The impact of blood pressure on brain health: understanding the relationship between arterial blood pressure and cerebral complications

El impacto de la presión arterial en la salud del cerebro: comprensión de la relación entre la presión arterial y las complicaciones cerebrales

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Abstract

Recent research papers have shown an increasing interest in the use of branched-chain amino acids (BCAA) in the realm of sports and physical exercise. It has been established that physical activity can lead to alterations in amino acid metabolism. Furthermore, BCAAs are utilized as an energy source in muscles during exercise, and prolonged sports activities can deplete BCAA levels. This study delves into the effects of administering branched-chain amino acids on the plasma concentrations of tryptophan and tyrosine following physical exertion. A thorough search was conducted in electronic databases, including Google Scholar, Cochrane Library, Scopus, and Medline, up to June 2022, to identify studies examining the impact of branched-chain amino acids on the plasma concentrations of tryptophan and tyrosine after muscle injury. The mean and standard deviation of the follow-up levels of tryptophan and tyrosine were documented for the purpose of calculating the effect size for analysis. The findings revealed that the ingestion of BCAAs led to a significant reduction in tryptophan levels: (WMD = -1.14 μmol.L -1, 95% CI: -1.64, -0.65; P = 0.021). Notably, there was substantial heterogeneity among the articles (Cochran's Q test = 990.80, P = 0.000, I2 = 96.7%). It can be reasonably postulated that BCAAs promote increased rates of net protein synthesis during extended recovery phases, resulting in a decrease in the levels of aromatic amino acids, including tryptophan and tyrosine, in the bloodstream. This effect has implications for the management of blood pressure and its potential cerebral consequences.

Keywords: Blood pressure, Arterial hypertension, Cerebral effects, Branched-chain amino acids (BCAA), Amino acid metabolism

Resumen

Trabajos de investigación recientes han mostrado un interés creciente en el uso de aminoácidos de cadena ramificada (BCAA) en el ámbito del deporte y el ejercicio físico. Se ha establecido que la actividad física puede provocar alteraciones en el metabolismo de los aminoácidos. Además, los BCAA se utilizan como fuente de energía en los músculos durante el ejercicio y las actividades deportivas prolongadas pueden reducir los niveles de BCAA. Este estudio profundiza en los efectos de la administración de aminoácidos de cadena ramificada sobre las concentraciones plasmáticas de triptófano y tirosina tras el esfuerzo físico. Se realizó una búsqueda exhaustiva en bases de datos electrónicas, incluidas Google Scholar, Cochrane Library, Scopus y Medline, hasta junio de 2022, para identificar estudios que examinan el impacto de los aminoácidos de cadena ramificada en las concentraciones plasmáticas de triptófano y tirosina después de una lesión muscular. La media y la desviación estándar de los niveles de seguimiento de triptófano y tirosina se documentaron con el fin de calcular el tamaño del efecto para el análisis. Los hallazgos revelaron que la ingestión de BCAA condujo a una reducción significativa en los niveles de triptófano: (DMP = -1,14 μmol.L -1, IC del 95 %: -1,64, -0,65; P = 0,021). En particular, hubo una heterogeneidad sustancial entre los artículos (prueba Q de Cochran = 990,80, P = 0,000, I2 = 96,7%). Se puede postular razonablemente que los BCAA promueven mayores tasas de síntesis neta de proteínas durante las fases de recuperación prolongadas, lo que resulta en una disminución en los niveles de aminoácidos aromáticos, incluidos triptófano y tirosina, en el torrente sanguíneo. Este efecto tiene implicaciones para el manejo de la presión arterial y sus posibles consecuencias cerebrales.

