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ORIGINAL

Branched-Chain amino acids intake is negatively related to body adiposity in individuals at cardiometabolic risk

Consumo de aminoácidos de cadeia ramificada está negativamente relacionado com adiposidade corporal em indivíduos com risco cardiometabólico

Alinne Paula de ALMEIDA[1] 0000-0003-4158-8595
Fernanda Santos FORTES[2] 0000-0003-1724-1540
Brenda Kelly Souza SILVEIRA[1] 0000-0003-3339-3747
Nínive de Almeida REIS[3] 0000-0002-0401-3437
Helen Hermana Miranda HERMSDORFF[1] 0000-0002-4441-6572

ABSTRACT

Objective

To assess the relationship between branched-chain amino acids intake in the current diet and the metabolic and body adiposity markers in a population at cardiovascular risk.

Methods

This is a cross-sectional study with 282 adults and elderly people from the Cardiovascular Health Care Program of the *Universidade Federal de Viçosa*. Sociodemographic, anthropometric and body composition data, as well as metabolic biomarkers were collected using standardized protocols. Dietary intake of branched amino acids was assessed using a 24-hour recall.

[1] Universidade Federal de Viçosa, Centro Ciências Biológicas e da Saúde, Programa de Pós-Graduação em Ciência da Nutrição. Av. P. H. Rolfs, s/n., *Campus* Universitário, 36570-900, Viçosa, Minas Gerais, Brasil. Correspondence to: HHM HERMSDORFF. E-mail: <helenhermana@ufv.br>.
[2] Universidade Federal do Paraná, Complexo Hospital de Clínicas, Clínica de Cardiologia. Curitiba, PR, Brasil.
[3] Nutricionista. São Geraldo, MG, Brasil.

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Results

Individuals with a higher branched-chain amino acids intake (≥2.6g/day, median value) had lower body fat (29.6 vs 32.2%; *p*=0.019), and higher serum ferritin (113.2 vs. 60.1mg/dL; *p*=0.006) and uric acid concentrations (4.4 vs. 4.0; *p*=0.023). In addition, a lower prevalence of overweight and excessive abdominal fat (*p*<0.05) was found in the individuals with higher branched-chain amino acids intake. They also had a higher daily intake of fiber, copper, zinc, magnesium, and iron, as well as a lower intake of total lipids.

Conclusion

In the present study, the intake of branched amino acids is negatively related to total and central adiposity, but more studies are needed to fully elucidate this possible relationship. (Brazilian Registry of Clinical Trials, code RBR-5n4y2g).

Keywords: Cardiovascular diseases. Feeding behavior. Isoleucine. Leucine. Overweight. Valine.

RESUMO

Objetivo

Avaliar a relação entre o consumo de aminoácidos de cadeia ramificada na dieta atual e os marcadores de adiposidade metabólica e corporal em uma população com perfil de elevado risco cardiovascular.

Métodos

Trata-se de um estudo transversal com 282 adultos e idosos do Programa de Atenção Cardiovascular da Universidade Federal de Viçosa. Dados sociodemográficos, antropométricos e de composição corporal, além de biomarcadores metabólicos, foram coletados utilizando protocolos padronizados. O consumo alimentar de aminoácidos ramificados foi avaliado através de um recordatório de 24 horas.

Resultados

Indivíduos com maior consumo de aminoácidos de cadeia ramificada (≥2,6g/dia, valor da mediana) apresentaram menores valores de gordura corporal (29,6 vs 32,2%; p=0,019) e maiores valores de séricos de ferritina (113,2 vs. 60,1mg/dL; p=0,006) e ácido úrico (4,4 vs. 4,0; p=0,023). Além disso, foi encontrada uma menor prevalência de sobrepeso e excesso de gordura abdominal (p<0,05) nos indivíduos com maior consumo de aminoácidos de cadeia ramificada. Eles também apresentaram um maior consumo diário de fibra, cobre, zinco, magnésio e ferro, além de um menor consumo de lipídios totais.

Conclusão

No presente estudo, o consumo de aminoácidos ramificados está negativamente relacionado à adiposidade total e central, porém mais estudos são necessários para elucidar completamente essa possível relação. (Registro Brasileiro de Ensaios Clínicos, código RBR-5n4y2g)

Palavras-chave: *Doenças cardiovasculares. Comportamento alimentar. Isoleucina. Leucina. Sobrepeso. Valina.*

INTRODUCTION

Excess weight is the main risk factor for the development of Cardiovascular Diseases (CVD), being one of the biggest public health problems worldwide. It should be noted that eating habits are an important modifiable risk factor for such changes [1-5].

