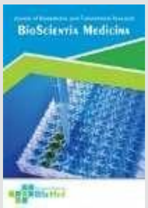
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Dietary BCAAs (Branched Chain Amino Acids) and Cognitive Function: Implications for Nutritional Interventions in Elderly Populations

Willya Eka Putri[1], Nur Indrawaty Lipoeto[2*], Roza Mulyana[3]

[1]Biomedicine Science, Master Program, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Department of Nutrition, Dr. M. Djamil General Hospital, Padang, Indonesia

[3]Department of Internal Medicine, Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:

Branched-chain amino acids

Cognitive function

Elderly

MoCA-Ina

Nutritional interventions

***Corresponding author:**

Nur Indrawaty Lipoeto

E-mail address:

indra.liputo@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i5.1286

A B S T R A C T

Background: The aging process is often accompanied by a decline in cognitive function, impacting memory, attention, and decision-making. Malnutrition, including protein deficiency, is recognized as a contributing factor to cognitive decline in elderly populations. Branched-chain amino acids (BCAAs), essential amino acids obtained solely from dietary sources, play a pivotal role in various physiological processes, including neurotransmitter synthesis and protein synthesis in the brain. This study aims to investigate the relationship between serum BCAA levels and cognitive function in elderly individuals. **Methods:** A cross-sectional study was conducted on 25 elderly subjects (age > 60 years) in Padang, Indonesia. Serum BCAA levels were measured using High-Performance Liquid Chromatography (HPLC), and cognitive function was assessed using the Montreal Cognitive Assessment - Indonesian version (MoCA-Ina). Statistical analysis was performed to determine the correlation between BCAA levels and MoCA-Ina scores. **Results:** The mean serum levels of total BCAAs, leucine, isoleucine, and valine in the elderly subjects were 0.40 ± 0.15 mM, 0.09 ± 0.06 mM, 0.05 ± 0.02 mM, and 0.26 ± 0.10 mM, respectively. The median MoCA-Ina score was 23 (range: 8-27), indicating a significant proportion of participants with cognitive impairment. Statistical analysis revealed no significant correlation between total BCAA levels and MoCA-Ina scores ($r = 0.071$, $p = 0.735$). However, a moderate positive correlation was observed between isoleucine levels and MoCA-Ina scores ($r = 0.344$, $p = 0.092$), although not statistically significant. **Conclusion:** This study suggests that serum BCAA levels, particularly isoleucine, may have implications for cognitive function in elderly populations. Further research with a larger sample size and longitudinal design is warranted to elucidate the complex relationship between dietary BCAAs, serum BCAA levels, and cognitive health in aging individuals.

1. Introduction

The global population is aging at an unprecedented rate, with the number of individuals aged 60 years and older projected to reach a staggering 2.1 billion by the year 2050. This demographic shift presents a unique set of challenges, including the increasing prevalence of age-related health concerns, most notably the decline in cognitive function. Cognitive function, a multifaceted concept encompassing a range of mental processes such as memory, attention, language, and executive functions, is paramount for daily living and the maintenance of overall well-being. As individuals advance in age, the brain undergoes a series of physiological changes, including neuronal loss, reduced neurotransmitter production, and decreased cerebral blood flow. These age-related alterations can contribute to a gradual decline in cognitive abilities, impacting memory, processing speed, and executive functions, ultimately affecting an individual's ability to perform daily tasks and maintain independence.[1-4]

Among the various factors contributing to cognitive decline in the elderly, malnutrition, particularly protein deficiency, has emerged as a significant concern. Protein plays a pivotal role in brain function, providing the essential building blocks for neurotransmitters and supporting a myriad of cellular processes critical for optimal cognitive performance. Within the realm of protein nutrition, branched-chain amino acids (BCAAs) – leucine, isoleucine, and valine – stand out as essential amino acids that cannot be synthesized by the human body and must be obtained solely from dietary sources. BCAAs possess unique properties that distinguish them from other amino acids, primarily their metabolism, which occurs predominantly in skeletal muscle, unlike other amino acids that are primarily metabolized in the liver. This extrahepatic metabolism allows BCAAs to directly influence muscle protein synthesis and energy production, making them crucial for muscle health and maintenance.[5-7]

In the context of brain function, BCAAs serve as precursors for neurotransmitter synthesis, particularly glutamate and gamma-aminobutyric acid (GABA). Glutamate, the primary excitatory neurotransmitter in the brain, plays a critical role in learning and memory formation, while GABA, the primary inhibitory neurotransmitter, contributes to the regulation of neuronal excitability, ensuring a balance in brain activity. Leucine, one of the BCAAs, has also been shown to activate the mammalian target of rapamycin (mTOR) signaling pathway, a critical pathway involved in protein synthesis, cell growth, and autophagy. mTOR signaling has been implicated in various age-related processes, including cognitive decline and neurodegenerative diseases, making it a focal point in aging research.[8-10] Given the importance of protein nutrition and the unique roles of BCAAs in brain function, this study aims to investigate the relationship between dietary BCAAs and cognitive function in elderly populations.

2. Methods

This research employed a cross-sectional design to investigate the relationship between dietary branched-chain amino acids (BCAAs) and cognitive function in elderly individuals. The study was conducted in Padang, Indonesia, spanning a two-month period from November to December 2024. The study population consisted of individuals aged 60 years and older, recruited from two primary healthcare centers (Puskesmas Ambacang and Puskesmas Alai) in Padang. The sample size was determined using a formula specifically designed for correlation studies, taking into account the significance level, power of the study, and estimated correlation coefficient. This calculation ensured that the study had sufficient statistical power to detect meaningful relationships between the variables of interest.