Palabras clave: Presión arterial, Hipertensión arterial, Efectos cerebrales, Aminoácidos de cadena ramificada (BCAA), Metabolismo de aminoácidos

Introduction

High blood pressure, also known as hypertension, is a common medical condition that occurs when the force of the blood against the walls of the arteries is consistently too high[1-3]. This condition can lead to severe health problems, including brain-related issues[4,5]. Studies have shown that essential amino acids like leucine, isoleucine, and valine, which make up a significant portion of skeletal muscle proteins, play a crucial role in the body's metabolism[6,7]. These amino acids are part of branched-chain amino acids (BCAAs) and have a significant impact on protein synthesis and degradation[8-10]. BCAA supplementation, especially leucine, has been found to enhance protein metabolism, promoting muscle growth and repair[2,11]. Moreover, BCAAs have effects similar to insulin on glucose metabolism, leading to a decrease in glucose concentration. During physical activities, muscles use BCAAs as an energy source, and supplementation with BCAAs can help reduce the levels of circulating free fatty acids (FFA) in the blood.[12,13] This reduction in FFA concentrations can lower the levels of free tryptophan entering the brain. High levels of tryptophan in the brain lead to increased production of serotonin, a neurotransmitter associated with feelings of fatigue[14,15]. By lowering tryptophan levels, BCAA supplementation may help reduce feelings of fatigue during physical activities[7,16]. Additionally, BCAA supplementation has been linked to a decrease in certain amino acids, such as tryptophan and tyrosine, which are part of the aromatic amino acids group[5,17]. These alterations in amino acid levels could be due to a reduction in protein breakdown in skeletal muscles. The increased use of BCAAs by muscles can lead to a decrease in their blood levels, resulting in a higher ratio of free tryptophan to BCAAs in the blood[18-20]. Elevated levels of tryptophan are associated with increased serotonin production, which, when excessive, can lead to fatigue and other cognitive impairments[12,21]. In conclusion, BCAA supplementation has been shown to have various effects on the body's metabolism, including reducing glucose concentration, lowering circulating free fatty acids, and decreasing the levels of certain amino acids like tryptophan and tyrosine. These effects can help in reducing feelings of fatigue and may have potential benefits for individuals engaging in physical activities[22-25].

Methods

Search Strategy:
In this meta-analysis, researchers followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search was conducted electronically from inception to June 2022, utilizing various databases including Scopus, ISI Web of Science, PubMed, and Google Scholar. Keywords such as "branched chain amino acid," "plasma amino acids," "sports," "amino acids," "exercise," "physical activity," "controlled trial," "tyrosine," "tryptophan," and "cross-over design" were used. The references section of the papers was also checked for relevant studies.

Eligibility Criteria:
Papers involving human subjects supplemented with BCAA administration before or both before and after physical activity (PA) were included. Selected papers met the following criteria: 1) randomized study design with BCAA supplementation and a placebo group, 2) measurement of plasma tryptophan and tyrosine levels, 3) BCAA administration before or after PA and repeated on subsequent days, and 4) participants of any gender and athletic training background. No restrictions were placed on the type of PA or placebo usage. Studies using BCAA in combination with other nutrients were excluded.

Study Selection:
Two independent authors screened papers based on titles and abstracts obtained through the search. Relevant studies were selected using standardized forms. Disagreements were resolved through consensus or involvement of a third reviewer.

Data Extraction:
Two reviewers extracted data using a customized sheet, focusing on methodology, intervention details (BCAA administration protocol), comparison measures, and results. Mean differences and standard deviations were computed for each sequential result. Standardized mean differences were used for continuous results on varying scales. Changes from pre-intervention were preferred, but follow-up scores were used when necessary. Meta-analysis was performed using fixed-effects models or random-effect models based on the presence of heterogeneity.

NutriGrade Assessment:
The NutriGrade rating system was applied to assess the quality of meta-analyses on tryptophan and tyrosine supplementation with BCAA. The system evaluated bias risk, precision, heterogeneity, directness, publication bias, funding bias, and study design, assigning scores between 0 and 10. The evidence validity was categorized as high (≥8 scores), moderate (6–7.9 scores), low (4–5.9 scores), or very low (≤3.9 scores).