In this context, dietary Branched-Chain Amino Acids (BCAA), such as leucine, isoleucine, and valine, are essential for a healthy cellular and organ function [1,6-9]. The impact of BCAA intake on cardiometabolic risk factors, such as overweight and body fat, has been investigated in previous studies [10-12].

A recent meta-analysis [13] reported that a higher dietary intake of BCAA was inversely related to the prevalence of overweight and obesity in adults. The possible mechanisms for the effect of

BCAA on body weight are still poorly understood, however it is known that BCAA, especially leucine, can act in ways to control cellular metabolism, providing a decrease in food intake and body weight [14-16]. However, few studies have assessed BCAA intake, especially in the Brazilian population and, to date, few studies have assessed the relationship of these nutrients with metabolic and adiposity markers in a population at cardiovascular risk [10]. Therefore, the aim of this article is to assess the relationship between BCAA intake, included in the current diet, and metabolic and adiposity biomarkers in a population at cardiovascular risk.

METHODS

A cross-sectional study with 282 patients included in the *Programa de Atenção à Saúde Cardiovascular da Universidade Federal de Viçosa* (PROCARDIO-UFV, Cardiovascular Health Care Program of the *Universidade Federal de Viçosa*), who had their first medical appointment until July 2016, with complete data concerning their BCAA intake. The PROCARDIO-UFV performs nutritional intervention to promote cardiovascular health in the academic community of the *Universidade Federal de Viçosa* (UFV), registered in the *Registro Brasileiro de Ensaios Clínicos* (ReBEC, Brazilian Registry of Clinical Trials), code RBR-5n4y2g [17].

The criteria for inclusion in the program are: age ≥20 years; both sexes; being a student, worker, or a dependent family member of UFV workers; present cardiovascular diseases or the occurrence of cardiometabolic risk factors such as overweight or obesity (Body Mass Index (BMI) ≥25 or 27kg/m²) or/and dyslipidemia (Triglycerides (TG) ≥150mg/dL; Total Cholesterol (TC) ≥ 200 mg/dL or/and High Density Lipoprotein (HDL-c) <40 or <50mg/dL for men and women, respectively), or/and blood pressure ≥130/≥85mmHg or diagnosed arterial hypertension or/and fasting blood glucose ≥100mg/dL or diagnosed diabetes *mellitus*. The data used were related to the first medical consultation at the PROCARDIO-UFV. Among the 417 users of the program, 282 were selected for having complete data on their BCAA intake.

The study was approved by the UFV's Human Research Ethics Committee (Protocol number 066/2012/CEPH), in accordance with Resolution 466/2012 of the *Conselho Nacional de Saúde* (CNS, National Health Council/Ministry of Health, Brazil) and with the principles of the Helsinki Declaration. All study participants read and signed the informed consent form.

The participants responded to a 24-hour food recall (R24h), reporting all the food and drinks consumed the day before (weekday or weekend) the medical consultation, as well as their quantities. In the present study, the daily intake of calories, carbohydrates, proteins, lipids, fibers, vitamins A, C, D and E, selenium, copper, manganese, magnesium, zinc, calcium, iron, and sodium were assessed using the DietPRO software, version 5.0i [18].

The determination of BCAA intake (leucine, isoleucine, and valine) was performed using the National Nutrient Database for Standard Reference (USDA, 2015), as such data are not available in the Brazilian tables [19]. The foods reported in the R24h and not listed in the USDA table had their estimated composition considering the foods that showed nutritional composition and similar cooking methods. The preparations were broken down into their constituent ingredients and, if there was no choice of composition for the prepared food, the composition of the raw foods was used. The intake of each amino acid was performed in an electronic spreadsheet (Microsoft Excel®), developed especially for this purpose.