To maintain the integrity and focus of the study, specific inclusion and exclusion criteria were established. Participants were included in the study if they met the following criteria; Age above 60 years; Ability to communicate effectively, ensuring meaningful participation in the study procedures; Willingness to participate in the study and provide informed consent, adhering to ethical research practices. Conversely, individuals were excluded from the study if they met any of the following criteria; Diagnosis of Alzheimer's disease, as this condition could confound the assessment of cognitive function related to dietary BCAAs; History of stroke, which could impact cognitive abilities independent of BCAA intake; Hearing impairment, which could interfere with the cognitive assessments; Liver disease, as BCAAs are primarily metabolized in the liver, and liver dysfunction could affect BCAA levels and metabolism; Acute illness, which could temporarily affect cognitive function and BCAA levels. These criteria ensured that the study population was representative of the target group and minimized the influence of confounding factors that could affect the interpretation of the results.

A comprehensive data collection approach was employed, incorporating interviews, physical examinations, and blood tests to gather relevant information from the participants; Interviews: Structured interviews were conducted to collect demographic information, including age, gender, education level, occupation, and medical history. This information provided valuable insights into the background and potential confounding factors of the participants; Physical Examinations: Body weight and height were measured to calculate body mass index (BMI), a measure of body fat based on weight and height. BMI was included as a potential confounding factor in the analysis, as obesity has been linked to cognitive decline; Blood Tests: Blood samples were collected from participants after an overnight fast to minimize the influence of recent food intake on serum BCAA levels. Serum was separated from the blood samples and stored at -80°C until analysis, ensuring sample stability and integrity.

Serum BCAA levels were measured using High-Performance Liquid Chromatography (HPLC) at Vahana Scientific Laboratory in Siteba, Padang. HPLC is a widely used analytical technique for separating, identifying, and quantifying components in a mixture. In this study, HPLC was employed to accurately measure the levels of individual BCAAs (leucine, isoleucine, and valine) in the serum samples. The HPLC procedure involved several key steps; Deproteinization: Serum samples were treated with sulfosalicylic acid to precipitate proteins, which could interfere with the HPLC analysis. The mixture was then centrifuged to remove the precipitated proteins, leaving a clear supernatant containing the BCAAs; Derivatization: The supernatant was mixed with a derivatization reagent and incubated at a specific temperature to enhance the detection of amino acids. Derivatization involves chemically modifying the amino acids to improve their separation and detection by HPLC; HPLC Analysis: The derivatized sample was injected into the HPLC system, where the amino acids were separated based on their chemical properties and detected using a fluorescence detector (FLD). FLD is a highly sensitive detection method that measures the fluorescence emitted by the derivatized amino acids; Data Analysis: The HPLC chromatogram, a graphical representation of the separated amino acids, was analyzed to identify and quantify the levels of individual BCAAs in the serum samples. This data provided valuable information on the BCAA profiles of the participants.

Cognitive function was assessed using the Montreal Cognitive Assessment - Indonesian version (MoCA-Ina), a validated tool specifically designed for assessing cognitive function in elderly populations. The MoCA-Ina covers a wide range of cognitive domains, including attention, memory, language, and executive functions, providing a comprehensive evaluation of cognitive abilities. The MoCA-Ina is a 30-point test that assesses various cognitive domains through a series of tasks and questions. The tasks are designed to evaluate different aspects of cognitive function, such as; Visuospatial/Executive: This domain assesses the ability to perceive and organize visual information and plan and execute tasks; Naming: This task evaluates the ability to name common objects, assessing language and semantic memory; Memory: This domain assesses short-term memory through recall tasks; Attention: This domain evaluates the ability to focus and sustain attention through digit span and serial subtraction tasks; Language: This domain assesses language comprehension and production through sentence repetition and fluency tasks; Abstraction: This task evaluates the ability to identify similarities between concepts, assessing abstract reasoning; Delayed Recall: This task assesses long-term memory by asking participants to recall words presented earlier in the test; Orientation: This task evaluates the ability to orient to time and place. The MoCA-Ina is a valuable tool for identifying individuals with mild cognitive impairment (MCI) and early-stage dementia. It is widely used in clinical and research settings due to its sensitivity, specificity, and ease of administration.

The data collected in this study were analyzed using appropriate statistical methods to ensure accurate and meaningful interpretation of the results. Descriptive statistics were used to summarize the demographic characteristics of the participants, providing a clear overview of the study population. The distribution of serum BCAA levels and MoCA-Ina scores was assessed for normality using the Shapiro-Wilk test. This test determines whether the data follows a normal distribution, which is an assumption for certain statistical analyses. Pearson correlation analysis was used to examine the relationship between serum BCAA levels and MoCA-Ina scores for normally distributed data. Pearson correlation measures the strength and direction of the linear relationship between two continuous variables. For non-normally distributed data, Spearman correlation analysis was used. Spearman correlation assesses the monotonic relationship between two variables, which does not require the assumption of normality. Statistical significance was set at $p < 0.05$, indicating that the observed results were unlikely to occur by chance alone. This threshold is commonly used in research to determine the significance of findings. This comprehensive and rigorous methodological approach ensured that the study was conducted with scientific integrity and provided reliable and valid results. The combination of data collection methods, BCAA measurement techniques, cognitive function assessment, and statistical analysis allowed for a thorough investigation of the relationship between dietary BCAAs and cognitive function in elderly individuals.

