Original Article

Branched chain and other amino acid intakes are inversely associated with sarcopenia among community elders in Qingdao, China

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Background and Objectives: The present study aimed to investigate the hypothesis that dietary amino acid intakes are associated with the risk of sarcopenia through a community-based observational study. **Methods and Study Design:** A total of 1,140 participants (72.7±6.3 y) were recruited from an annual health check-up program in Qingdao, China. Skeletal muscle mass, muscle mass functions and biochemical parameters were measured by standard methods. Dietary intake was assessed by 3-day, 24-hour food records. The odds ratios (ORs) and 95% confidence intervals (CIs) of sarcopenic risk across quartiles of amino acid intakes were calculated using a multivariable-adjusted logistic regression model. Generalized linear models were used to assess the associations between dietary amino acid intakes and muscle mass functions. **Results:** The prevalence of sarcopenia was 4.1%. Compared with the lowest category intake, the highest category of branched chain amino acids (BCAAs) (OR=0.11; 95% CI: 0.01, 0.90; *p* for trend=0.119), isoleucine (OR=0.11; 95% CI: 0.01, 0.89; *p* for trend=0.122) and tryptophan (OR=0.10; 95% CI: 0.01, 0.87; *p* for trend=0.176) was negatively correlated with sarcopenic risk with adjustment for potential confounding factors. Generalized linear model analysis showed that gait speed was positively correlated with dietary intakes of lysine, threonine, leucine, valine, tryptophan, BCAAs and aromatic amino acids ($p<0.05$). **Conclusions:** Higher intakes of BCAAs were associated with a lower risk of sarcopenia, which might beneficially protect against sarcopenia and improve physical function of the elderly.

Key Words: sarcopenia, muscle mass functions, branched chain amino acid, protein, amino acids

INTRODUCTION

Sarcopenia is an age-related muscle mass loss accompanied by a reduction in muscle strength and/or physical performance.[1] The pathogenesis of sarcopenia is complex, involving changes in body composition and hormones related to aging, inflammatory response, insulin resistance and mitochondrial dysfunction.[2] With the increase in muscle loss, the risks of falls, physical disability, depression, cardiovascular disease, hospitalization and even death have been substantially increased in the elderly. When sarcopenia is associated with malnutrition, chronic inflammation, liver cirrhosis, renal function disease or vitamin D deficiency, the quality of life is inevitable to be further compromised.[3-9] Thus, improving muscle mass and functions are a meaningful public health issue.[10-12]

Cross-sectional surveys have found the prevalence of sarcopenia to be between 0.4% and 13.9%. Age, gender, body mass index (BMI), dietary energy and protein, and physical activity were identified as independent risk factors of sarcopenia.[13-17] However, the results have been inconsistent. The findings from epidemiological studies showed that malnutrition and hypoproteinemia exerted vital roles in patients with sarcopenia,[5] and insufficient dietary protein intake was positively correlated with the risk of sarcopenia, contributing to the decline of body muscle mass.[18] Furthermore, supplemental essential amino acids could enhance muscle protein synthesis,[19] and improve muscle quality, physical function and quality of life. Specifically, branched chain amino acids (BCAAs), including leucine, isoleucine and valine, are considered to improve skeletal muscle atrophy induced by angiotensin II.[20,21]

In China and Japan, 30% of the residents living in the community had the risk of malnutrition or malnutrition,

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and the risk of malnutrition was higher among the elderly over 70 years.[22] To date, no study has been conducted to investigate the associations of dietary protein and amino acid intakes with risk of sarcopenia. Meanwhile, the relationships remained inconclusive between amino acid intakes and muscle mass functions. In the present study, we hypothesized that different amino acids have differential functions associated with the risk of sarcopenia in the elderly. Therefore, we conducted the present study to illuminate these relationships according to residents over 65 years old in the Qingdao community.

METHODS

Study design and participants

Community-dwelling of Qingdao residents (Fushan and Ningxia Community) aged 65 and over were screened and enrolled between Mar. and Nov. 2020. The recruiting process is shown in Figure 1. This study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of Affiliated Hospital of Qingdao University (QYFYWZLL25549), and written informed consent was obtained from all subjects.

To guarantee the accuracy of the results, the participants were excluded: (1) participants with stroke, parkinsonism, malignant tumor, and chronic kidney disease; (2) participants with factors that affected the gait speed, grip strength and bioelectrical impedance analysis (BIA) measurement, such as implanted with metal, pacemaker, severe edema or physical disability; and (3) participants with severe cognitive impairment or those with poor compliance.

Sarcopenia determination

According to the diagnostic criteria defined by the 2019 Asian Working Group for Sarcopenia (AWGS),[1] the participants with sarcopenia were screened in Qingdao, China. Bioelectrical impedance analysis (BIA; InBoyS10, Korea) was applied to measure muscle mass. The appendicular skeletal muscle mass (ASM) was calculated as the sum of lean muscle mass in the arms and legs. Appendicular skeletal muscle mass index (ASMI) was calculated as the ratio of ASM to the square of height (ASM/height^2). According to the 2019 AWGS consensus, the standard of low muscle mass for males was ASMI <7 kg/m^2, and for females was ASMI <5.7 kg/m^2. Grip strength was measured using a grip strength meter to indicate muscle strength. The maximum grip strength of the dominant hand was measured three times with an interval of one minute, and the maximum value was recorded. The muscle strength was less than 26 kg for males and 18 kg for females defined as a reduction in grip strength. The 6-meter (meter per second, m/s) walking test was conducted to measure the gait speed with normal walking speed. Gait speed <1 m/s was defined as a decrease in physical function. Based on the diagnostic criteria of the 2019 AWGS, sarcopenia was defined as a decrease in the ASMI accompanied by a decrease in muscle strength and/or physical function.[1]

