Food & Function

PAPER

View Article Online
View Journal | View Issue

Cite this: *Food Funct.*, 2024, **15**, 3744

Dietary serine intake is associated with cognitive function among US adults

Jingyi Chen,†[a,d] Shuhua Fang,†[b] Zeman Cai,[c] Qing Zhao[a] and Nian Yang *[a,d]

Aims: Diet can modify the risk of cognitive decline. However, research on the relationship between dietary intake of serine and cognitive decline remains limited and this study aims to reveal the relationship between them. *Methods*: Data from the National Health and Nutrition Examination Survey (NHANES) 1988–1994 (n = 1837) were used to explore the relationship between dietary intakes of serine and cognitive function through quantile multiple linear analysis and restricted cubic splines (RCS) regression. We also investigated 9 food groups for serine intake according to the USDA food code to determine which food sources of serine are beneficial for cognitive function. *Results*: The top three serine intakes were attributed to meat/poultry/fish, grain products, and milk or milk products. Multivariable linear regression analysis showed that a significant negative linear trend was observed between serine intake and SDLT. RCS results showed a non-linear relationship between serine intake and SDLT or SDST. Among the 9 food group intakes, milk or milk products sourced serine intake was good for memory ability. *Conclusion*: serine, particularly serine from milk or milk products, has a beneficial impact on memory ability in adults.

Received 12th November 2023,
Accepted 4th March 2024

DOI: 10.1039/d3fo04972h

rsc.li/food-function

Introduction

Cognitive health has become an important public health issue. The incidence of cognitive decline is associated with education, socioeconomic status, gender, and/or genetics. Investigation into several modifiable factors, including diet and nutrition, offers valuable insights and recommendations for preserving and enhancing cognitive abilities.[1] Dietary patterns rely on proteins and essential amino acids they contain, playing a vital role in preserving the function and structure of cells, including those in the brain. Many studies indicate that dietary amino acids can enhance cognitive function and may have a substantial impact on cognitive health.[2–4]

Serine is a nutritionally non-essential necessity for humans and animals. It plays a crucial role in cell proliferation, brain development, neuronal connections, synaptic plasticity, and regulation of learning and memory.[5,6] Decreased levels of serine may lead to cognitive decline.[7] Serine is an essential neurotrophic factor and serves as a precursor to neurotransmitters. L-Serine plays a vital role in modulating the release of various brain cytokines, which, in turn, facilitates the restoration of cognitive function, enhances cerebral blood circulation, suppresses inflammation, and supports the regeneration of myelin. These combined effects demonstrate its neuroprotective potential against neural damage.[8] Serine racemase, with the assistance of pyridoxal-5-phosphate as a coenzyme, catalyzes the conversion of a minor portion of serine in the human body into D-serine. During the normal aging process, the expression of serine racemase decreases, leading to a decline in D-serine levels, which may impair synaptic plasticity and diminish learning and memory abilities.[9] Based on a recent clinical study, serum D-serine levels increase during cognitive enhancement therapy for schizophrenia.[10] Handzlik *et al.* discovered that dietary supplementation of serine effectively alleviated neuropathies in diabetic mice.[11]

This study is the first attempt to evaluate the relationship between dietary serine intake and cognitive function through a large cross-sectional analysis. The primary objective of this study is to identify dietary sources of serine, with particular attention to the ranking of food categories and their contributions to serine content. This information will be highly valuable for diet and health experts in assessing dietary quality and meeting nutritional recommendations, enabling the improvement of strategies for the prevention and better management of cognitive decline.

[a]*Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China. E-mail: 20nyang@stu.edu.cn*
[b]*Department of Pharmacy, Nanjing Lishui People's Hospital, Zhongda Hospital Lishui Branch Southeast University, Nanjing 211200, China*
[c]*Department of Radiation Oncology, Cancer Hospital of Shantou University Medical College, Shantou 515000, Guangdong, China*
[d]*Institute of Precision Medicine, The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong 515041, China*
† These authors contributed equally to this work.

Methods

Population under investigation

The National Institute of Health in the United States conducts the NHANES III, a survey that uses a multistage sample to evaluate the health status and lifestyle changes of Americans. Our study utilized data from 12 061 people aged 20–59 years old surveyed between 1988 and 1994. Then, we excluded interviewees who did not provide information for age, gender, ethnicity, educational level, ratio of family income to poverty (PIR), BMI, smoking, drinking, physical activity, and disease history (hypertension, diabetes mellitus (DM), stroke and Alzheimer's Disease (AD)) from our analysis, which led to the exclusion of 4664 individuals (n = 7397). Additionally, we excluded participants who either did not undergo cognitive function tests or did not successfully complete three cognitive tests (n = 4081); those who lacked amino acid information were also excluded (n = 1479). Finally, our analysis included only 1837 participants.