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Anthropometric measurements (body weight, height, hip, and waist circumference) were measured using a standardized, previously established protocol [20]. Waist-to-Hip (WHR) and Waist-to-Height (WHtR) ratios were calculated. Total Body Fat (BF%) was assessed by tetrapolar electrical bioimpedance (Biodynamics 310 model, Washington, USA), according to the manufacturer's protocol. Excess weight was classified according to a BMI greater than or equal to 25 (adults) and 27 (elderly) kg/m^2 [21,22]. Excess abdominal fat was assessed using waist circumference values equal to or greater than 80 cm and 90 cm for women and men, respectively [23].

Fasting blood glucose, triglycerides, total and fraction cholesterol (Low Density Lipoprotein [LDL-c], High Density Lipoprotein [HDL-c], and Very Low Density Lipoprotein [VLDL-c]), ferritin, uric acid, total leukocytes, and Ultrasensitive C-Reactive Protein (Us-CRP) were determined at the Clinical Analysis Laboratory of the Health Department of the UFV, according to its standardized protocol.

Insulin resistance was estimated using the Homeostasis-Insulin Resistance Model (HOMA-IR), calculated as follows: HOMA-IR=[fasting glucose (mmol/L)] fasting insulin (μUI/ml)]/22.5 and the triglycerides/glycemia (TyG) index, calculated using the formula: Ln [fasting triglycerides (mg/dl)×fasting glycemia (mg/dL)/2] [24].

The age, sex, educational level, relationship to the UFV, income, smoking, regular practice of physical activities, and intake of alcoholic beverages variables were collected by interviewing participants through a questionnaire.

The results were presented in absolute and relative frequencies, mean±standard deviation, and/or median (25th-75th percentile). The normality of each variable was assessed using the Kolmogorov-Smirnov test. To assess the possible association of BCAA intake and other variables of interest, the sample of the present study was categorized according to the median BCAA intake (2.6g/day). The use of the median as a cut-off point for statistical analysis has been used before [25,26]. All food intake variables were adjusted for total caloric intake using the residual method [27].

The Student t and Mann-Whitney-U tests were used to compare the two groups, when appropriate. Pearson's Chi-square, linear trend chi-square or Fischer's exact test were used when appropriate to verify associations between sociodemographic and body composition variables, and the median BCAA intake. Spearman's correlation was used to assess the relationship between BCAA intake and other nutrients with variables of interest. All statistical analyses were performed using the SSPS 21.0® program, considering the level of statistical significance as 5%.

RESULTS

Of the individuals who had a higher BCAA intake (≥2.6g/day), 28.4% (n=40) were male, 28.2% (n=40) were employees of the university, and 75.9% (n=107) were not smokers (Table 1). Regarding food intake, those with a BCAA intake ≥2.6g/day had a higher intake of fibers, copper, zinc, magnesium, and iron (Table 2).

Individuals with the highest BCAA intake (≥2.6g/day) had higher concentrations of ferritin and uric acid, in addition to lower body fat and HDL-c values (Table 3).

Moreover, there was a higher prevalence of overweight and excessive abdominal fat in individuals with a lower BCAA intake (Figure 1). In addition, BCAA intake was negatively correlated with body fat (Figure 2).

Table 1. Sociodemographic characteristics, according to the Branched-Chain Amino Acids intake (median value).

Variable	Lower BCAA intake <2.6g/day (n=139)		Higher BCAA intake ≥2.6g/day (n=142)		*p*-values
	n	%	n	%	
Sex					<0.001*
Male	75	53.9	40	28.4	
Female	64	46.1	101	71.6	
Age					0.084
Adults	115	82.7	114	80.9	
Elderly individuals	24	17.3	27	19.1	
Educational level					0.260
Illiterate- incomplete high school	26	19.7	36	27.1	
Complete high school	26	20.5	19	14.3	
Complete or incomplete undergraduate	79	59.8	78	58.6	
Relationship to the UFV					0.032*
Worker	61	44.5	40	28.2	
Student	50	36.5	62	43.6	
Worker's dependent	26	19.0	40	28.2	
Marital status					0.159
Single	56	40.6	66	46.8	
Legally married or in a stable relationship	74	53.6	61	43.3	
Widowed or separated/divorced	8	5.8	14	9.9	
Income					0.610
Did not state	11	7.9	16	11.4	
Up to 2 minimum wages	34	24.7	32	22.9	
2 to 4 minimum wages	52	37.7	50	35.7	
4 to 10 minimum wages	33	23.9	38	27.1	
More than 10 minimum wages	8	5.8	4	2.9	
Smoking					0.007*
Never	81	58.3	107	75.9	
Ex-smoker	51	36.7	29	20.6	
Smoker	7	5.0	5	3.5	
Physical activities					0.513
No	63	45.7	67	47.2	
Yes	75	54.3	75	52.8	
Alcoholic beverage intake					0.384
Does not drink	51	37.2	63	45.3	
Socially	82	59.9	73	52.5	
One or more drinks per day	4	2.9	3	2.2	

Note: *p-values: <0.05 using the Chi-Square test.