3. Results

Table 1 provides a comprehensive overview of the characteristics of the 25 elderly participants involved in the study; Gender: A majority of the participants were female (64%), with a smaller proportion being male (36%). This distribution may be reflective of the demographics of the study area or could be due to chance; Age Group: The participants were fairly evenly distributed across the age ranges of 60-65, 66-70, and 71-75 years, with each group comprising around 30% of the sample. A smaller proportion (12%) were over 75 years old. This distribution suggests that the study captured a representative sample of the older population; Occupation: The most common occupation among participants was "housewife" (52%), followed by "retired" (28%). This is likely reflective of the typical occupational patterns in older age groups. A small proportion (4%) were still engaged in labor-intensive occupations, while 16% were traders or self-employed; History of Disease: A significant proportion of participants reported having hypertension (52%) and diabetes mellitus (32%). These are common chronic conditions in older adults and could potentially influence cognitive function; Education Level: The education level of participants varied, with the largest group (44%) having completed primary school. 32% had completed senior high school, while smaller proportions had lower or higher levels of education. This distribution suggests that the study included individuals with a range of educational backgrounds; BMI: The BMI distribution showed that a large proportion of participants were obese (>25 kg/m^2) (32%), while 40% had a normal weight (18.5-22.9 kg/m^2). 16% were underweight (<18.5 kg/m^2) and 12% were overweight (23-25 kg/m^2). This distribution highlights the prevalence of obesity in this population, which could be a factor influencing cognitive health; Cognitive Impairment: A striking observation is that a majority of the participants (76%) showed signs of cognitive impairment based on their MoCA-Ina scores. This finding underscores the prevalence of cognitive decline in elderly populations and highlights the importance of investigating potential contributing factors, such as dietary BCAAs.

Table 2 presents the serum levels of Branched-Chain Amino Acids (BCAAs) in the 25 elderly participants. The average total BCAA level was 0.40 mM with a standard deviation of 0.15 mM. This indicates some variability in BCAA levels among participants. The median value (0.39 mM) is close to the mean, suggesting a fairly symmetrical distribution of total BCAA levels. The range (0.15 - 0.74 mM) shows the spread of the data, with the lowest and highest observed values. The mean leucine level was 0.09 mM (SD 0.06), with a median of 0.08 mM. Similar to total BCAA, the distribution appears fairly symmetrical.

Leucine levels ranged from 0.02 to 0.23 mM. Isoleucine had the lowest mean level among the BCAAs at 0.05 mM (SD 0.02). The median was also 0.05 mM, and the range was 0.02 to 0.10 mM. Valine had the highest mean level among the BCAAs at 0.26 mM (SD 0.10), with a median of 0.25 mM. The range was 0.09 to 0.48 mM.

Table 1. Participant characteristics (n=25).

Characteristic	Category	Frequency	Percentage (%)
Gender			
	Male	9	36
	Female	16	64
Age group (years)			
	60-65	6	24
	66-70	8	32
	71-75	8	32
	>75	3	12
Occupation			
	Housewife	13	52
	Retired	7	28
	Laborer	1	4
	Trader/Self-Employed	4	16
History of disease			
	Diabetes Mellitus	8	32
	Hypertension	13	52
Education level			
	Primary School	11	44
	Junior High School	2	8
	Senior High School	8	32
	Diploma 3	1	4
	Bachelor's Degree	2	8
	Master's Degree	1	4
BMI (kg/m²)			
	Underweight (<18.5)	4	16
	Normal Weight (18.5-22.9)	10	40
	Overweight (23-25)	3	12
	Obese (>25)	8	32
Cognitive impairment			
	Yes	19	76
	No	6	24

Table 2. Serum BCAA levels in elderly participants (n=25).

BCAA	Mean (SD) (mM)	Median (mM)	Range (mM)
Total BCAA	0.40 (0.15)	0.39	0.15 - 0.74
Leucine	0.09 (0.06)	0.08	0.02 - 0.23
Isoleucine	0.05 (0.02)	0.05	0.02 - 0.10
Valine	0.26 (0.10)	0.25	0.09 - 0.48

Table 3 focuses on the MoCA-Ina scores of the 25 elderly participants, providing insights into their cognitive function. The median MoCA-Ina score was 23. This is important because it gives us a central tendency of the cognitive performance in the group. In a 30-point test, a median of 23 suggests that the participants, on average, might be experiencing some degree of cognitive decline. The range of MoCA-Ina scores was quite wide, spanning from 8 to 27. This indicates significant variability in cognitive abilities among the participants. Some individuals performed relatively well, while others showed considerably lower scores, suggesting more pronounced cognitive impairment. The IQR, which represents the spread of the middle 50% of the data, was 7. This indicates that the scores within the middle half of the participants were relatively spread out. A key finding is that 19 participants (76%) had MoCA-Ina scores of 25 or lower. This is a significant proportion, indicating that a majority of the participants likely have some level of cognitive impairment. This aligns with the general understanding that cognitive decline is prevalent in aging populations.

Table 3. MoCA-Ina scores in elderly participants (n=25).