Cognitive function testing

In the NHANES III, the assessment of cognitive function consisted of three computerized tests—simple reaction time test (SRTT), symbol-digit substitution test (SDST) and serial digit learning test (SDLT).

SRTT provides a valuable measure of motor response speed and basic cognitive processing abilities. The SRTT summary mean reaction time scores observed varied from 154 to 660 ms, and a higher score signified a slower visuomotor speed.

SDST involves matching symbols with their corresponding numbers under a time limit. This test measures cognitive abilities such as attention, psychomotor speed, and executive function. Participants were required to match nine symbols to their corresponding digits quickly and accurately. Time to complete the task was recorded in seconds, and the number of correct responses was counted. SDST mean scores observed varied from 1.38 to 22.2 seconds, and a higher score signified a poorer processing speed or concentration.

The SDLT evaluates short-term memory by asking participants to recall a series of digits immediately after hearing them. This test measures the ability of the individual to remember and reproduce the sequence of digits accurately, providing insights into their short-term memory ability. SDLT summary total score observed varied from 0 to 16, and a higher score signified a poor short-term memory.

Covariates

The NHANES III is a national survey that encompasses demographic information, dietary data, laboratory tests, physical examinations and health history to assess the health and nutrition status of the U.S. population. We incorporated some of them into our analysis as covariates, such as age (20–59 years), gender (male and female), ethnicity (Mexican-American, non-Hispanic white, non-Hispanic black and others), educational level (less than high school, high school and college or higher), ratio of family income to poverty (PIR) (<1.3 and ≥1.3–3.5 and >3.5), body mass index (BMI) (normal: <25 kg m^{-2}, overweight: 25 to <30 kg m^{-2}, obesity: ≥30 kg m^{-2}), drinking, smoking status and physical activity. Drinking status was categorized as: non-drinker, low-to-moderate drinker (<2 drinks per day for men, <1 drink per day for women) and heavy drinker (≥2 drinks per day for men, ≥1 drink per day for women).[12] Individuals who reported smoking less than 100 cigarettes during their lifetime were categorized as never smokers. Current smokers were defined as those who had smoked more than 100 cigarettes in their lifetime and were still smoking at the time of the study. Former smokers were classified as individuals who had smoked more than 100 cigarettes in their lifetime but had since quit smoking.[13,14] Individuals who had no leisure-time physical activity were characterized as the inactive group; those who engaged in leisure-time moderate activity 1–5 times per week for a MET 3–6 or leisure-time vigorous activity 1–3 times per week for MET6 or higher were characterized as the insufficiently active group; and those who had a higher level of leisure-time for the corresponding activity were characterized as the active group.[12,15] Additionally, disease history (hypertension, DM, AD and stroke) was included in covariates. Other amino acids that NHANES III have provided (tryptophan, threonine, isoleucine, leucine, lysine, methionine, cysteine, phenylalanine, tyrosine, valine, arginine, histidine, alanine, aspartic acid, glutamic acid, glycine, and proline) and energy intake were considered as covariables.

Dietary intake of serine

Dietary intake data for serine in the NHANES III study were collected from the total nutrient intake document and individual foods detail document. The first digit of the USDA food code categorizes dietary intake information into nine major food groups: milk/milk products, meat/poultry/fish, eggs, legumes/nuts/seeds, grain products, fruits, vegetables, fats/oils, and sugars/sweets/beverages. Thus, the serine intake derived from each of the nine food groups was calculated.

Statistical analysis

Participants were divided into quartiles according to their dietary serine intake. The basic characteristics of all the participants in each quartile of serine intake were presented as number and percentage for categorical variables, and as the mean ± standard deviation (SD) for continuous variables. We conducted linear regression analysis to investigate the relationship between cognitive function and serine intake quartiles. Model 1 did not make any adjustments. Model 2 adjusted for age, gender, ethnicity, educational level, PIR, BMI, drinking, smoking status, physical activity and disease history. Model 3 for associations between the three cognitive scores and total serine intake further adjusted for energy intake, other amino acids. Notably, Model 3 for the associations between three cognitive scores and serine intake derived from top three groups, further adjusted for energy intake, other amino acids and serine derived from other eight foods. To explore dose–