Below the median: educational level (n=132), relationship to the institution (n=137), marital status (n=138), income (n=138), physical activities (n=138), alcoholic beverage intake (n=137); Above the median: sex (n=141), age (n=141), education (n=133), marital status (n=141), income (n=140), smoking (n=141), physical activities (n=142), alcoholic beverage intake (n=139).

BCAA: Branched-Chain Amino Acids.

DISCUSSION

Amino acids can play an important role in the development of CVD [10,28-35]. This relationship can be justified by the food source of these nutrients (legumes, oilseeds, eggs, fish, meat, milk, and dairy products). In fact, the cardiometabolic effects related to animal protein food sources are probably better explained by the non-protein components than by the protein components of these foods [36-38].

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Table 2. Current dietary habits according to the branched-chain amino acids intake (median value).

Intake/day	Lower BCAA intake <2,6g/day (n=139)		Higher BCAA intake ≥2,6g/day (n= 142)		*p*-values
Macronutrients					
Carbohydrates (%CI)	51.4	46.5-58.6	54.9	47.3-60.3	0.061
Proteins (%CI)	17.4	14.7-20.7	18.7	15.0-21.9	0.068
Total lipids (%CI)	30.3	24.4-34.9	26.8	23.0-33.4	0.008*
Fibers (g)	21.5	15.6-29.9	25.3	17.5-33.5	0.019*
Micronutrients					
Vitamin E (mg)	5.0	3.4-6.4	4.9	3.7-6.8	0.329
Vitamin A (µg)	502.8	298.8-790.9	464.1	297.8-620.8	0.211
Vitamin C (mg)	45.2	25.6-129.9	58.3	28.9-140.5	0.168
Vitamin D (UI)	30.2	16.3-87.3	32.5	18.6-70.1	0.813
Selenium (µg)	90.9	75.7-106.8	92.9	74.3-112.3	0.400
Copper (mg)	1.9	1.7-2.1	2.0	1.9-2.3	0.000*
Manganese (mg)	3.8	3.0-4.9	3.7	2.7-5.3	0.994
Zinc (mg)	10.1	8.3-12.1	10.9	8.5-13.7	0.019*
Magnesium (mg)	234.5	198.5-273.1	251.2	212.5-306.5	0.018*
Calcium (mg)	503.8	364.2-780.3	540.3	392.1-767.7	0.771
Iron (mg)	9.3	7.7-11.7	10.4	8.6-12.6	0.006*
Sodium (mg)	2368.9	2056.7-2952.0	2336.9	1984.9-2692.7	0.144

Note: *$p<0.05$. Data presented median and quartiles ($p25$-$p75$).
BCAA: Branched-Chain Amino Acids; CI: Caloric Intake.

Table 3. Adiposity indicators and cardiometabolic risk markers, according to branched-chain amino acids intake (median value).

Intake/day	Lower BCAA intake <2,6g/day (n=139)		Higher BCAA intake ≥2,6g/day (n=142)		*p*-values
BMI (kg/m^2)	28.74	5.49	28.97	5.56	0.723
Waist circumference (cm)	96.24	14.84	97.35	14.14	0.525
Waist-to-hip ratio	0.92	0.09	0.93	0.09	0.627
Waist-to-height ratio	0.59	0.09	0.58	0.9	0.482
Body fat (%)	32.2	7.1	29.6	8.7	0.019*
Total leukocytes (1.000/mm^3)	6,270	1,551	6,375	1,837	0.647
Ferritin (µg/L)	60.1	26.6-152	113.2	56.1-230.7	0.006*
Urea (mg/dL)	29.0	23.2-37.0	32.0	25.0-38.0	0.227
Uric acid (mg/dL)	4.0	3.2-4.8	4.4	3.5-5.8	0.023*
Blood glucose (mg/dL)	90.0	83.0-100.7	93.0	85.0-108	0.122
HOMA-IR	2.1	1.3-2.9	2.2	1.3-3.3	0.370
TyG index	4.78	0.3	4.8	0.3	0.762
Total cholesterol (mg/dL)	210	41.1	200	44.2	0.074
LDL-c (mg/dL)	128	37.2	120	38.2	0.084
HDL-c (mg/dL)	48.0	39.0-58.0	43.1	36.0-54.0	0.040*
VLDL-c (mg/dL)	27.90	20.4-40.0	26.4	19.3-41.4	0.451
Total cholesterol / HDL-c	4.34	3.57-5.07	4.34	3.45-5.47	0.597
LDL-c / HDL -c	2.55	1.99-3.34	2.59	1.99-3.38	0.883
Triglycerides (mg/dL)	147	100-210	139	101-238	0.956
C-reactive protein (mg/dL)	1.92	0.68-5.09	1.51	0.43-3.90	0.344