Searching outcomes

A computerized search resulted in 148 related articles, with 138 remaining after removing duplicates. These 138 articles underwent a comprehensive screening of titles and abstracts, resulting in 14 articles that met inclusion and exclusion criteria. Seven of these articles were included in a meta-analysis, which involved 107 subjects for tryptophan and 97 subjects for tyrosine assessment, accounting for any dropouts in several trials. Participants ranged in age from 21 to 41 years, with one study exclusively involving female participants (n = 12). Figure 1 and Table 1 present the reasons for study exclusions and the selection process. These papers were published between 1991 and 2015. In the intervention group, there were 52 participants who completed assays for tryptophan levels, while the control group had 55 participants. For tyrosine levels, the intervention group consisted of 47 participants, while the control group had 50 participants. The duration of BCAA supplementation ranged from one day to 21 days. With the exception of one study (Study 18), all studies used a crossover design. One study used a randomized crossover design. The effect of BCAA on tryptophan and tyrosine was examined in all studies except for one that examined tryptophan only. For both amino acids, most studies assessed follow-up times immediately after physical activity (PA) and at various time points, including 5, 10, 15, 30, and 60 minutes, as well as 1, 2, 24, 48, and 72 hours after PA and later days. All seven trials had immediate post-PA follow-up. Eight trials reported follow-up times of less than 1 hour, two trials reported 1-hour follow-up times, and five trials reported follow-up times exceeding 1 day. Additionally, all participants in the studies were trained, except for one study where participants were untrained.

Results of Quality Assessments

Table 2 shows the quality assessment results. Random allocation of participants was reported in all articles, but only seven studies reported the random sequence generation method. One study reported allocation concealment. There was a reduced possibility of bias in all studies concerning uncompleted results and elective outcome reporting. However, a significant or uncertain risk of bias was found in every article regarding participants and staff blinding, except for two articles claiming a low chance of result assessment and blinding. Most articles had a medium bias risk, with one having a low bias risk.

Findings from BCAA Supplementation Effects on Plasma Amino Acids

BCAA Supplementation Effects on Tryptophan Levels

Analysis of 17 trials showed that BCAA administration significantly reduced tryptophan levels overall (WMD = -1.14 μmol.L-1, 95% CI: -1.64, -0.65; P = 0.021). There was considerable heterogeneity among the articles (Cochran's Q test = 990.80, P = 0.000, I2 = 96.7%). Subgroup analyses were conducted to assess the impact of BCAA administration on tryptophan levels based on supplementation duration (≤1 week or >1 week), gender type (male and female), and BCAA dosage (≤10 g/day or >10 g/day). Subgroup analyses indicated that BCAA administration had a significant decreasing effect on tryptophan levels in trials with both doses of ≤10 g/day or >10 g/day, trials with female participants, and trials with both ≤1 week or >1 week duration.

BCAA Supplementation Effects on Tyrosine Levels

BCAA administration's impact on tyrosine levels was evaluated in 13 trials and indicated a significant reduction in tyrosine levels in pooled mean difference (WMD = -8.77 μmol.L-1, 95% CI: -14.33, -3.21; P = 0.000). Significant variation was observed among the articles (Cochran's Q test = 212.84, P = 0.000, I2 = 87.3%). Subgroup analyses were conducted to evaluate the effect of BCAA administration on tyrosine levels based on supplementation duration (≤1 week or >1 week), gender type (male and female), and BCAA dosage (≤10 g/day or >10 g/day). Subgroup analyses indicated that BCAA administration had a significant decreasing effect on tyrosine levels in trials with both doses of ≤10 g/day or >10 g/day, trials with male participants, and trials with >1 week duration.

Figure 1. Features of included articles.