Table 1 Characteristics of the participants grouped by serine intake levels

Variable	Q1	Q2	Q3	Q4	*P*
Age	37.46(0.54)	37.38(0.79)	36.95(0.60)	35.07(0.68)	0.13
BMI (kg m^{-2})	25.89(0.34)	26.49(0.40)	26.17(0.26)	26.44(0.46)	0.61
Food energy (kcal)	1411.31(35.77)	1988.76(44.10)	2528.68(46.24)	3467.50(83.20)	<0.0001
Serine (g per d)	1.76(0.04)	2.94(0.02)	4.05(0.03)	6.44(0.12)	<0.0001
Tryptophan (g d^{-1})	0.46(0.01)	0.77(0.01)	1.05(0.01)	1.69(0.03)	<0.0001
Threonine (g d^{-1})	1.48(0.03)	2.51(0.02)	3.46(0.03)	5.64(0.10)	<0.0001
Isoleucine (g d^{-1})	1.76(0.04)	2.96(0.02)	4.07(0.04)	6.59(0.12)	<0.0001
Leucine (g d^{-1})	3.03(0.06)	5.10(0.04)	7.01(0.07)	11.30(0.21)	<0.0001
Lysine (g d^{-1})	2.54(0.06)	4.34(0.05)	6.08(0.07)	10.13(0.19)	<0.0001
Methionine (g d^{-1})	0.87(0.02)	1.46(0.02)	2.04(0.02)	3.34(0.06)	<0.0001
Cysteine (g d^{-1})	0.53(0.01)	0.86(0.01)	1.17(0.01)	1.82(0.03)	<0.0001
Phenylalanine (g d^{-1})	1.73(0.03)	2.86(0.02)	3.93(0.03)	6.26(0.10)	<0.0001
Tyrosine (g d^{-1})	1.41(0.03)	2.33(0.02)	3.21(0.03)	5.19(0.10)	<0.0001
Valine (g d^{-1})	1.99(0.04)	3.33(0.03)	4.57(0.04)	7.37(0.13)	<0.0001
Arginine (g d^{-1})	2.11(0.05)	3.48(0.04)	4.85(0.04)	7.90(0.15)	<0.0001
Histidine (g d^{-1})	1.08(0.02)	1.82(0.02)	2.52(0.04)	4.12(0.08)	<0.0001
Alanine (g d^{-1})	1.82(0.04)	3.07(0.04)	4.20(0.05)	6.89(0.13)	<0.0001
Aspartic Acid (g d^{-1})	72.50(9.59)	76.43(14.38)	72.73(9.23)	59.23(14.41)	0.83
Glutamic Acid (g d^{-1})	8.11(0.17)	13.09(0.14)	17.61(0.24)	27.36(0.52)	<0.0001
Glycine (g d^{-1})	1.65(0.04)	2.75(0.05)	3.74(0.05)	6.16(0.12)	<0.0001
Proline (g d^{-1})	2.73(0.06)	4.48(0.06)	5.98(0.10)	9.35(0.21)	<0.0001
SRTT	235.89(2.79)	228.79(3.61)	229.45(3.11)	222.97(1.90)	0.04
SDST	2.73(0.06)	2.70(0.05)	2.63(0.04)	2.61(0.04)	0.15
SDLT	5.11(0.33)	4.55(0.29)	4.11(0.36)	3.71(0.21)	0.01
Gender					<0.0001
Male	133(23.11)	184(43.04)	266(54.74)	345(76.33)	
Female	343(76.89)	263(56.96)	196(45.26)	107(23.67)	
Ethnicity					0.20
White	199(80.86)	199(80.66)	194(80.59)	182(78.58)	
Black	155(12.68)	110(8.75)	104(8.28)	124(10.21)	
Mexican	115(4.13)	125(4.47)	146(5.14)	131(5.50)	
Other	7(2.32)	13(6.12)	18(5.99)	15(5.71)	
Smoking status					0.28
Never smoker	243(46.73)	202(36.52)	207(40.85)	204(43.92)	
Former smoker	79(17.76)	95(25.69)	106(23.37)	100(24.12)	
Current smoker	154(35.51)	150(37.78)	149(35.78)	148(31.96)	
Drinking status					0.14
Nondrinker	361(75.17)	345(73.35)	342(70.92)	318(63.83)	
Moderate drinker	45(5.98)	38(11.03)	44(9.78)	52(12.02)	
Heavy drinker	70(18.85)	64(15.62)	76(19.30)	82(24.15)	
Education					0.25
Less than high school	63(7.83)	51(4.39)	57(5.35)	55(5.25)	
High school	261(54.39)	235(48.89)	244(50.33)	229(45.67)	
College or higher	152(37.79)	161(46.72)	161(44.32)	168(49.09)	
PIR					0.11
<1.5	166(23.98)	131(16.27)	137(15.58)	142(18.96)	
1.5–3.5	193(44.21)	185(42.69)	201(41.55)	199(41.56)	
>3.5	117(31.81)	131(41.03)	124(42.86)	111(39.48)	
Leisure time physical activity				0.86	
Active	207(48.67)	188(50.81)	214(53.84)	230(51.60)	
Insufficiently activity	193(40.35)	183(38.60)	175(36.57)	157(39.62)	
Inactive	76(10.98)	76(10.59)	73(9.59)	65(8.77)	
Hypertension					0.50
No	445(94.59)	409(92.53)	438(95.38)	425(93.17)	
Yes	31(5.41)	38(7.47)	24(4.62)	27(6.83)	
DM					0.19
No	349(82.02)	350(85.06)	345(78.59)	331(76.89)	
Pre_DM	112(16.72)	80(12.36)	103(18.87)	103(18.50)	
DM	15(1.26)	17(2.58)	14(2.53)	18(4.60)	
Stroke					0.51
No	474(99.38)	444(99.45)	461(99.23)	450(99.96)	
Yes	2(0.62)	3(0.55)	1(0.77)	2(0.04)	