Variable	**Median**	**Range**	**IQR (Interquartile Range)**	**Number (%) of participants with cognitive impairment (MoCA-Ina ≤ 25)**
MoCA-Ina score	23	8 - 27	7	19 (76%)

Table 4 presents the correlation coefficients and p-values for the relationships between serum BCAA levels (Leucine, Isoleucine, and Valine) and MoCA-Ina scores in the elderly participants; Leucine: 0.071. This indicates a very weak positive correlation between serum leucine levels and MoCA-Ina scores. 0.033. This means that only 3.3% of the variability in MoCA-Ina scores can be explained by leucine levels. 0.735. This is greater than the typical significance level of 0.05, indicating that the correlation is not statistically significant. In other words, there is no strong evidence to suggest a relationship between leucine levels and cognitive function in this sample; Isoleucine: 0.344. This suggests a moderate positive correlation between serum isoleucine levels and MoCA-Ina scores. 0.116. This means that 11.6% of the variability in MoCA-Ina scores can be explained by isoleucine levels. 0.092. While this shows a trend towards significance, it is still above the 0.05 threshold. Therefore, the correlation between isoleucine and cognitive function is not statistically significant in this study; Valine: -0.087. This indicates a very weak negative correlation between serum valine levels and MoCA-Ina scores. 0.000026. This means that valine levels explain a negligible amount of the variability in MoCA-Ina scores. 0.679. This is much higher than 0.05, indicating no statistically significant relationship between valine levels and cognitive function.

Table 4. Correlation between serum BCAA levels and MoCA-Ina scores in elderly participants (n=25).

BCAA	**Correlation coefficient (r)**	**r^2**	**p-value**	**Interpretation**
Leucine	0.071	0.033	0.735	Very weak positive correlation, not statistically significant. Leucine levels explain 3.3% of the variability in MoCA-Ina scores.
Isoleucine	0.344	0.116	0.092	Moderate positive correlation, not statistically significant. Isoleucine levels explain 11.6% of the variability in MoCA-Ina scores.
Valine	-0.087	0.000026	0.679	Very weak negative correlation, not statistically significant. Valine levels explain 0.0026% of the variability in MoCA-Ina scores.

4. Discussion

This study aimed to unravel the intricate connection between dietary branched-chain amino acids (BCAAs) and cognitive function in an elderly population. While the results did not demonstrate statistically significant correlations between total serum BCAA levels and cognitive performance, they nonetheless offer valuable insights and contribute to the ongoing discourse regarding the role of nutrition in cognitive health during aging. The study's findings revealed that the mean serum levels of total BCAAs, encompassing leucine, isoleucine, and valine, in the elderly participants were within the normal range for human serum. This observation implies that overt BCAA deficiency was not a widespread concern among the study population. However, despite having sufficient BCAA levels, a significant proportion of participants displayed cognitive impairment, as evidenced by their median MoCA-Ina score of 23. This result is consistent with the well-established trend of cognitive decline associated with aging, underscoring the multifactorial nature of cognitive health in elderly individuals. The absence of a statistically significant correlation between total BCAA levels and MoCA-Ina scores emphasizes the complexity of the relationship between these two variables. Several factors may have contributed to this observation, warranting careful consideration when interpreting the results. The relatively small sample size of 25 participants may have limited the statistical power of the study to detect subtle correlations between BCAA levels and cognitive function. Larger studies with greater statistical power are necessary to explore these relationships more comprehensively. The cross-sectional nature of the study design presents a limitation in establishing a causal relationship between BCAA levels and cognitive function. It is conceivable that cognitive decline may precede and influence dietary habits and BCAA intake, rather than the converse. Longitudinal studies that follow participants over time are better equipped to investigate the causal direction of this relationship. A multitude of confounding factors, including age, education level, occupation, medical history, and overall nutritional status, may have influenced the relationship between BCAAs and cognitive function. These factors can independently affect both BCAA levels and cognitive performance, making it challenging to isolate the specific effects of BCAAs. Future studies should strive to control for these confounding factors to gain a clearer understanding of the BCAA-cognitive function relationship. Despite the lack of a significant correlation between total BCAA levels and cognitive function, the moderate positive correlation observed between isoleucine levels and MoCA-Ina scores is particularly noteworthy. Isoleucine, one of the three BCAAs, plays a multifaceted role in various metabolic processes that are critical for brain function. Isoleucine has demonstrated the ability to improve glucose uptake in skeletal muscle and enhance insulin signaling. These effects may indirectly benefit brain function by ensuring adequate energy supply and neuronal function. The brain relies heavily on glucose as its primary energy source, and disruptions in glucose metabolism and insulin signaling have been implicated in cognitive decline. Isoleucine serves as a precursor for the synthesis of neurotransmitters, particularly glutamate and gamma-aminobutyric acid (GABA). Glutamate is the main excitatory neurotransmitter in the brain, involved in learning and memory formation, while GABA is the primary inhibitory neurotransmitter, contributing to the regulation of neuronal excitability. Maintaining a balance between these neurotransmitters is essential for optimal cognitive function. Isoleucine has also been implicated in mitochondrial function, which is crucial for energy production in cells, including neurons. Studies have shown that isoleucine can increase mitochondrial biogenesis and improve mitochondrial efficiency, potentially leading to enhanced neuronal energy metabolism and cognitive function. Emerging evidence suggests that isoleucine may have anti-inflammatory properties, which could be beneficial for brain health. Chronic inflammation has been linked to cognitive decline and neurodegenerative diseases, and isoleucine's potential anti-inflammatory effects may contribute to its role in cognitive health. Recent research has highlighted the role of the gut microbiota in brain health and cognitive function. Isoleucine may influence the composition and function of the gut microbiota, potentially leading to beneficial effects on brain health. The gut-brain axis, a bidirectional communication system between the gut and the brain, is increasingly recognized as an important player in cognitive health, and isoleucine's potential to modulate the gut microbiota may contribute to its cognitive benefits. The blood-brain barrier (BBB) is a semipermeable membrane that separates the circulating blood from the brain and extracellular fluid in the central nervous system. It plays a crucial role in maintaining brain homeostasis and protecting the brain from harmful substances. Isoleucine may contribute to BBB integrity by promoting the expression of tight junction proteins, which are essential for maintaining the barrier function. Neurotrophic factors are proteins that support the growth, survival, and differentiation of neurons. Isoleucine may influence the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which is crucial for neuronal plasticity and cognitive function. Myelin is a fatty substance that surrounds nerve fibers, providing insulation and facilitating the rapid transmission of nerve impulses. Isoleucine may play a role in myelination processes, potentially contributing to improved neuronal communication and cognitive function. Stress can have detrimental effects on cognitive function, and isoleucine may play a role in modulating the stress response. Studies have shown that isoleucine can reduce stress hormone levels and improve stress resilience, potentially contributing to its cognitive benefits. Sleep is essential for cognitive function, and isoleucine may influence sleep quality and duration. Studies have shown that isoleucine can promote sleep and improve sleep architecture, potentially leading to enhanced cognitive performance. The observed correlation between isoleucine levels and MoCA-Ina scores, although not statistically significant in this study, suggests that isoleucine may have a unique role in cognitive health. This finding warrants further investigation to elucidate the specific mechanisms by which isoleucine may influence cognitive function and to explore its potential as a nutritional intervention target.[11-13]