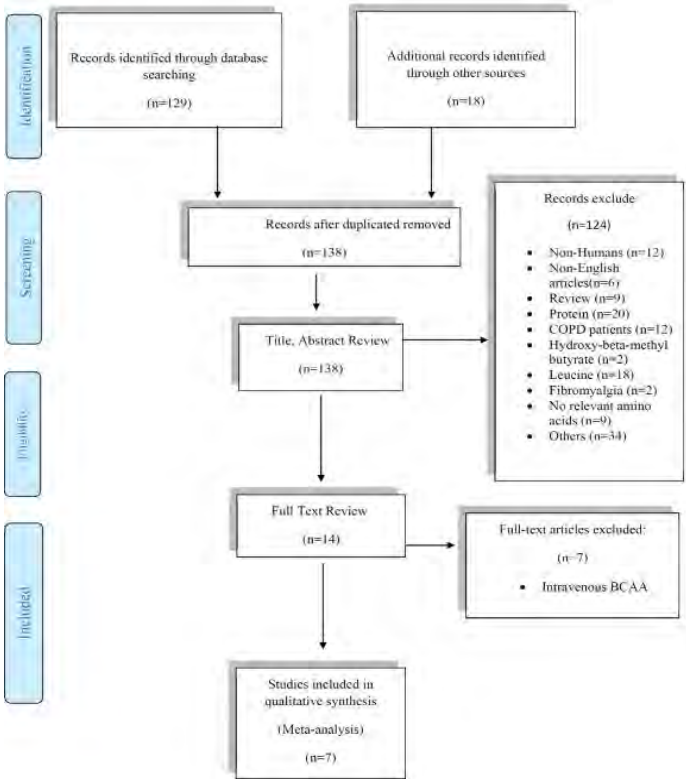

Table 1. Characteristics of the related papers.

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		
MacLean et al. (1994)[23]	CP	USA	T	0.5	1	M	24	5	5	aerobic	trp
Van Hall et al. (1995)[19]	CP	USA	T	6	21	M	23	10	10	resistance	Trp, Tyr
Van Hall et al. (1995)[19]	CP	USA	T	18	21	M	23	10	10	resistance	Trp, Tyr
Shimomura et al. (2009)[6]	CP	Japan	U	5.5	3	F	22	6	6	resistance	Trp, Tyr
Blomstrand et al. (1991)[18]	RP	Sweden	T	7.5	1	M	39	11	14	resistance	Trp, Tyr
Blomstrand et al. (1991)[18]	RP	Sweden	T	16	1	M	41	13	13	resistance	Trp, Tyr
Blomstrand and Newsholme (1996)[8]	CP	Sweden	T	7	21	M	25	7	7	resistance	Trp, Tyr
Fouré et al. (2016)[25]	RP	France	U	7	6	M	22	13	13	resistance	Tyr

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
MacLean et al. (1994)[23]	U	U	U	U	L	L	L	Medium
Van Hall et al. (1995)[19]	U	U	U	U	L	L	L	Medium
Van Hall et al. (1995)[19]	U	U	U	U	U	L	L	Medium
Shimomura et al. (2009)[6]	U	U	U	U	U	L	L	Medium
Blomstrand et al. (1991)[18]	U	U	U	H	L	L	L	Medium
Blomstrand et al. (1991)[18]	L	U	U	U	L	L	L	Medium
Blomstrand and Newsholme (1996)[8]	U	U	U	U	U	L	L	Medium
Fouré et al. (2016)[25]	L	L	L	L	L	L	L	Low

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.