SRTT: simple reaction time test; SDST: symbol-digit substitution test; SDLT: serial digit learning test; PIR: ratio of family income to poverty; DM: diabetes mellitus; and Pre_DM: pre_diabetes mellitus. Continuous variables are represented by the mean ± standard deviation (SD), whereas categorical variables are represented by sample size and percentage (%).

response relationships between serine intake and the three cognitive function scores, restricted cubic spline (RCS) models were applied. RCS plots were adjusted for all covariates. When adopting RCS for non-linear analysis, it is common to set a reference value as a baseline to compare changes in other values relative to this baseline. Serine is a non-essential amino acid and some of the participants did not intake serine from food, thus we set the reference parameter as 0 for RCS analysis. P < 0.05 indicated statistical significance. Statistical analyses were conducted using R (4.2.2).

Results

Baseline characteristics

The characteristics of the individuals, categorized by their serine intake levels, are displayed in Table 1. For quartiles 1 to 4, the mean serine intake levels were 1.76 g d^{-1}, 2.94 g d^{-1}, 4.05 g d^{-1}, and 6.44 g d^{-1}, respectively. Higher levels of serine were associated with male (P < 0.0001), higher food energy intake (P < 0.0001), lower SRTT (P = 0.04) and lower SDLT (P = 0.04). Additionally, high serine intake is accompanied by a high intake of other amino acids.

Food sources of serine

To identify the food groups that play a significant role in total serine intake, we calculated the serine content from nine food groups (Table 2). The top three food groups were meat/poultry/fish, grain products and milk/milk products. Meat accounted for the highest contribution, at 38.65%, followed by grain at 27.77% and milk at 17.22%.

Table 2 A list of food groups that contributed to the intake of total serine

Food Groups	Intake (g d^{-1})	Contribution (%)
Meat/poultry/fish	1.46 ± 0.05	38.65
Grain products	1.05 ± 0.03	27.77
Milk/milk products	0.65 ± 0.03	17.22
Eggs	0.18 ± 0.02	4.87
Vegetables	0.18 ± 0.01	4.72
Legumes/nuts/seeds	0.15 ± 0.01	3.86
Sugars/sweets/beverages	0.03 ± 0.00	0.74
Fruits	0.02 ± 0.00	0.40
Fats/oils	0.01 ± 0.00	0.21

The individuals were divided into quartiles according to their total intake of serine. Subsequently, we conducted a comparison of the intake of serine sourced from the nine food groups among the four quartile groups (Table 3). The top three serine intakes were from meat/poultry/fish, grain products, and milk/milk products.

Association between serine and cognitive function

In Table 4, the association between serine intake and three cognitive scores was presented. After adjusting for age, gender, ethnicity, education, smoking status, drinking status, leisure time physical activity and disease history (Model 2), there was a significant negative linear trend between serine intake and SDLT (P = 0.003). Furthermore, after adjusting for all covariates (Model 3), the associations remained significant (P = 0.01). We also explored the associations between the three cognitive scores and serine intake derived from the top three groups. We also found that serine derived from milk/milk products presented a significantly negative linear trend with SDLT in unadjusted and adjusted models (Table 5).

Dose–response relationship between serine and cognitive function

To evaluate the non-linear relationships between the three cognitive scores and serine intake, restricted cubic splines (RCS) regression was conducted with all covariates adjusted for. However, there was no non-linear association between SRTT and serine intake. In SDLT (Fig. 1A) and SDST (Fig. 1B), we detected a downhill shaped non-linear relationship between serine intake and SDST (P = 0.014), but there was a wave-shaped non-linear relationship between serine intake and SDLT (P = 0.0076), indicating that higher serine intake does not always result in better SDLT.

Furthermore, we conducted restricted cubic splines (RCS) regression between serine derived from the top three food groups and cognitive function. We still found a wave-shaped non-linear relationship between milk-sourced serine intake and SDLT (P = 0.0014) and serine intake less than 2.63 g from milk was good for SDLT (Fig. 2A). Serine derived from the top three food groups did not exhibit a non-linear relationship with SDST. Although there is no non-linear relationship between total serine intake and SRTT, serine intake from grain products or meat/poultry/fish sources exhibits a non-linear

Table 3 Serine intake (g d^{-1}) from different food groups according to the quartiles of serine intake