Dietary assessment

The dietary intakes of protein and amino acids were calculated based on 3-day (2 working days and 1 weekend), 24-hour food records.[15] Prior to the survey, participants were instructed how to correctly record dietary intakes and estimate the amount of liquid and solid foods. The nutrition system of traditional Chinese medicine combined with western medicine (NCCW version 12.0) was applied to yield daily intakes of total energy intake (kcal), carbohydrate intake (g), fat intake (g), protein intake (g), and each amino acid intake (mg). Investigators and dietary recorders had received professional guidance and training before conducting investigation and dietary analysis.

Other variables

Demographic parameters and lifestyles were collected based on a face-to-face questionnaire. According to the current smoking status, the participants were divided into

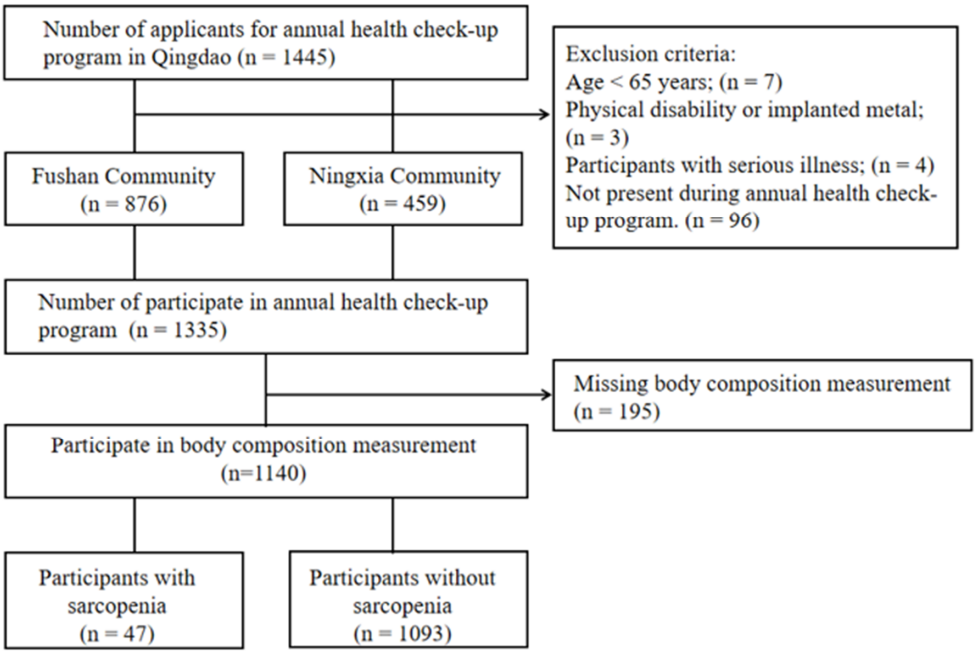

Figure 1. The flow chat of the included participants.

smoking, quitting and never smoking. The participants were defined as alcohol drinking if the females drank 70 grams per week and males drank 140 grams per week. The physical activity scale for the elderly (PASE) was used to evaluate the physical activity of the participants.[23] According to the scores of the PASE, the participants were divided into the low-impact exercise group (<33rd percentile), the moderate-impact exercise group (33rd-66th percentile) and the high-impact exercise group (>66th percentile).

After 10 h fasting, the waist circumference, hip circumference, height and weight of the participants were measured by a trained staff. Accordingly, BMI was calculated as weight divided by height squared (kg/m^2). Meanwhile, blood samples (5 mL) were obtained into vacuum tubes for laboratory analysis. Serum was collected after centrifugation at 3500 rpm for 10 min at 4 °C. Then, serum fasting glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured by an automatic biochemical analyser (TBA-40FR, Toshiba, Japan) using an enzyme-based colorimetric test.

Statistical analysis

Statistical analysis was performed with STATA version 15.0. After the normality test of the continuous variable data, the quantitative data with normal distribution and non-normal distribution were expressed as mean ± standard deviation (SD) and median (Q25, Q75), respectively. Categorical variables were presented as frequencies (percentages). The continuous parameters with normal distribution between groups were compared with the Student's t-test. Besides, the categorical and non-normally distributed variables were analysed with Pearson's chi-square and Wilcoxon rank sum test, respectively.

Multivariable-adjusted logistical regression models were adopted to estimate odds ratios (ORs) with 95% confidence intervals (CIs) of sarcopenic risk across quartiles of protein and amino acid intakes, with the lowest category as the reference.[24] Tests for trends were conducted by assigning the median value for each category and modelling this variable as a continuous variable. The generalized linear model (GLM) was used to analyse the associations of daily protein and amino acid intakes with muscle mass functions. The multivariable-adjusted models of logistic regression and generalized linear analyses were adjusted for age, gender, height, weight, BMI, waist circumference, hip circumference, waist hip ratio, blood pressure, marital status, education level, smoking, alcohol drinking, physical activity, fasting blood glucose, TC, TG, HDL-C, LDL-C, and for daily energy, carbohydrate, and fat intakes. The two-tailed p values <0.05 were considered as statistically significant.