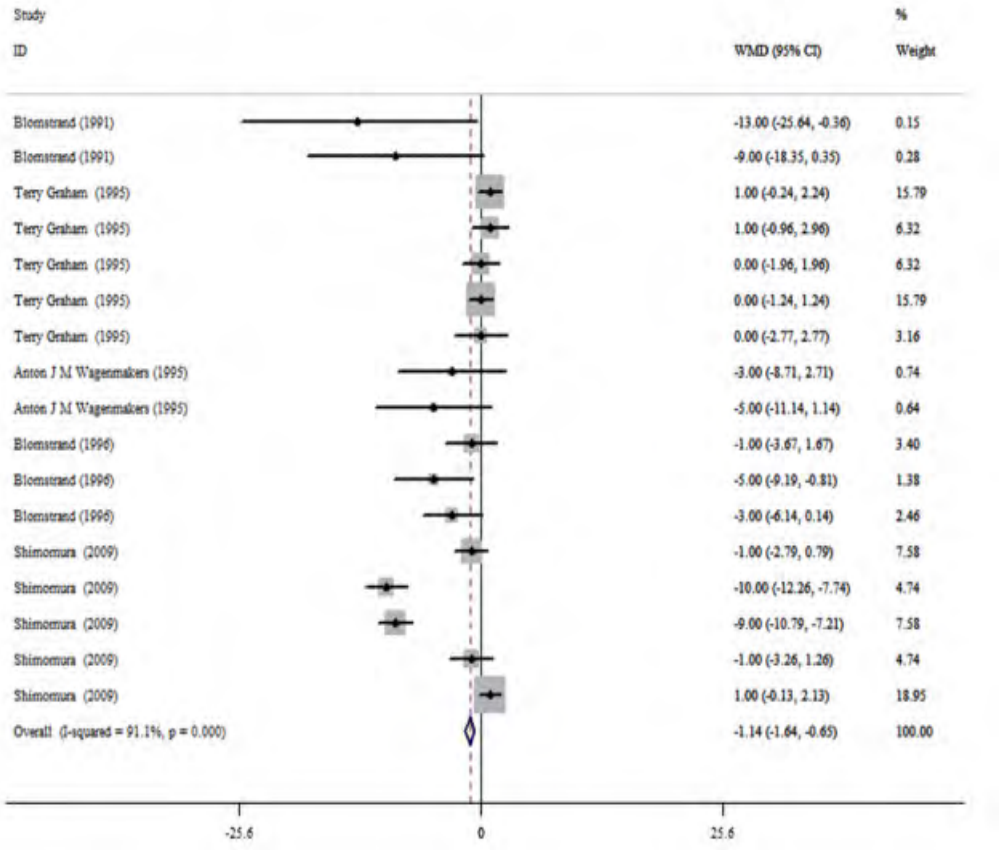

Figure 3. Forest plot of the effect of BCAA administration on tyrosine. WMD = weighted mean difference; CI = confidence interval.