Food Group	Q1	Q2	Q3	Q4	P for trend
Meat/poultry/fish	0.588 ± 0.028	1.070 ± 0.037	1.429 ± 0.065	2.702 ± 0.112	<0.0001
Grain products	0.515 ± 0.029	0.842 ± 0.045	1.188 ± 0.060	1.520 ± 0.089	<0.0001
Milk/milk products	0.259 ± 0.021	0.485 ± 0.030	0.637 ± 0.045	1.020 ± 0.073	<0.0001
Eggs	0.079 ± 0.016	0.109 ± 0.013	0.233 ± 0.037	0.308 ± 0.031	0.003
Legumes/nuts/seeds	0.059 ± 0.008	0.102 ± 0.017	0.141 ± 0.019	0.269 ± 0.038	0.002
Vegetables	0.125 ± 0.010	0.145 ± 0.011	0.187 ± 0.015	0.246 ± 0.026	0.011
Sugars/sweets/beverages	0.024 ± 0.004	0.023 ± 0.004	0.028 ± 0.006	0.032 ± 0.006	0.631
Fruits	0.009 ± 0.002	0.014 ± 0.003	0.013 ± 0.002	0.023 ± 0.004	0.043
Fats/oils	0.003 ± 0.001	0.010 ± 0.002	0.010 ± 0.003	0.010 ± 0.004	0.032

Table 4 Association between serine intake and the three cognitive scores

	Serine Intake				
	Q1	Q2 β-Coefficient ± SE	Q3 β-Coefficient ± SE	Q4 β-Coefficient ± SE	*P* for trend
SRTT					
Model 1	Ref	−7.11(−17.74, 3.53)	−6.44(−13.91, 1.03)	−12.92(−21.49, −4.35)	0.01
Model 2	Ref	−1.64(−11.16, 7.88)	0.94(−5.93, 7.81)	−0.67(−8.87, 7.52)	0.94
Model 3	Ref	−2.74(−12.25, 6.77)	−0.47(−7.58, 6.64)	−3.59(−17.07, 9.88)	0.76
SDST					
Model 1	Ref	−0.03(−0.18,0.12)	−0.11(−0.22,0.01)	−0.12(−0.26,0.02)	0.04
Model 2	Ref	0.01(−0.11, 0.13)	−0.08(−0.19, 0.02)	−0.06(−0.16, 0.04)	0.07
Model 3	Ref	0.01(−0.12, 0.13)	−0.08(−0.19, 0.03)	−0.08(−0.27, 0.10)	0.13
SDLT					
Model 1	Ref	−0.56(−1.33, 0.21)	−1(−1.88, −0.12)*	−1.4(−2.08, −0.72)*	<0.001
Model 2	Ref	−0.24(−0.88, 0.40)	−0.82(−1.58, −0.06)*	−1(−1.65, −0.35)*	0.003
Model 3	Ref	−0.23(−0.90, 0.44)	−0.89(−1.67, −0.10)*	−1.36(−2.39, −0.33)*	0.01

Model 1 did not make any adjustments. Model 2 adjusted for age, gender, ethnicity, educational level, PIR, BMI, drinking, smoking status, physical activity and disease history. Model 3 further adjusted for energy intake and other amino acids in addition to factors from Model 2. *P < 0.05.

Table 5 Associations between the three cognitive scores and serine intake derived from the top three groups