This study's findings on the relationship between branched-chain amino acids (BCAAs) and cognitive function in elderly individuals present a complex picture, with some aspects aligning with existing literature and others diverging. This intricate pattern highlights the multifaceted nature of nutrient-brain interactions and the challenges in elucidating the precise role of BCAAs in cognitive health during aging. The current study's observation of no significant correlation between total BCAA levels and cognitive performance, as measured by the MoCA-Ina, is not entirely unexpected. Previous research on the BCAA-cognitive function relationship has yielded mixed results, with some studies reporting positive associations and others finding no significant links. Different studies have employed diverse methodologies, including cross-sectional, longitudinal, and interventional designs. Each design has its strengths and limitations, and the choice of design can influence the observed outcomes. Cross-sectional studies, like the present one, provide a snapshot of the relationship between variables at a specific point in time but cannot establish causality. Longitudinal studies, which follow participants over time, can better assess the causal direction of associations but are often more resource-intensive. Interventional studies, which involve manipulating BCAA intake, can provide stronger evidence for causality but may be limited by ethical considerations and feasibility. The characteristics of the study populations, such as age, gender, health status, and nutritional background, can significantly influence the outcomes of BCAA research. Studies conducted in different populations may yield varying results due to these inherent differences. For instance, studies focusing on individuals with specific health conditions, such as mild cognitive impairment or Alzheimer's disease, may observe different BCAA-cognitive function relationships compared to studies involving healthy older adults. Cognitive function is a multidimensional construct encompassing various domains, including memory, attention, executive function, and language. Different studies may focus on different cognitive domains or use different assessment tools, leading to variations in the observed relationships with BCAA levels. Some studies may find associations between BCAAs and specific cognitive domains, while others may not, depending on the chosen assessment methods. The methods used to assess dietary BCAA intake can also contribute to inconsistencies in the literature. Some studies may rely on self-reported dietary intake, which can be subject to recall bias and inaccuracies. Others may use more objective measures, such as blood or urine biomarkers, which may reflect recent dietary intake but not necessarily long-term dietary patterns. The analytical techniques used to measure BCAA levels in blood or other biological samples can also vary between studies. Different techniques may have different sensitivities and specificities, potentially leading to variations in the measured BCAA levels and influencing the observed associations with cognitive function. Individual genetic variations can influence BCAA metabolism and utilization, potentially contributing to the heterogeneity in BCAA-cognitive function relationships observed across studies. Some individuals may have genetic predispositions that make them more or less responsive to the effects of BCAAs on cognitive function. Lifestyle factors, such as physical activity levels, sleep quality, and stress levels, can also influence cognitive function and interact with the effects of BCAAs. Studies that do not adequately control for these lifestyle factors may observe inconsistent results. BCAAs do not function in isolation, and their effects on cognitive function may be influenced by interactions with other nutrients, such as other amino acids, vitamins, and minerals. Studies that do not consider these interactions may observe varying results depending on the overall nutritional context. Despite the inconsistencies in the literature, some aspects of the current study's findings align with previous research. The moderate positive correlation observed between isoleucine levels and MoCA-Ina scores, although not statistically significant, is supported by research highlighting the role of isoleucine in glucose metabolism, insulin sensitivity, neurotransmitter synthesis, mitochondrial function, anti-inflammatory effects, gut microbiota modulation, blood-brain barrier integrity, neurotrophic factor regulation, myelination, stress response modulation, and sleep regulation. Studies have shown that isoleucine can improve glucose uptake in skeletal muscle and enhance insulin signaling, potentially benefiting brain function by ensuring adequate energy supply and neuronal function. The brain is highly dependent on glucose as its primary energy source, and disruptions in glucose metabolism and insulin signaling have been implicated in cognitive decline. Isoleucine's ability to enhance glucose metabolism and insulin sensitivity may contribute to its potential cognitive benefits. In addition to its metabolic effects, isoleucine serves as a precursor for the synthesis of neurotransmitters, particularly glutamate and gamma-aminobutyric