RESULTS

Participants Characteristics

A total of 1335 participants aged 73.0±6.8 years were recruited in this study. Of these, 1,140 participants completed the BIA measurement, and were included for data analysis. According to the 2019 AWGS consensus, 47 participants were regarded as sarcopenia, and the prevalence of sarcopenia was 4.1%, including 13 males and 34 females.

The characteristics between healthy and sarcopenic participants

The average age of participants with sarcopenia was significantly higher than that of healthy participants (p<0.001). The prevalence of sarcopenia was significantly higher in females than males (p=0.022). Compared with healthy participants, patients with sarcopenia had a higher widowhood rate (p<0.001) and a lower alcohol drinking rate (p=0.007). Meanwhile, the height, weight, BMI, waist circumference and hip circumference of sarcopenic patients were significantly lower than those of healthy participants (p<0.001). In addition, the levels of serum TC (p=0.050) and HDL-C (p=0.036) in sarcopenic patients were significantly higher than healthy participants, while the levels of serum TG (p=0.023) were significantly lower than those healthy participants. Besides, the healthy participants showed significantly higher intakes of energy (p=0.026), protein (p=0.013) and carbohydrate (p=0.031) compared with sarcopenic patients (Table 1).

Dietary factors associated with sarcopenic risk

In univariate logistic regression analyses, dietary intake of protein in the third category was associated with a lower risk of sarcopenia (OR=0.19; 95% CI: 0.05, 0.67; p for trend=0.340), and the association remained significant with adjustment for potential confounding factors (OR=0.02; 95% CI: 0.01, 0.53; p for trend=0.056) (Figure 2A). Regarding amino acids, dietary intakes of branched chain amino acids (OR=0.11; 95% CI: 0.01, 0.90; p for trend=0.119) (Figure 2B), isoleucine (OR=0.11; 95% CI: 0.01, 0.89; p for trend=0.122) (Figure 3A) and tryptophan (OR=0.10; 95% CI: 0.01, 0.87; p for trend=0.176) (Figure 3B) were negatively correlated with sarcopenic risk (Table 2).

The associations of amino acids with muscle mass function

By using GLM analysis, dietary intakes of lysine (p=0.011), threonine (p=0.022), leucine (p=0.025), valine (p=0.021), tryptophan (p=0.011), branched chain amino acids (p=0.032), and aromatic amino acids (p=0.033) were positively correlated with gait speed, respectively (Table 3).

DISCUSSION

This study is the first to investigate the associations of dietary protein and amino acid intakes with sarcopenic risk through a community-based study in participants over 65 years. The present study demonstrated that higher intakes of BCAAs were associated with a lower risk of sarcopenia. Additionally, BCAAs had significant benefits in improving the physical functions of the elderly. Meanwhile, appropriate protein intake (70 g) was associated with reduced risk of sarcopenia.

Based on recent cross-sectional surveys, the prevalence of sarcopenia of the present study (4.1%) was in the range of sarcopenia prevalence (0.4-13.9%).[13-17] Previous epidemiological studies have identified several factors affecting sarcopenia, including age, gender, BMI, physical

Table 1. Basic characteristics of subjects with and without sarcopenia

	n (%) or M (Q25, Q75) or Mean±SD†			p‡
	Total (n=1140)	Sarcopenia (n=47)	No sarcopenia (n=1093)	
Sarcopenia status, n (%)				
Sarcopenia	1093 (95.9)			
No sarcopenia	47 (4.12)			
Age, years	72.0 (68.0, 76.5)	82.0 (73.0, 86.0)	71.0 (68.0, 76.0)	<0.001
Gender, n (%)				0.022
Male	500 (43.9)	13 (27.7)	487 (44.6)	
Female	640 (56.1)	34 (72.3)	606 (55.4)	
Body height, cm	163 (157, 170)	156 (150, 160)	163.0 (158, 170)	<0.001
Body weight, kg	67.8 (60.3, 75.3)	51.3 (49.0, 55.7)	68.1 (61.4, 75.7)	<0.001
Body mass index, kg/m^2	25.5 (23.2, 27.6)	21.8 (19.8, 22.8)	25.7 (23.4, 27.7)	<0.001
Waist circumstance, cm	91.3±9.4	83.9±8.2	91.6±9.3	<0.001
Hip circumstance, cm	99 (94, 103)	92 (89.5, 95.5)	99 (95, 103)	<0.001
Waist hip ratio, %	0.92 (0.88, 0.96)	0.90 (0.85, 0.95)	0.92 (0.88, 0.96)	0.081
Blood pressure, mmHg				
Systolic pressure	136 (128, 148)	136 (125, 152)	136 (128, 147)	0.894
Diastolic pressure	78 (71, 85)	76 (71, 85)	78 (71, 85)	0.889
Marital status, n (%)				<0.001
Single	1 (0.09)	0 (0.00)	1 (0.10)	
Married	939 (86.8)	24 (60.0)	915 (87.8)	
Widowed	140 (12.9)	16 (40.0)	124 (11.9)	
Separated	2 (0.18)	0 (0.00)	2 (0.19)	
Education, n (%)				0.560
≤ Junior high school and others	662 (61.2)	27 (67.5)	635 (60.9)	
High school	267 (24.7)	7 (17.5)	260 (25.0)	
≥ Some college	153 (14.1)	6 (15.0)	147 (14.1)	
Current smoking, n (%)				0.759
Yes	119 (11.0)	5 (12.5)	114 (11.0)	
No	962 (89.0)	35 (87.5)	927 (89.1)	
Alcohol drinking, n (%)				0.007
Yes	202 (18.7)	1 (2.50)	201 (19.3)	
No	879 (81.3)	39 (97.5)	840 (80.7)	
Fasting blood glucose (mmol/L)	5.78 (5.22, 6.85)	5.62 (4.97, 7.02)	5.79 (5.23, 6.84)	0.219
TC (mmol/L)	5.91 (4.97, 6.84)	6.21 (5.49, 7.35)	5.89 (4.96, 6.81)	0.050
TG (mmol/L)	1.34 (0.92, 2.04)	1.07 (0.86, 1.69)	1.36 (0.92, 2.08)	0.023
LDL-C (mmol/L)	2.85 (2.33, 3.38)	3.02 (2.40, 3.57)	2.84 (2.32, 3.37)	0.138
HDL-C (mmol/L)	1.92 (1.60, 2.23)	2.04 (1.73, 2.42)	1.91 (1.60, 2.22)	0.036
Physical activity, n (%)				0.071
Low-impact exercise	403 (35.4)	24 (51.1)	379 (34.7)	
Moderate-impact exercise	328 (28.8)	10 (21.3)	318 (29.1)	
High-impact exercise	409 (35.9)	13 (27.7)	396 (36.2)	
Energy intake, kcal/d	1797 (1537, 2126)	1621 (1308, 1996)	1800 (1540, 2137)	0.026
Macronutrient intake				
Total protein, g/d	60.9 (47.8, 74.3)	51.1 (41.0, 65.1)	61.2 (48.2, 74.4)	0.013
Fat, g/d	75.4 (63.4, 90.8)	66.4 (59.6, 85.3)	75.9 (63.5, 90.9)	0.054
Carbohydrate, g/d	216 (173, 261)	186 (159, 237)	217 (173.9, 263)	0.031