	Q1	Q2 β-Coefficient ± SE	Q3 β-Coefficient ± SE	Q4 β-Coefficient ± SE	*P* for Trend
SRTT					
Meat/poultry/fish					
Model 1	Ref	3.06(−6.13,12.24)	−3.53(−11.51, 4.45)	−7.66(−14.72, −0.59)*	0.02
Model 2	Ref	4.47(−3.86,12.80)	−2.55(−9.73, 4.63)	−1.3(−7.85, 5.24)	0.34
Model 3	Ref	2.39(−5.52, 10.30)	−7(−16.59, 2.58)	−9.5(−22.81, 3.81)	0.10
Grain products					
Model 1	Ref	−8.5(−17.05, 0.05)*	−10.02(−18.82, −1.23)*	−11.25(−20.22, −2.28)*	0.02
Model 2	Ref	−6.4(−13.71, 0.91)	−5.02(−12.81, 2.77)	−3.94(−12.92, 5.05)	0.40
Model 3	Ref	−7.56(−15.09, −0.04)*	−5.82(−14.42, 2.79)	−6.93(−20.36, 6.50)	0.21
Milk/milk products					
Model 1	Ref	−1(−9.89, 7.89)	1.64(−5.33, 8.61)	2.04(−6.75,10.83)	0.45
Model 2	Ref	−2.35(−9.92, 5.23)	3.19(−3.29, 9.68)	6.69(−0.52,13.91)	0.02
Model 3	Ref	−2.83(−11.17, 5.51)	1.88(−4.47, 8.23)	4.99(−5.20, 15.18)	0.24
SDST					
Meat/poultry/fish					
Model 1	Ref	0(−0.14,0.13)	0.15(0.03,0.26)*	0.05(−0.09,0.18)	0.12
Model 2	Ref	−0.03(−0.12, 0.06)	0.02(−0.07, 0.12)	−0.04(−0.13, 0.04)	0.53
Model 3	Ref	−0.07(−0.18, 0.04)	−0.02(−0.16, 0.11)	−0.12(−0.29, 0.05)	0.35
Grain products					
Model 1	Ref	−0.16(−0.33, 0.00)	−0.14(−0.30, 0.01)	−0.29(−0.43, −0.16)*	0.002
Model 2	Ref	−0.12(−0.24, 0.00)	−0.1(−0.20, 0.00)	−0.14(−0.24, −0.04)*	0.01
Model 3	Ref	−0.12(−0.23, −0.01)*	−0.1(−0.20, 0.00)	−0.12(−0.27, 0.03)	0.07
Milk/milk products					
Model 1	Ref	−0.03(−0.17, 0.11)	−0.06(−0.19, 0.06)	−0.17(−0.29, −0.05)*	0.01
Model 2	Ref	−0.02(−0.12, 0.09)	0.01(−0.11, 0.13)	−0.03(−0.12, 0.06)	0.67
Model 3	Ref	−0.02(−0.13, 0.08)	−0.02(−0.16, 0.11)	−0.08(−0.21, 0.04)	0.40
SDLT					
Meat/poultry/fish					
Model 1	Ref	0.34(−0.44, 1.11)	0.22(−0.78, 1.22)	0.03(−0.82, 0.87)	0.98
Model 2	Ref	0.34(−0.31, 0.98)	−0.12(−1.00, 0.77)	−0.1(−0.91, 0.71)	0.60
Model 3	Ref	0.28(−0.39, 0.95)	−0.09(−1.05, 0.87)	−0.1(−1.35, 1.15)	0.78
Grain products					
Model 1	Ref	−0.47(−1.76, 0.82)	−1.08(−1.89, −0.26)*	−1.46(−2.12, −0.80)*	<0.001
Model 2	Ref	−0.3(−1.33, 0.73)	−0.78(−1.44, −0.13)*	−0.87(−1.47, −0.27)*	0.005
Model 3	Ref	−0.15(−1.16, 0.87)	−0.53(−1.34, 0.27)	−0.31(−1.20, 0.58)	0.24
Milk/milk products					
Model 1	Ref	−0.81(−1.66, 0.04)	−1.02(−1.71, −0.32)*	−1.86(−2.50, −1.23)*	<0.001
Model 2	Ref	−0.75(−1.53, 0.03)	−0.67(−1.31, −0.04)*	−1.23(−1.81, −0.66)*	0.002
Model 3	Ref	−0.72(−1.44, 0.00)*	−0.67(−1.23, −0.11)*	−1.27(−1.98, −0.57)*	0.001

Model 1 did not make any adjustments. Model 2 adjusted for age, gender, ethnicity, educational level, PIR, BMI, drinking, smoking status, physical activity and disease history. Model 3 further adjusted for energy intake and other amino acids and serine derived from other eight foods in addition to factors from Model 2. *P < 0.05.

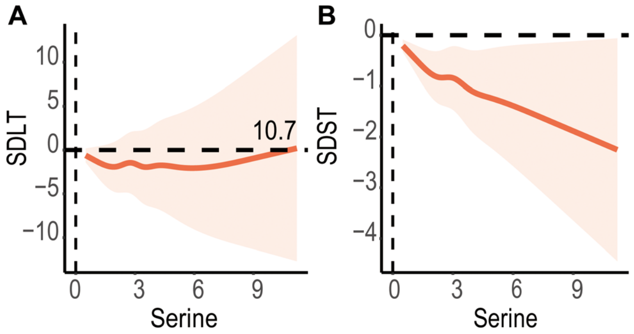

Fig. 1 Dose–response relationship between total serine intake and cognitive function. Covariates included age, gender, ethnicity, educational level, PIR, BMI, drinking, smoking status, physical activity, disease history, energy intake and other amino acids.

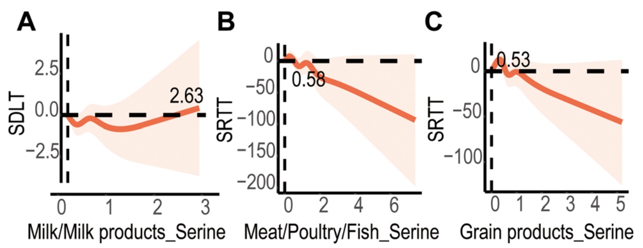

Fig. 2 Dose–response relationship between serine sourced from the top three food groups and cognitive function. Covariates included age, gender, ethnicity, educational level, PIR, BMI, drinking, smoking status, physical activity, disease history energy intake, other amino acids and serine derived from other eight foods.

relationship with SRTT. Serine intake exceeding 0.53 g from meat/poultry/fish (Fig. 2B) or exceeding 0.58 g from grain products (Fig. 2C) has a beneficial effect on visuomotor speed (SRTT).