acid (GABA). Glutamate is the main excitatory neurotransmitter in the brain, involved in learning and memory formation, while GABA is the primary inhibitory neurotransmitter, contributing to the regulation of neuronal excitability. Maintaining a balance between these neurotransmitters is essential for optimal cognitive function. Isoleucine's role in neurotransmitter synthesis may further contribute to its potential cognitive benefits. Isoleucine has also been implicated in mitochondrial function, which is crucial for energy production in cells, including neurons. Studies have shown that isoleucine can increase mitochondrial biogenesis and improve mitochondrial efficiency, potentially leading to enhanced neuronal energy metabolism and cognitive function. Emerging evidence suggests that isoleucine may have anti-inflammatory properties, which could be beneficial for brain health. Chronic inflammation has been linked to cognitive decline and neurodegenerative diseases, and isoleucine's potential anti-inflammatory effects may contribute to its role in cognitive health. Recent research has highlighted the role of the gut microbiota in brain health and cognitive function. Isoleucine may influence the composition and function of the gut microbiota, potentially leading to beneficial effects on brain health. The gut-brain axis, a bidirectional communication system between the gut and the brain, is increasingly recognized as an important player in cognitive health, and isoleucine's potential to modulate the gut microbiota may contribute to its cognitive benefits. The blood-brain barrier (BBB) is a semipermeable membrane that separates the circulating blood from the brain and extracellular fluid in the central nervous system. It plays a crucial role in maintaining brain homeostasis and protecting the brain from harmful substances. Isoleucine may contribute to BBB integrity by promoting the expression of tight junction proteins, which are essential for maintaining the barrier function. Neurotrophic factors are proteins that support the growth, survival, and differentiation of neurons. Isoleucine may influence the expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which is crucial for neuronal plasticity and cognitive function. Myelin is a fatty substance that surrounds nerve fibers, providing insulation and facilitating the rapid transmission of nerve impulses. Isoleucine may play a role in myelination processes, potentially contributing to improved neuronal communication and cognitive function. Stress can have detrimental effects on cognitive function, and isoleucine may play a role in modulating the stress response. Studies have shown that isoleucine can reduce stress hormone levels and improve stress resilience, potentially contributing to its cognitive benefits. Sleep is essential for cognitive function, and isoleucine may influence sleep quality and duration. Studies have shown that isoleucine can promote sleep and improve sleep architecture, potentially leading to enhanced cognitive performance. The convergence of these findings suggests that isoleucine may have a unique and multifaceted role in cognitive health, warranting further investigation and consideration in nutritional strategies aimed at supporting cognitive function in aging populations. While some aspects of the current study align with existing literature, others diverge, highlighting the complexity and ongoing evolution of BCAA research. The lack of a significant correlation between total BCAA levels and cognitive performance in this study contrasts with some previous research that reported positive associations. This discrepancy may be attributed to differences in study populations, methodologies, and the specific cognitive domains assessed. It is crucial to acknowledge that the relationship between BCAAs and cognitive function is likely not a simple, linear one, and various factors can influence this relationship. The current study did not find significant correlations between leucine or valine levels and cognitive function. This contrasts with some studies that have reported positive associations between leucine intake and cognitive performance, particularly in the context of exercise or specific health conditions. However, other studies have also found no significant links between leucine or valine and cognitive function. The roles of leucine and valine in cognitive health require further investigation to clarify their specific contributions and potential interactions with other nutrients. Some studies have investigated the effects of BCAA supplementation on cognitive function, with mixed results. Some studies have reported cognitive benefits, while others have found no significant effects. The efficacy of BCAA supplementation may depend on various factors, such as the dosage, timing, and duration of supplementation, as well as the characteristics of the study population. BCAA catabolism, the breakdown of BCAAs, has been linked to cognitive decline in some studies. Elevated levels of BCAA catabolites, such as 3-hydroxyisobutyrate, have been associated with cognitive impairment and Alzheimer's disease. However, other studies have found no such association. The role of BCAA catabolism in cognitive health requires further investigation.[14-17]