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation; TC: total cholesterol; TG: triglyceride.

†Data are presented as median (interquartile range) for continuous variables with non-normal distributions, as mean±SD for continuous variables with normal distributions or participants (percentage %) for categorical variables.

‡p for difference between groups was tested by Student's t-test, chi-square, and Wilcoxon rank sum test, respectively.

activity, dietary of energy and protein intakes.[25-27] Except the above-mentioned factors, this study also found that there were significant differences in height, weight, waist circumference, hip circumference, alcohol drinking, marital status and carbohydrate intake between healthy participants and sarcopenic patients. In addition, higher levels of serum TC and HDL-C, but lower TG levels might potentially increase in patients with sarcopenia. Regarding dietary factors, intake of dietary protein was a crucial factor associated with the risk of sarcopenia.

After adjusting for potential confounding factors, the risk of sarcopenia was significantly reduced when the protein intake ranged from 60.9 to 74.3 g/d. Among amino acids, dietary intakes of BCAAs, isoleucine and tryptophan were also negatively correlated with sarcopenic risk. It has been demonstrated that 15-20 grams of protein (7.5 g of essential amino acids) was sufficient to promote muscle protein synthesis in adult subjects. Compared with younger subjects, the elderly might need more protein to maintain muscle protein synthesis.[28] Santiago et al. reported that the protein intake of patients with sarcopenia was significantly lower than that of healthy participants.[29] In a cross-sectional study of the elderly in the Netherlands, a higher protein intake was associated with a 4% reduc-

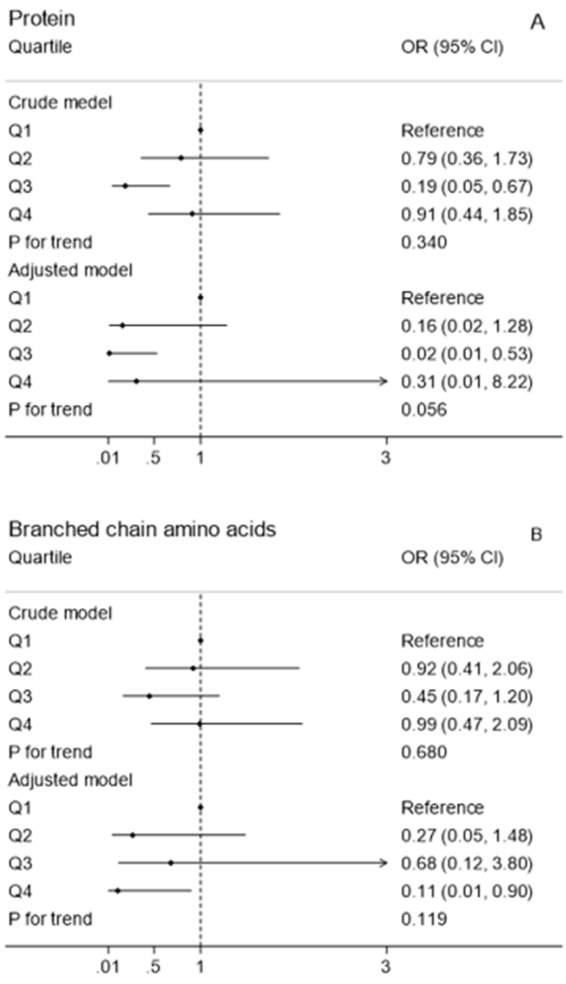

Figure 2. Association of dietary protein (A), branched chain amino acids (B) intakes with risk of sarcopenia.

tion in the incidence of sarcopenia.[30] A meta-analysis of randomized controlled trials study found that protein and amino acids supplementation exerted a positive impact on muscle mass in the elderly.[31] Supplemental 1-1.5 gram protein per kilogram bodyweight could prevent sarcopenia and maintain skeletal muscle mass in the elderly.[26,32,33] However, excessive protein intake (3 gram per kilogram) had no beneficial effect on muscle protein synthesis, potentially causing appetite loss,[34] tasting inhibition,[35] and resulting in impaired renal function in the elderly.[36] A previous study was consistent with the present results, indicating that appropriate protein intake might be beneficial in prevention of sarcopenia.

