supplementation post of diverse types of endurance and injuring PA. The benefits in relation to a reduction in aromatic amino acids, and improved muscles functions due to a debilitation of muscles strengths and muscles powers detriment post of PA. These effects quality appears to be relevant in treatment although can be utmost useful for professional PA.

All authors declare no potential conflict of interest related to this article

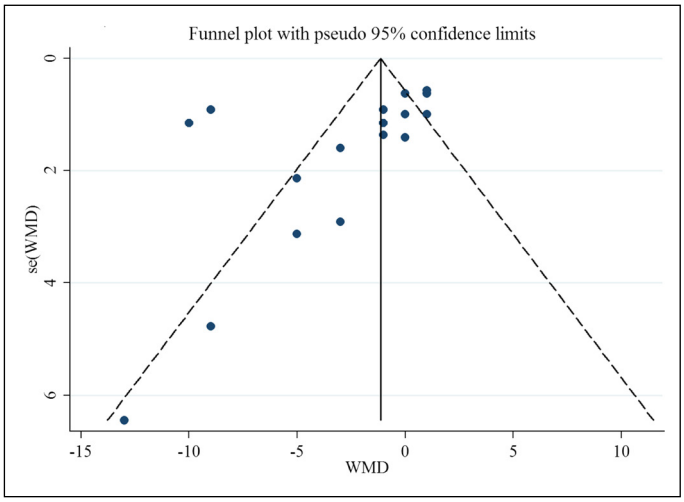

Figure 4. Funnel plot for evaluating publication bias in tryptophan.

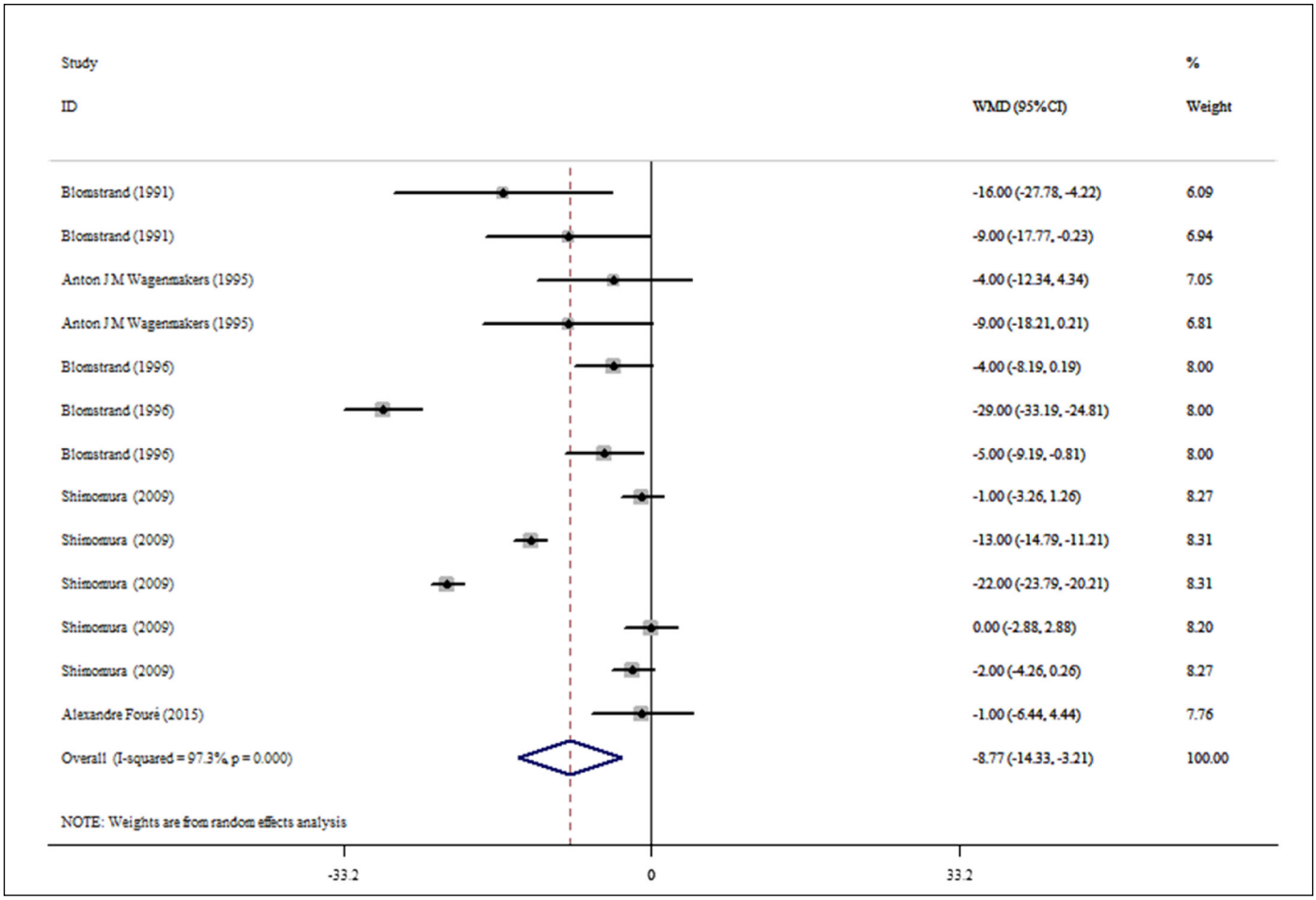

Figure 3. Forest plot of the effect of BCAA administration on tyrosine. WMD = weighted mean difference; CI = confidence interval.

AUTHORS' CONTRIBUTIONS: The work is conceived and its knowledge content is completed by Lei Liu (ORCID: 0000-0002-6129-1054). The manuscript is drafted by Fu-gao Jiang (ORCID: 0000-0001-7539-2369). Each authors contributed in execution and writing of this manuscript.

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