Note: *p=<0.05.
Data presented mean ± SD (standard deviation) or median and quartiles (p25-p75), when appropriate.
BCAA: Branched-Chain Amino Acids; BMI: Body Mass Index; HOMA-IR: Homeostasis-Insulin Resistance Model; LDL-C: Low Density Lipoprotein; HDL-c: High Density Lipoprotein; TYG: Triglycerides/Blood Glucose Index; VLDL-c: Very Low Density Lipoprotein.

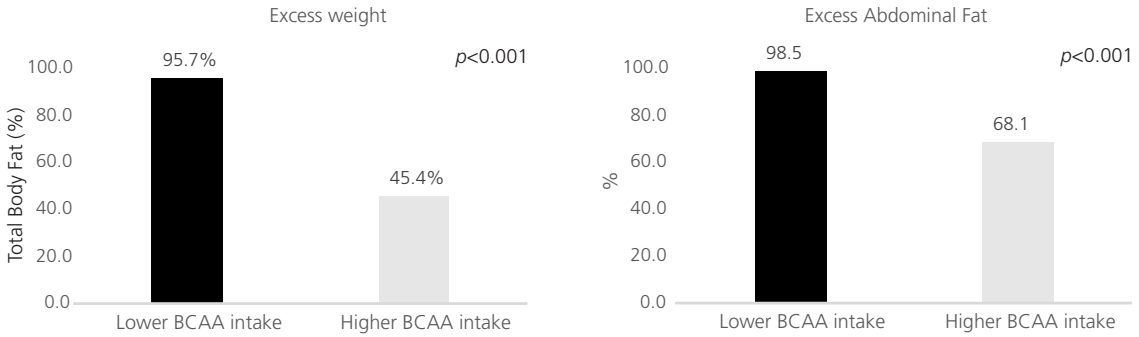

Figure 1. Prevalence of overweight (BMI>25 and 27kg/m² for adults and elderly individuals) and excess abdominal fat (Waist circumference ≥80 and 90cm for women and men, respectively), according to the branched amino acids intake (median: 2.6 g/day). *p*-values according to the Chi-Square test.

Note: BCAA: Branched-Chain Amino Acids.

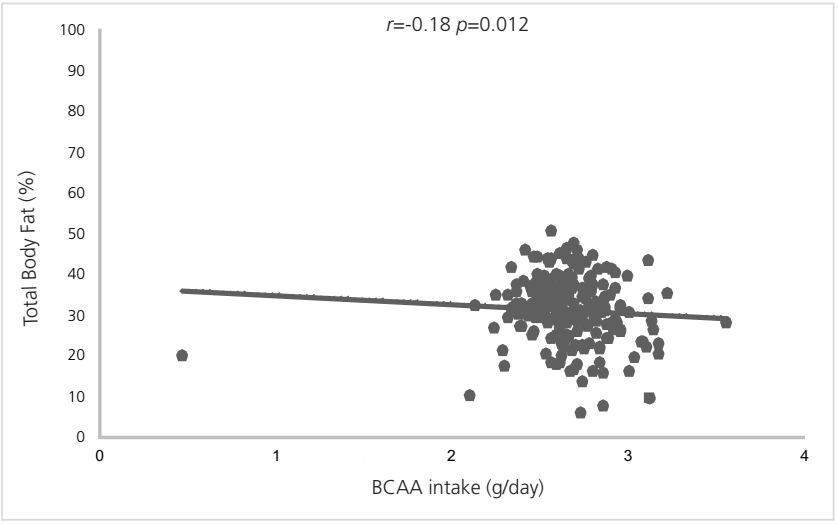

Figure 2. Spearman's correlation between the branched amino acids intake and total body fat (%) in individuals at cardiometabolic risk (n=206).