Discussion

In this large cross-sectional study that included American adults, we observed an association between serine intake and cognitive function. The higher the intake of serine amino acid in the diet, the better the cognitive abilities observed in American adults.

Previous research has primarily focused on dietary protein or essential amino acids.[16–21] Due to its crucial role in metabolism and neural development, serine is considered a conditionally essential amino acid.[22] Individuals with low serine intake had significantly higher odds ratio (OR) of cognitive impairment compared to those with moderate or high intake,[23] which is consistent with our results.

Multivariable linear regression analysis after adjusting for all covariates showed a significant negative linear trend between serine intake quartiles and memory ability (SDLT), suggesting a beneficial impact of serine on memory function. Additionally, we investigated the main contributor food groups for serine intake among American adults according to the USDA food code. Our findings revealed that the primary sources of serine in the diet were meat/poultry/fish, grain products, and milk/milk products, contributing 38.65%, 27.77%, and 17.22%, respectively. To further investigate which food sources of serine are significantly associated with cognitive function, we conducted multivariable linear regression analysis on nine food categories as serine sources. After adjusting for all covariates, we found that serine sourced from milk or milk products showed a significant negative correlation with SDLT score. Consistently, previous research has pointed out that total dairy product consumption is associated with better immediate memory recall.[24]

In addition to adopting multivariable linear regression analysis, we used non-linear analysis to investigate the complex dose–response relationship between serine and cognitive function. We found a 'downhill'-shaped non-linear relationship between serine intake and processing speed or concentration (SDST), and a wave-shaped non-linear relationship between serine intake and memory ability (SDLT) among American adults. Our non-linear analysis results indicate that serine intake less than 10.7 benefits memory ability (SDLT) and processing speed or concentration (SDST). Serine sourced from milk or milk products plays a central role in SDLT; serine intake less than 2.63 g from milk was good for memory ability (SDLT). Moreover, serine intake exceeding 0.58 g from grain products or exceeding 0.53 g from meat/poultry/fish has a beneficial impact on visuomotor speed (SRTT). Therefore, it is important to pay attention to the source and quantity of serine intake.

To our knowledge, this is the first examination of the association between dietary serine intake and cognitive function in a nationally representative sample of American adults. Linear and non-linear models were adopted to dissect the intricate relationship between them. We carefully accounted for potential confounding factors. Notably, serine intake from foods is associated with the intake of other amino acids. The amino acid composition of dietary proteins may introduce uncontrolled variables into the data, thus we adjusted for the intake of other amino acids in our analysis. Additionally, we adjusted serine from other foods when exploring the relationship between cognitive function and serine intake from the top three groups. The current study has limitations, including the use of self-reported dietary recalls. Second, due to the limitations of NHANES III data, we cannot separately investigate the impact of L-serine and D-serine on cognitive function. Additional research is warranted to delve into the potential effects of two different forms of serine on cognitive performance.

Conclusions

Serine, particularly serine from milk or milk products, has a beneficial impact on memory ability in adults.

Author contributions

Jingyi Chen & Shuhua Fang: investigation, data curation, writing – original draft preparation. Nian Yang: conceptualization, writing – review and editing. Zeman Cai: investigation and resource acquisition. Qing Zhao: validation, visualization and supervision. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Not applicable.

References

1 J. Y. Chen, N. Yang, Y. L. Peng, H. H. Zhou and Q. Li, Association between Nonfood Pre- or Probiotic Use and Cognitive Function: Results from NHANES 2011-2014, *Nutrients*, 2023, **15**, 3408.

2 K. Kinoshita, R. Otsuka, M. Takada, M. Tsukamoto-Yasui, Y. Nishita, C. Tange, M. Tomida, H. Shimokata, M. Kuzuya, A. Imaizumi and H. Arai, The Association between Dietary Amino Acid Intake and Cognitive Decline 8 Years Later in Japanese Community-Dwelling Older Adults, *J. Nutr., Health Aging*, 2021, **25**, 165–171.

3 J. M. Glenn, E. N. Madero and N. T. Bott, Dietary Protein and Amino Acid Intake: Links to the Maintenance of Cognitive Health, *Nutrients*, 2019, **11**, 1315.

4 O. van de Rest, N. L. van der Zwaluw and L. C. de Groot, Literature review on the role of dietary protein and amino acids in cognitive functioning and cognitive decline, *Amino Acids*, 2013, **45**, 1035–1045.

5 J. M. Billard, D-serine signalling as a prominent determinant of neuronal-glial dialogue in the healthy and diseased brain, *J. Cell. Mol. Med.*, 2008, **12**, 1872–1884.

6 S. J. Parker and C. M. Metallo, Chasing One-Carbon Units to Understand the Role of Serine in Epigenetics, *Mol. Cell*, 2016, **61**, 185–186.