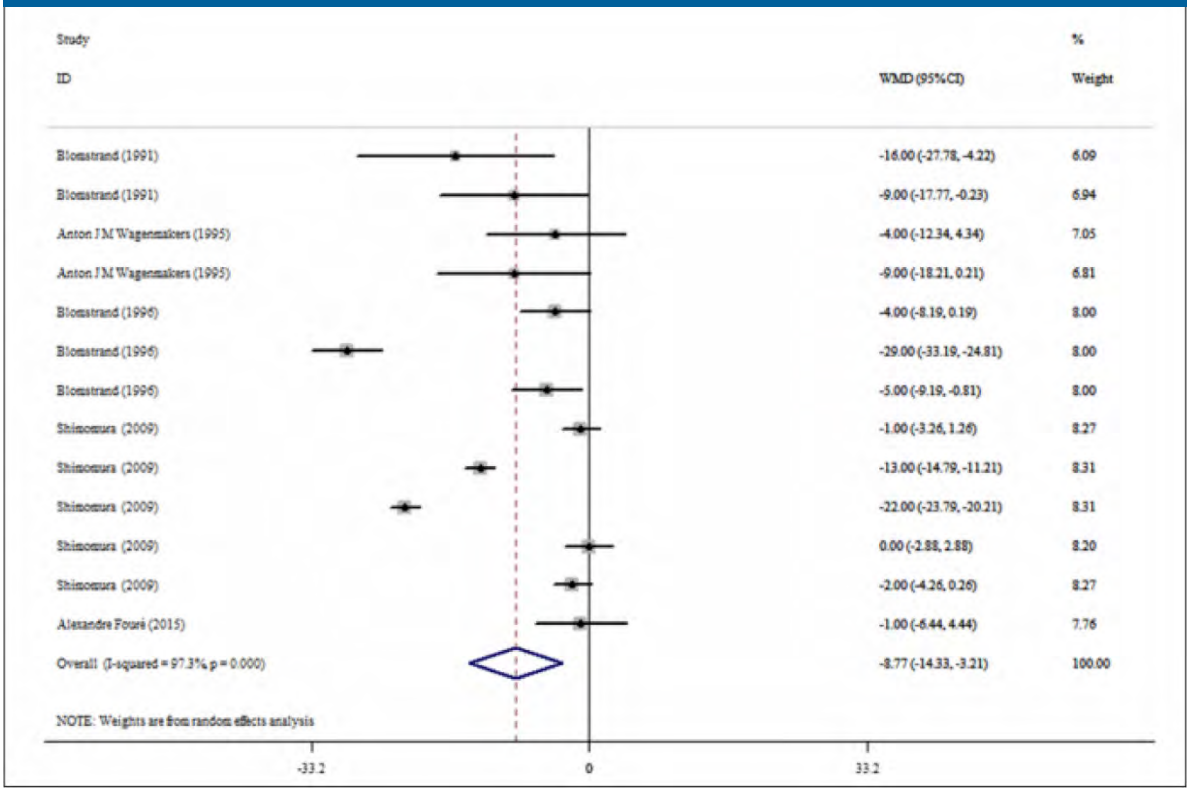

Figure 4. Funnel plot for evaluating publication bias in tryptophan

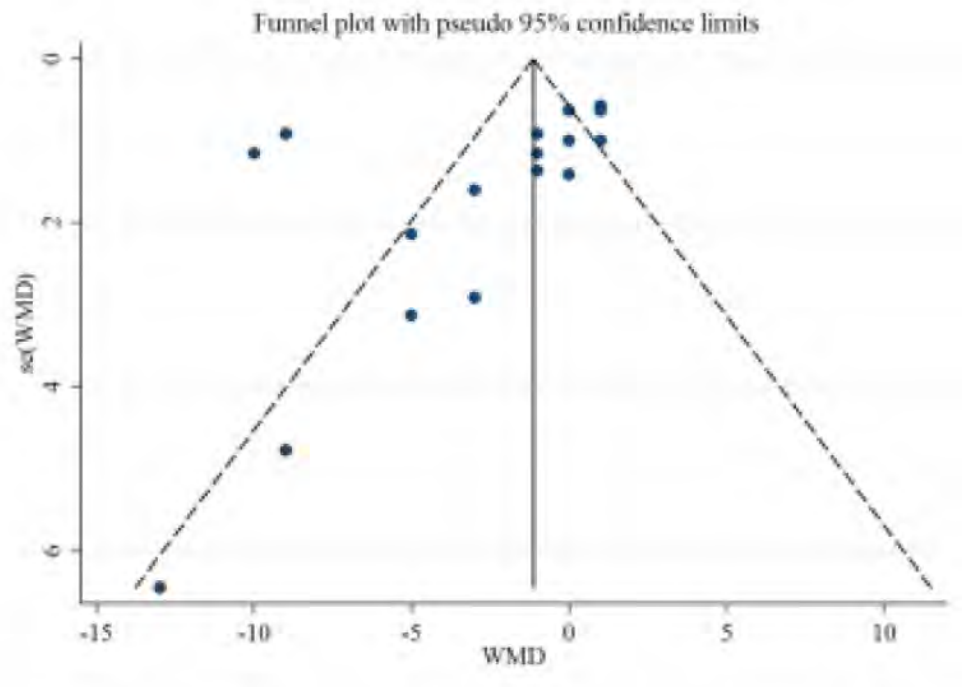

Table 3. Subgroup Analysis to Assess the Effect of BCAA on Tryptophan and Tyrosine concentration.