The relationships between dietary amino acid intakes and sarcopenic risk have received extensive attention. Amino acids generated by protein decomposition are the main essential amino acids to maintain muscle health in the elderly, especially BCAAs.[28,37] BCAAs (leucine, valine, and isoleucine) are the most abundant amino acids in proteins and can be exclusively obtained from dietary sources rather than endogenous synthesis. Meat, dairy products, eggs, beans, and cereals are rich in BCAAs, and these foods have important physiological roles in the regulation of protein synthesis, metabolism, food intake, and aging.[21] Le Couteur et al. summarized the effect of BCAAs supplementation on sarcopenia. They found that BCAAs supplementation alone was unlikely to be useful in sarcopenia; however, a diet rich in protein to increase the proportion of BCAAs had a positive effect on muscle mass in elders.[21] In an open-label clinical trial demonstrated that supplementation with BCAAs enriched mixture significant improved muscle mass and physical function in malnourished patients.[38] In addition, a randomized controlled trial showed that BCAAs supplementation (7.2 g/day) had positive effects on muscle strength and mass during a 5-week of intervention, but these positive effects were decreased after a 12-week of intervention.[39] Contrarily, animal model showed that supplementation with BCAAs or leucine contributed to increasing protein catabolism, while the weight of muscle remained unchanged.[40] Furthermore, several studies focused on the roles of BCAAs supplementation on muscle mass and function in patients with sarcopenia accompanied by other diseases.[21,28,38-47] Accordingly, the roles of BCAAs on muscle mass and functions were summarized and discussed in Table 4. In summary, BCAAs have beneficial effects on muscle mass and function. It is worth noting that when sarcopenia is combined with liver and kidney disease differs from sarcopenia alone, so the results of BCAAs supplementation in sarcopenia combined with liver and kidney disease should be interpreted with caution. Therefore, the effects of BCAAs on skeletal muscle mass and functions remain to be further investigated.

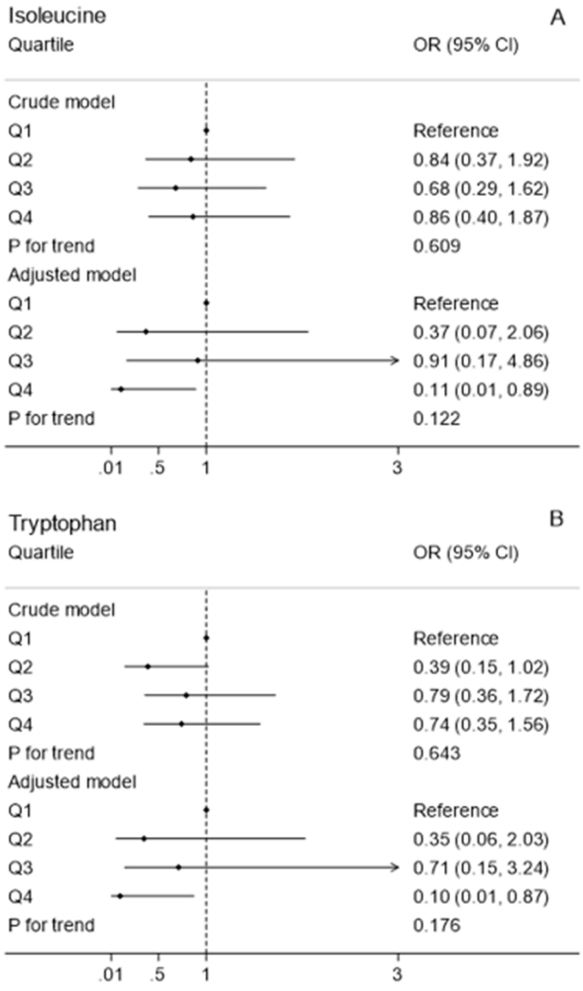

Figure 3. Association of dietary isoleucine (A), tryptophan (B) intakes with risk of sarcopenia.

Table 2. Multivariate adjusted odds ratios and 95% confidence intervals for sarcopenia compared to no sarcopenia by quartile of protein and amino acid intakes among 1140 elderly subjects[†]