The findings of this study, while preliminary, offer valuable insights that can inform the development of nutritional strategies aimed at supporting cognitive health in aging populations. While further research is needed to solidify these implications, the study provides a foundation for exploring the potential of dietary interventions to promote cognitive well-being in elderly individuals. The study's observation that a significant proportion of elderly participants exhibited cognitive impairment despite having BCAA levels within the normal range underscores the importance of considering overall protein intake in relation to cognitive health. While BCAAs play specific roles in brain function, they are just one component of the broader picture of protein nutrition. Protein provides the essential amino acids necessary for the synthesis of neurotransmitters, enzymes, and other proteins involved in various brain functions. Adequate protein intake is crucial for maintaining the structural and functional integrity of the brain, supporting neuronal communication, and promoting cognitive processes such as learning and memory. Aging is associated with changes in protein metabolism, including decreased protein synthesis and increased protein breakdown. These changes can contribute to a decline in muscle mass and strength, as well as impaired cognitive function. Ensuring adequate protein intake can help mitigate these age-related changes and support cognitive health. Current dietary recommendations suggest that older adults should consume at least 0.8 grams of protein per kilogram of body weight per day. However, some experts recommend higher protein intake for older adults, ranging from 1.0 to 1.2 grams per kilogram of body weight per day, to account for age-related changes in protein metabolism and to support muscle and cognitive health. A variety of protein-rich foods can contribute to meeting the recommended protein intake for older adults. These include lean meats, poultry, fish, eggs, dairy products, legumes, nuts, and seeds. A balanced dietary approach that incorporates a variety of protein sources can ensure adequate intake of all essential amino acids, including BCAAs. While the study did not find a significant correlation between total BCAA levels and cognitive function, it is important to acknowledge that BCAAs play specific roles in brain function and may contribute to cognitive health as part of a balanced dietary pattern. BCAAs, particularly leucine, isoleucine, and valine, serve as precursors for the synthesis of neurotransmitters, including glutamate, GABA, and dopamine. These neurotransmitters are involved in various cognitive processes, such as learning, memory, attention, and mood regulation. BCAAs can be utilized as an energy source by the brain, particularly during periods of glucose deprivation or increased energy demand. This metabolic flexibility may be beneficial for maintaining cognitive function under challenging conditions. BCAAs play a crucial role in muscle protein synthesis and maintenance, which is important for overall health and mobility in older adults. Maintaining muscle mass and strength can indirectly support cognitive health by promoting physical activity and reducing the risk of falls and injuries, which can impair cognitive function. BCAAs are found in a variety of protein-rich foods, including meat, poultry, fish, eggs, dairy products, legumes, nuts, and seeds. A balanced dietary approach that incorporates a variety of protein sources can ensure adequate intake of BCAAs. The study's observation of a moderate positive correlation between isoleucine levels and MoCA-Ina scores, although not statistically significant, suggests that isoleucine may have a unique role in cognitive health. This finding warrants further investigation and consideration in nutritional strategies aimed at supporting cognitive function in aging populations. Isoleucine has been implicated in various processes that are critical for brain health, including glucose metabolism, insulin sensitivity, neurotransmitter synthesis, mitochondrial function, anti-inflammatory effects, gut microbiota modulation, blood-brain barrier integrity, neurotrophic factor regulation, myelination, stress response modulation, and sleep regulation. Isoleucine's ability to enhance glucose metabolism and insulin sensitivity may indirectly benefit brain function by ensuring adequate energy supply and neuronal function. Its role in neurotransmitter synthesis may further contribute to its potential cognitive benefits. Additionally, isoleucine's potential anti-inflammatory effects, gut microbiota modulation, and other brain-related functions may also play a role in its cognitive effects. Isoleucine is found in a variety of protein-rich foods, including meat, poultry, fish, eggs, dairy products, legumes, nuts, and seeds. A balanced dietary approach that incorporates a variety of protein sources can ensure adequate intake of isoleucine. While specific nutrients, such as BCAAs and isoleucine, may have potential benefits for cognitive health, it is crucial to emphasize the importance of a balanced dietary approach that provides all essential nutrients in adequate amounts. The brain relies on a complex interplay of nutrients for optimal function, and focusing on isolated nutrients may not yield the desired cognitive benefits. A diverse dietary pattern that includes a variety of fruits, vegetables, whole grains, lean protein sources, and healthy fats can provide the brain with the necessary nutrients for optimal function. This approach can also ensure adequate intake of vitamins, minerals, and other bioactive compounds that may contribute to cognitive health. Micronutrients, such as vitamins B6, B12, and folate, as well as minerals like iron and zinc, are essential for various brain functions, including neurotransmitter synthesis, energy metabolism, and antioxidant defense. Ensuring adequate intake of these micronutrients is crucial for maintaining cognitive health. The Mediterranean diet, characterized by high intake of fruits, vegetables, whole grains, legumes, nuts, and olive oil, and moderate intake of fish and poultry, has been associated with better cognitive function and a reduced risk of cognitive decline. This dietary pattern provides a balanced intake of various nutrients that may contribute to brain health. The field of personalized nutrition is rapidly evolving, and future research may enable the development of tailored nutritional interventions based on individual needs and genetic predispositions. This approach may involve assessing individual BCAA levels, metabolic profiles, and genetic variations to determine the optimal dietary intake of BCAAs and other nutrients for cognitive health.[18-20]