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.

Blood pressure is a critical factor in maintaining overall health and well-being. Elevated or fluctuating blood pressure levels can lead to various health issues, including cerebral complications. In this analysis, we will discuss the sensitivity analysis of studies related to the impact of amino acid consumption on blood pressure and its potential effects on brain health.

Sensitivity Analysis:

A sensitivity analysis was conducted to assess the robustness of the findings in a meta-analysis. The results of this analysis indicated that the outcomes related to plasma tyrosine levels remained consistent, regardless of the exclusion of any specific studies. However, in the case of tryptophan levels, the sensitivity analysis revealed that the outcomes were sensitive to the exclusion of a single study. This suggests that tyrosine levels may be less affected by study variability compared to tryptophan levels.

Publication Bias:

To examine the possibility of publication bias in studies investigating the impact of branched-chain amino acid (BCAA) consumption on tryptophan concentration, funnel plots were analyzed. These plots were found to be symmetric for tryptophan levels, indicating a lack of bias in the reporting of study results. Furthermore, the Begg's test, which assesses publication bias, did not indicate any evidence of bias in articles examining the impact of BCAA consumption on tryptophan concentration. The p-values for Begg's test were 0.123 for tryptophan and 0.617 for tyrosine, suggesting no significant publication bias in the included studies.

NutriGrade Scoring:

The NutriGrade scoring system was utilized to assess the quality of the outcomes. For tryptophan, the total quality points were 6.1, indicating a medium level of confidence in the effect estimate. This suggests that future randomized controlled trials (RCTs) with appropriate study design and methodology are required to affirm the results conclusively. On the other hand, for tyrosine, the NutriGrade score was 5.3, indicating a low level of confidence in the effect estimate. This signifies that further research is needed to provide more substantial evidence on the confidence in the effect estimate and the potential health implications of tyrosine levels.

Conclusions

High blood pressure, also known as hypertension, is a prevalent health concern that can have severe consequences, particularly on cerebral health. This article explores the impact of high blood pressure on the brain, its potential implications, and the importance of managing this condition for overall well-being. Hypertension is a condition characterized by elevated arterial blood pressure, which forces the heart to work harder to pump blood throughout the body. While the primary focus of hypertension has traditionally been on its effects on the cardiovascular system, its consequences on cerebral health have gained increasing attention in recent research. One of the critical concerns associated with high blood pressure is its potential to cause cerebral damage. The constant force of blood against the arterial walls can lead to the thickening and narrowing of blood vessels, a condition known as atherosclerosis. This can impede blood flow to the brain, reducing the delivery of essential nutrients and oxygen, and increasing the risk of cerebrovascular events such as strokes. Moreover, hypertension has been linked to cognitive decline and an increased risk of neurodegenerative diseases, such as Alzheimer's and vascular dementia. Chronic high blood pressure may cause damage to small blood vessels in the brain, leading to microbleeds and white matter lesions, both of which have been associated with cognitive impairment. In addition to these direct consequences, high blood pressure can exacerbate other risk factors for cerebral damage, including diabetes and high cholesterol. It can also contribute to the development of conditions such as hypertensive encephalopathy, which can lead to symptoms like severe headaches, confusion, and seizures. Fortunately, hypertension is a manageable condition. Lifestyle changes, including a healthy diet, regular exercise, and stress management, can play a significant role in blood pressure control. Medications may also be prescribed by healthcare professionals when necessary. In conclusion, high blood pressure is not merely a cardiovascular concern; it can have severe consequences for cerebral health as well. Recognizing the potential implications of hypertension on the brain underscores the importance of early detection and proactive management. By maintaining a healthy lifestyle and seeking medical guidance, individuals can reduce the risks associated with high blood pressure and safeguard their cerebral well-being.

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

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