	Q1	Q2	Q3	Q4	p[‡] for trend
Total protein, g/d	≤47.8	47.8-60.9	60.9-74.3	>74.3	
No. of sarcopenia/no sarcopenia	15/254	12/256	3/265	17/318	
OR (95% CI)	1.00 (reference)	0.79 (0.36, 1.73)	0.19 (0.05, 0.67)	0.91 (0.44, 1.85)	0.340
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.16 (0.02, 1.28)	0.02 (0.01, 0.53)	0.31 (0.01, 8.22)	0.056
Branched chain amino acids, mg/d	≤3002.2	3002.2-4653.4	4653.4-6593.0	>6593.0	
No. of sarcopenia/no sarcopenia	13/256	12/256	6/262	16/319	
OR (95% CI)	1.00 (reference)	0.92 (0.41, 2.06)	0.45 (0.17, 1.20)	0.99 (0.47, 2.09)	0.680
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.27 (0.05, 1.48)	0.68 (0.12, 3.80)	0.11 (0.01, 0.90)	0.119
Sulfur amino acids, mg/d	≤629.9	629.9-994.5	994.5-1417.5	>1417.5	
No. of sarcopenia/no sarcopenia	11/258	10/258	9/260	17/317	
OR (95% CI)	1.00 (reference)	0.91 (0.38, 2.18)	0.81 (0.33, 1.99)	1.26 (0.58, 2.73)	0.604
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.71 (0.13, 3.79)	0.84 (0.16, 4.37)	0.35 (0.04, 3.09)	0.589
Aromatic amino acids, mg/d	≤1399.0	1399.0-2147.7	2147.7-3053.1	>3053.1	
No. of sarcopenia/no sarcopenia	13/256	12/256	6/262	16/319	
OR (95% CI)	1.00 (reference)	0.92 (0.41, 2.06)	0.45 (0.17, 1.20)	0.99 (0.47, 2.09)	0.682
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.53 (0.10, 2.70)	0.76 (0.14, 4.14)	0.16 (0.02, 1.18)	0.190
Histidine, mg/d	≤436.0	436.0-675.5	675.5-960.3	>960.3	
No. of sarcopenia/no sarcopenia	13/256	10/258	8/261	16/318	
OR (95% CI)	1.00 (reference)	0.76 (0.33, 1.77)	0.60 (0.25, 1.48)	0.99 (0.47, 2.10)	0.873
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.63 (0.13, 3.09)	0.71 (0.14, 3.60)	0.22 (0.03, 1.85)	0.287
Lysine, mg/d	≤1052.5	1052.5-1781.2	1781.2-2622.7	>2622.7	
No. of sarcopenia/no sarcopenia	14/255	7/261	10/259	16/318	
OR (95% CI)	1.00 (reference)	0.49 (0.19, 1.23)	0.70 (0.31, 1.61)	0.92 (0.44, 1.91)	0.977
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.19 (0.03, 1.18)	1.21 (0.23, 6.38)	0.14 (0.02, 1.11)	0.283
Threonine, mg/d	≤672.2	672.2-1092.9	1092.9-1543.0	>1543.0	
No. of sarcopenia/no sarcopenia	14/255	11/257	6/263	16/318	
OR (95% CI)	1.00 (reference)	0.78 (0.35, 1.75)	0.42 (0.16, 1.10)	0.92 (0.44, 1.91)	0.565
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.35 (0.07, 1.81)	1.15 (0.21, 6.20)	0.17 (0.02, 1.19)	0.217
Isoleucine, mg/d	≤717.5	717.5-1164.2	1164.2-1638.7	>1638.7	
No. of sarcopenia/no sarcopenia	13/256	11/257	299/260	14/320	
OR (95% CI)	1.00 (reference)	0.84 (0.37, 1.92)	0.68 (0.29, 1.62)	0.86 (0.40, 1.87)	0.609
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.37 (0.07, 2.06)	0.91 (0.17, 4.86)	0.11 (0.01, 0.89)	0.122
Leucine, mg/d	≤1377.0	1377.0-2154.7	2154.7-2994.0	>2994.0	
No. of sarcopenia/no sarcopenia	13/256	10/258	8/260	16/319	
OR (95% CI)	1.00 (reference)	0.76 (0.33, 1.77)	0.61 (0.25, 1.49)	0.99 (0.47, 2.09)	0.858
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.25 (0.04, 1.48)	0.61 (0.12, 3.15)	0.13 (0.01, 1.13)	0.212

CI: confidence interval; No.: number of subjects; OR: odds ratio.

[†]The multivariable-adjusted model of logistic regression was adjustment for age, gender, height, weight, BMI, waist circumference, hip circumference, waist hip ratio, blood pressure, marital status, education level, smoking, alcohol drinking, physical activity, fasting blood glucose, TC, TG, HDL-C, LDL-C, daily energy intake, carbohydrate intake, fat intake.

[‡]p for trends were conducted by assigning the median value for each category and modelling this variable as a continuous variable.

Table 2. Multivariate adjusted odds ratios and 95% confidence intervals for sarcopenia compared to no sarcopenia by quartile of protein and amino acid intakes among 1140 elderly subjects[†] (cont.)

	Q1	Q2	Q3	Q4	p[‡] for trend
Valine, mg/d	≤877	877-1360	1360-1910	>1910	
No. of sarcopenia/no sarcopenia	14/254	10/259	7/262	16/318	
OR (95% CI)	1.00 (reference)	0.70 (0.31, 1.61)	0.48 (0.19, 1.22)	0.91 (0.44, 1.91)	0.646
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.53 (0.11, 2.63)	0.61 (0.12, 3.19)	0.16 (0.02, 1.16)	0.145
Tryptophan, mg/d	≤243	243-379	379-533	>533	
No. of sarcopenia/no sarcopenia	15/254	6/262	12/257	14/320	
OR (95% CI)	1.00 (reference)	0.39 (0.15, 1.02)	0.79 (0.36, 1.72)	0.74 (0.35, 1.56)	0.643
Multivariate adjusted OR (95% CI)	1.00 (reference)	0.35 (0.06, 2.03)	0.71 (0.15, 3.24)	0.10 (0.01, 0.87)	0.176

CI: confidence interval; No.: number of subjects; OR: odds ratio.
[†]The multivariable-adjusted model of logistic regression was adjustment for age, gender, height, weight, BMI, waist circumference, hip circumference, waist hip ratio, blood pressure, marital status, education level, smoking, alcohol drinking, physical activity, fasting blood glucose, TC, TG, HDL-C, LDL-C, daily energy intake, carbohydrate intake, fat intake.
[‡]p for trends were conducted by assigning the median value for each category and modelling this variable as a continuous variable.