Note: BCAA: Branched-Chain Amino Acids.

The first relevant result of this study was the higher body fat (%) in those individuals with a lower BCAA intake. Other results also were towards the inverse relationship between BCAA intake and body adiposity, as well as the results of other cross-sectional studies, carried out in Brazil, China, Japan, the United Kingdom and the United States [10,14,15,39]. Probably, leucine is the most influential BCAA regarding energy balance [40]. When these amino acids are released into the gastrointestinal tract after the hydrolysis of dietary proteins, the production of anorexigenic hormones is stimulated and thus the production of orexigenic hormone is inhibited. In addition, leucine induces the activation of the pro-opiomelanocortin, hypothalamic neuropeptide, as well as negatively regulating neuropeptide Y signaling.

In the central nervous system, these signals can affect food intake, increasing satiation and satiety. Also, leucine can act directly on adipocyte, liver, and muscle cells, influencing the expression

of fatty acid synthase (adipocytes) and lipid catabolism (adipocytes, liver and muscle cells), favoring, subsequently, the reduction of adiposity [40]. Leucine is also a potent activator of mTOR, a serine/threonine kinase involved in many cellular processes, which includes protein synthesis and cell growth. Central leucine administration can increase hypothalamic mTOR signaling and decrease food intake and body weight [14]. Another possible mechanism for the effect of BCAA on body weight is the improvement of glucose tolerance, since impaired glucose tolerance may be related as one of the possible causes of obesity [15].

As shown in Table 2, individuals with a higher BCAA intake also had a higher intake of fibers and minerals (iron, copper, zinc, and magnesium) ($p<0.05$), as well as a lower intake of total fats ($p<0.05$). We also observed a negative correlation between the percentage of body fat and the current intake of fibers, iron, zinc, and copper (r=-0.16 and $p=0.02$; r=-0.206 and $p=0.003$; r=-0,16 and $p=0.03$; r=-0.16 and $p=0.02$, respectively). Therefore, the lower body fat in these individuals with a higher BCAA intake may also be related to a better quality of food in general.

Still, in the present study, serum ferritin and uric acid concentrations were significantly higher in the individuals with higher BCAA intake. However, these concentrations, even though higher, are still within normal values. They do not represent an increase in the cardiometabolic risk for these individuals [20,41,42].

In addition, HDL-c concentrations were lower in those individuals with higher BCAA intake. The opposite result was observed in the study by Cocate *et al.*, in which HDL-c concentrations were higher in the third tertile, when compared to the first tertile of BCAA intake [10]. BCAA can act as signaling molecules to control energy homeostasis involving the disposition of glucose and lipid metabolism. Any changes in their intake could also lead to changes in the lipid profile [1,43], but additional studies that assess this relationship are necessary.

The present study has some limitations. First, its cross-sectional design makes impossible to infer about a cause-effect relationship in the results presented. However, the authors used the statistical tests that are suitable for this type of study and performed the interpretations of the results with scientific relevance. Another factor is the use of only a 24-hour recall, as it provides information only about the individual's current and unusual intake. However, this food survey has been used in epidemiological studies that evaluated the relation between food intake and cardiometabolic risk factors with promising results and acceptance by the scientific community [44-47].

CONCLUSION

The results of the present study indicate that a higher BCAA intake (>2.6g/day) has an inverse association with excess weight and body fat, in addition to a positive association with biomarkers (ferritin and uric acid) in individuals at cardiometabolic risk. Further studies are needed to assess the relationship between BCAA intake and chronic diseases.

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CONTRIBUTORS

AP ALMEIDA contributed to research design, obtaining data, analysis and interpretation of data, writing the article and critical review of the manuscript for important intellectual content. FS FORTES contributed to research design, obtaining data, analysis and interpretation of data and writing the article. BKS SILVEIRA and NA REIS contributed to research design and data collection. HHM HERMSDORFF contributed to research design, analysis and interpretation of data and critical review of the manuscript for important intellectual content.

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