5. Conclusion

This study investigated the relationship between serum branched-chain amino acid (BCAA) levels and cognitive function in elderly individuals. The findings revealed no significant correlation between total BCAA levels and cognitive function. However, a moderate positive correlation was observed between isoleucine levels and cognitive function, although not statistically significant. These findings suggest that isoleucine may have a unique role in cognitive health. The study had some limitations, including the small sample size and cross-sectional design. Future research with a larger sample size and longitudinal design is warranted to further investigate the complex relationship between dietary BCAAs, serum BCAA levels, and cognitive health in aging individuals. Despite these limitations, the study provides valuable insights into the relationship between BCAAs and cognitive function in elderly individuals. The findings suggest that isoleucine may have a unique role in cognitive health and warrant further investigation. The study also highlights the importance of considering overall protein intake in relation to cognitive health. In conclusion, this study suggests that serum BCAA levels, particularly isoleucine, may have implications for cognitive function in elderly populations. Further research is needed to confirm these findings and to explore the potential of dietary interventions to promote cognitive well-being in aging individuals.

6. References

1. Lou Y, Jiang Q, Huang S, Xie Y, Wang H, Wang L, et al. Association of dietary diversity and weight change with cognitive impairment among Chinese elderly: a prospective national cohort study. J Affect Disord. 2025; 368: 789–97.
2. Ramirez S, Haubrick K. Dietary habits and the risk of cognitive decline in the elderly. J Acad Nutr Diet. 2021; 121(10): A124.

3. Ju E-Y, Kim CY, Choi B-Y, Ryoo S-W, Min J-Y, Min K-B. Deficits of facial emotion recognition in elderly individuals with mild cognitive impairment. Dement Geriatr Cogn Disord. 2024; 53(6): 321–8.
4. Chen W, Siew-Pin JL, Wu Y, Huang N, Teo W-P. Identifying exercise and cognitive intervention parameters to optimize executive function in older adults with mild cognitive impairment and dementia: a systematic review and meta-analyses of randomized controlled trials. Eur Rev Aging Phys Act. 2024; 21(1):22.
5. Kaiser E, Schoenknecht P, Kassner S, Hildebrandt W, Kinscherf R, Schroeder J. Cerebrospinal fluid concentrations of functionally important amino acids and metabolic compounds in patients with mild cognitive impairment and Alzheimer's disease. Neurodegener Dis. 2010; 7(4): 251–9.
6. Suzuki H, Yamashiro D, Ogawa S, Kobayashi M, Cho D, Iizuka A, et al. Intake of seven essential amino acids improves cognitive function and psychological and social function in middle-aged and older adults: a double-blind, randomized, placebo-controlled trial. Front Nutr. 2020; 7: 586166.
7. Hooshmand B, Refsum H, Smith AD, Grande G, Marseglia A, Laukka EJ, et al. Methylation status and sulfur amino acids as risk factors for cognitive decline over 15 years: a longitudinal, population-based study. Alzheimers Dement. 2020; 16(S10).
8. Weits JJ, Cruthirds CL, Cavka L, Mizubuti Y, Deutz NE, Engelen MP. Mild cognitive impairment in chronic obstructive pulmonary disease is associated with an imbalance of specific non-essential amino acids. Clin Nutr ESPEN. 2020; 40: 429.
9. Russin KJ, Nair KS, Montine TJ, Baker LD, Craft S. Diet effects on cerebrospinal fluid amino acids levels in adults with normal cognition and mild cognitive impairment. J Alzheimers Dis. 2021; 84(2): 843–53.
10. Yang K-C, Chen Y-Y, Liu M-N, Yang B-H, Chou Y-H. Interactions between dopamine transporter and N-methyl-d-aspartate receptor-related amino acids on cognitive impairments in schizophrenia. Schizophr Res. 2022; 248: 263–70.
11. Aquilani R, Cotta Ramusino M, Maestri R, Iadarola P, Boselli M, Perini G, et al. Several dementia subtypes and mild cognitive impairment share brain reduction of neurotransmitter precursor amino acids, impaired energy metabolism, and lipid hyperoxidation. Front Aging Neurosci. 2023; 15: 1237469.
12. Rodziewicz-Flis E, Juhas U, Kortas JA, Jaworska J, Bidzan-Bluma I, Babińska A, et al. Nordic Walking training in BungyPump form improves cognitive functions and physical performance and induces changes in amino acids and kynurenine profiles in older adults. Front Endocrinol (Lausanne). 2023; 14: 1151184.
13. Cole JT, Mitala CM, Kundu S, Verma A, Elkind JA, Nissim I, et al. Dietary branched chain amino acids ameliorate injury-induced cognitive impairment. Proc Natl Acad Sci U S A. 2010; 107(1): 366–71.
14. Avery CL, Howard AG, Lee HH, Lee MP, Ballou AF, Raffield LM, et al. Abstract MP17: Multivariable Mendelian randomization identifies heterogeneity in the effects of individual branched chain amino acids across metabolic, cardiovascular, and cognitive phenotypes. Circulation. 2022; 145(Suppl_1).
15. Aquilani R, Iadarola P, Contardi A, Boselli M, Verri M, Pastoris O, et al. Branched-chain amino acids enhance the cognitive recovery of patients with severe traumatic brain injury. Arch Phys Med Rehabil. 2005; 86(9): 1729–35.
16. Fretwell LK, McCune S, Fone JV, Yates DJ. The effect of supplementation with branched-

chain amino acids on cognitive function in active dogs. J Nutr. 2006; 136(Suppl_7): 2069S-2071S.
17. Lieben CK, Deutz NE, Jonkers R, Veley E, Harrykissoon R, Zachria A, et al. SUN-P123: Deficits in cognitive flexibility in COPD are linked to changes in metabolism of branched-chain amino acids. Clin Nutr. 2017; 36: S99–100.
18. Siddik MAB, Mullins CA, Kramer A, Shah H, Gannaban RB, Zabet-Moghaddam M, et al. Branched-chain amino acids are linked with Alzheimer's disease-related pathology and cognitive deficits. Cells. 2022; 11(21): 3523.
19. Ikeuchi T, Kanda M, Kitamura H, Morikawa F, Toru S, Nishimura C, et al. Decreased circulating branched-chain amino acids are associated with development of Alzheimer's disease in elderly individuals with mild cognitive impairment. Front Nutr. 2022; 9: 1040476.
20. Yang Z, Wang J, Chen J, Luo M, Xie Q, Rong Y, et al. High-resolution NMR metabolomics of patients with subjective cognitive decline plus: Perturbations in the metabolism of glucose and branched-chain amino acids. Neurobiol Dis. 2022; 171(105782): 105782.