Table 3. Prediction of the relationships between dietary intakes of protein and amino acids and muscle mass functions by generalized linear regression[†]

	Grip strength				Gait speed			
	Crude model		Adjusted model		Crude model		Adjusted model	
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
Total protein, g/d	0.12 (0.01)	<0.001	-0.02 (0.02)	0.343	0.00 (0.00)	<0.001	0.00 (0.00)	0.054
BCAAs, g/d	0.57 (0.09)	<0.001	-0.11 (0.09)	0.186	0.01 (0.00)	<0.001	0.01 (0.00)	0.032
Sulfur amino acids, g/d	2.52 (0.44)	<0.001	-0.40 (0.38)	0.289	0.05 (0.01)	<0.001	0.02 (0.01)	0.203
Aromatic amino acids, g/d	1.23 (0.20)	<0.001	-0.21 (0.18)	0.262	0.02 (0.00)	<0.001	0.01 (0.01)	0.033
Histidine, g/d	4.07 (0.64)	<0.001	-0.75 (0.60)	0.214	0.08 (0.02)	<0.001	0.04 (0.02)	0.056
Lysine, g/d	1.24 (0.21)	<0.001	-0.28 (0.20)	0.171	0.03 (0.01)	<0.001	0.02 (0.01)	0.011
Threonine, g/d	2.27 (0.38)	<0.001	-0.52 (0.36)	0.151	0.05 (0.01)	<0.001	0.03 (0.01)	0.022
Isoleucine, g/d	2.19 (0.36)	<0.001	-0.38 (0.33)	0.253	0.04 (0.01)	<0.001	0.02 (0.01)	0.084
Leucine, g/d	1.21 (0.20)	<0.001	-0.25 (0.19)	0.176	0.02 (0.00)	<0.001	0.01 (0.01)	0.025
Valine, g/d	1.96 (0.32)	<0.001	-0.42 (0.30)	0.168	0.04 (0.01)	<0.001	0.02 (0.01)	0.021
Tryptophan, g/d	7.75 (1.20)	<0.001	-0.77 (1.09)	0.481	0.14 (0.03)	<0.001	0.09 (0.04)	0.011

BCAAs: branched chain amino acids; SE: standard error.
[†]The multivariable-adjusted model of generalized linear analyses was adjustment for age, gender, height, weight, BMI, waist circumference, hip circumference, waist hip ratio, blood pressure, marital status, education level, smoking, alcohol drinking, physical activity, fasting blood glucose, TC, TG, HDL-C, LDL-C, daily energy intake, carbohydrate intake, fat intake.

Table 4. Effect of Branched chain amino acids (BCAAs) on muscle mass and functions

Author, Year	Country	Type of article	Conclusions/ Evidence	Effect on muscles
Buondonno, 2020[38]	Italy	Open-label Randomized Trial	Supplementation with BCAAs enriched mixture significant improved muscle mass and physical function in malnourished patients.	Positively
Dasarathy, 2016[47]	Italy	Review Article	BCAAs improved protein synthesis and improve muscle mass by inhibiting the amino acid deficiency sensor, GCN2 and reversing eIF2α phosphorylation.	Positively
Hanai, 2015[41]	Japan	Retrospective Study	BCAAs supplementation were associated with improved survival of sarcopenic patients with liver cirrhosis.	Positively
Hanai, 2017[46]	Japan	Retrospective Study	Decreasing serum BCAAs levels was associated with sarcopenia, and BCAAs supplementation may be one of the therapeutic options for sarcopenia and minimal hepatic encephalopathy in patients with liver cirrhosis.	Positively
Hiraoka, 2017[45]	Japan	longitudinal Study	BCAAs supplementation and walking exercise were found to be effective and easily implemented for improving muscle volume and strength in liver cirrhosis patients.	Positively
Holecek, 2016[40]	Czech Republic	Animal Trial	The results failed to demonstrate positive effects of the chronic consumption of BCAAs or leucine-enriched diets on protein balance in skeletal muscle.	Negatively
Kitajima, 2018[42]	Japan	longitudinal Study	In patients with liver cirrhosis, supplementation with BCAAs were related to decreased fat accumulation in skeletal muscle, which maintained skeletal muscle mass and ameliorated glucose tolerance.	Positively
Ko, 2020[39]	China	Single-arm Intervention Study	Supplementation with enriched BCAAs for 5 weeks correlates with short-term positive effects on sarcopenic parameters but attenuation of those effects following discontinuation for 12 weeks.	Positively
Le Couteur, 2020[21]	Australia	Review Article	BCAAs supplements by themselves are unlikely to be useful in sarcopenia, however, BCAAs as part of higher protein intake, enriched amino acid supplement or a protein supplement are associated with improvements of muscle function in older people.	Neutrally
Nishikawa, 2016[44]	Japan	Review Article	Decreased BCAAs concentration in the blood and/or muscles could lower ammonia clearance from the blood, and lead to both the progression of hepatic encephalopathy and the increase of the severity of sarcopenia.	Positively
Rondanelli, 2015[28]	Italy	Review Article	At rest, BCAAs, in particular leucine, have an anabolic effect by an increasing protein synthesis and/or a reducing the rate of protein degradation, resulting in a positive net muscle protein balance.	Positively
Sinclair, 2016[43]	Australia	Review Article	In sarcopenic cirrhotic patients, both reduced circulating BCAAs levels and reduced muscle mass might contribute to impaired ammonia clearance.	Positively

BCAAs: branched chain amino acids; GCN2: general control nondepressed 2; eIF2α: eukaryotic initiation factor 2 α.

It is necessary and significant to supplemental essential amino acids contributing to skeletal muscle anabolism.[48] The positive effect of BCAAs on muscle is achieved by promoting protein synthesis and reducing protein degradation (Figure 4).[20] BCAAs stimulate muscle anabolism by promoting mTOR phosphorylation. With the activation of P70S6K, a downstream of mTOR, it increases protein synthesis through activating S6 and eIF4B.[49] Meanwhile, it has been reported that BCAAs could reduce the Atrogin-1 and MuRF-1 mRNA expression mediated by mTOR.[50] Atrogin-1 and MuRF-1 are E3 ubiquitin ligases expressed in skeletal muscle. Reduced levels of these two substances could decrease the ubiquitination of protein and reduce the degradation of muscle protein.[51] Isoleucine might have synergies with insulin to activate mTOR to reduce the loss of muscle mass or physical function.[21] Besides, one study found that tryptophan increased the lipid peroxidation of muscle by inducing the kynurenine pathway, thereby increasing the risk of muscle reduction.[52] But this mechanism is contrary to our findings. Further research is needed to explore the relationship between a single amino acid and sarcopenia.

The associations of dietary protein and amino acid intakes with muscle mass functions were also investigated. To date, no epidemiological study has reported the relationships between individual amino acids and muscle mass functions. A double-blind randomized controlled trial with 6 months of intervention showed that supplemental protein with a new chicken oral liquid significantly improved the gait speed in the higher-level physical activity group in the elderly over 70 years, compared with controls.[53] Meanwhile, BCAAs supplementation could improve muscle function in patients with sarcopenia in short period of intervention, but not for a long period of intervention.[39] Regarding the relationship between single amino acid and muscle mass function, tryptophan metabolites were associated with the increased risk of sarcopenia,[54,55] but another study showed that serum kynurenine levels (a tryptophan metabolite) were negatively associated with grip strength and gait speed.[52] Besides, no study has explored the effects of dietary aromatic amino acids, lysine and threonine supplementation on muscle mass function, and that needs further research.

There are several advantages of this study to highlight. To the best of our knowledge, this study is the first to explore the relationships between dietary intakes of protein and amino acids and sarcopenic risk. The associations of protein and amino acids with muscle mass functions have also been investigated. Secondly, the present community-based study provided strong evidence that appropriate protein intake with higher BCAAs intakes was inversely associated with risk of sarcopenia. We believe that the findings of this study have public health significance for the prevention of sarcopenia. They also deepen our understanding of the associations between BCAAs and sarcopenia. There are limitations of this study. Firstly, the accuracy of dietary protein and amino acid intakes is crucial for component-based epidemiological study, but uncertain. Although the validated 3-day food records were used to evaluate the dietary intakes of protein and amino acids, measurement error was inevitable in participants over 65 years. Secondly, epidemiological research is inevitably limited by potentially unrecognized confounding factors. The multivariable-adjusted models have inherent bias and residual confounding factors attributable to inaccurate or unmeasured risk factors which might affect the final relationships advanced.[24]

Conclusion

In conclusion, the present study demonstrates that a moderate increase in protein intake is associated with a reduced risk of sarcopenia. Furthermore, higher intakes of BCAAs are associated with reduced risk of sarcopenia and improved physical functions. We believe the findings of the present study have significant public health relevance for the prevention of sarcopenia. To confirm the

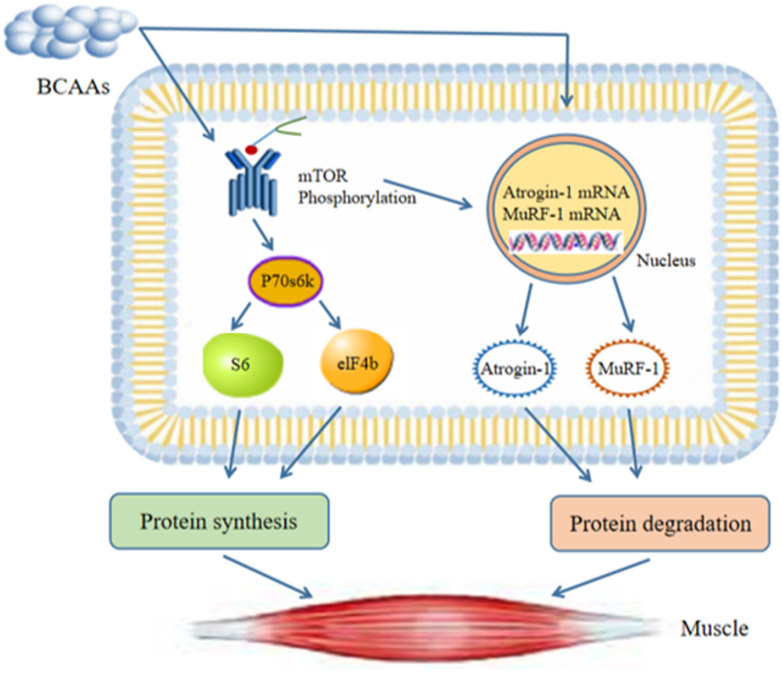

Figure 4. The mechanism of branched chain amino acids on muscle by affecting protein synthesis and degradation pathway.

findings of this study, high-quality epidemiological studies with larger sample-size are warranted to be implemented in other regions and ethnic origins.

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AUTHOR DISCLOSURES

The authors declare this work has no conflict of interest.

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