7 G. D. Guercio and R. Panizzutti, Potential and Challenges for the Clinical Use of d-Serine As a Cognitive Enhancer, *Front. Psychiatry*, 2018, **9**, 14.

8 L. Ye, Y. Sun, Z. Jiang and G. Wang, L-Serine, an Endogenous Amino Acid, Is a Potential Neuroprotective Agent for Neurological Disease and Injury, *Front. Mol. Neurosci.*, 2021, **14**, 726665.

9 M. Orzylowski, E. Fujiwara, D. D. Mousseau and G. B. Baker, An Overview of the Involvement of D-Serine in Cognitive Impairment in Normal Aging and Dementia, *Front. Psychiatry*, 2021, **12**, 754032.

10 R. Panizzutti, M. Fisher, C. Garrett, W. H. Man, W. Sena, C. Madeira and S. Vinogradov, Association between increased serum d-serine and cognitive gains induced by intensive cognitive training in schizophrenia, *Schizophr. Res.*, 2019, **207**, 63–69.

11 M. K. Handzlik, J. M. Gengatharan, K. E. Frizzi, G. H. McGregor, C. Martino, G. Rahman, A. Gonzalez, A. M. Moreno, C. R. Green, L. S. Guernsey, T. Lin, P. Tseng, Y. Ideguchi, R. J. Fallon, A. Chaix, S. Panda, P. Mali, M. Wallace, R. Knight, M. L. Gantner, N. A. Calcutt and C. M. Metallo, Insulin-regulated serine and lipid metabolism drive peripheral neuropathy, *Nature*, 2023, **614**, 118–124.

12 Z. Qiu, X. Chen, T. Geng, Z. Wan, Q. Lu, L. Li, K. Zhu, X. Zhang, Y. Liu, X. Lin, L. Chen, Z. Shan, L. Liu, A. Pan and G. Liu, Associations of Serum Carotenoids With Risk of Cardiovascular Mortality Among Individuals With Type 2 Diabetes: Results From NHANES, *Diabetes Care*, 2022, **45**, 1453–1461.

13 G. E. Swan and C. N. Lessov-Schlaggar, The effects of tobacco smoke and nicotine on cognition and the brain, *Neuropsychol. Rev.*, 2007, **17**, 259–273.

14 E. M. Klemperer, J. R. Hughes, P. W. Callas, J. C. West and A. C. Villanti, Tobacco and Nicotine Use Among US Adult "Never Smokers" in Wave 4 (2016–2018) of the Population Assessment of Tobacco and Health Study, *Nicotine Tob. Res.*, 2021, **23**, 1199–1207.

15 S. Beddhu, B. C. Baird, J. Zitterkoph, J. Neilson and T. Greene, Physical Activity and Mortality in Chronic Kidney Disease (NHANES III), *Clin. J. Am. Soc. Nephrol.*, 2009, **4**, 1901–1906.

16 T. S. Yeh, C. Yuan, A. Ascherio, B. A. Rosner, D. Blacker and W. C. Willett, Long-term dietary protein intake and subjective cognitive decline in US men and women, *Am. J. Clin. Nutr.*, 2022, **115**, 199–210.

17 J. Im, H. Park and K. Park, Higher Intake of Total Dietary Essential Amino Acids Is Associated with a Lower Prevalence of Metabolic Syndrome among Korean Adults, *Nutrients*, 2022, **14**, 4771.

18 L. Yu, Y. Li, Q. Zhang, L. Zhu, N. Ding, B. Zhang, J. Zhang, W. Liu, S. Li and J. Zhang, Association between dietary essential amino acids intake and metabolic biomarkers: influence of obesity among Chinese children and adolescents, *Amino Acids*, 2021, **53**, 635–644.

19 J. Im, H. Park and K. Park, Dietary Essential Amino Acid Intake Is Associated with High Muscle Strength in Korean Older Adults, *Nutrients*, 2022, **14**, 3104.

20 R. Katagiri, M. Song, X. Zhang, D. H. Lee, F. K. Tabung, C. S. Fuchs, J. A. Meyerhardt, R. Nishihara, A. T. Chan, A. D. Joshi, M. Iwasaki, S. Ogino, W. C. Willett, E. Giovannucci and K. Wu, Dietary Intake of Branched-Chain Amino Acids and Risk of Colorectal Cancer, *Cancer Prev. Res.*, 2020, **13**, 65–72.

21 S. Park, M. Chae, H. Park and K. Park, Higher Branched-Chain Amino Acid Intake Is Associated with Handgrip

Strength among Korean Older Adults, *Nutrients*, 2021, **13**, 1522.

22 M. Holecek, Serine Metabolism in Health and Disease and as a Conditionally Essential Amino Acid, *Nutrients*, 2022, **14**, 1987.

23 K. Kinoshita, R. Otsuka, M. Takada, Y. Nishita, C. Tange, H. Jinzu, K. Suzuki, H. Shimokata, A. Imaizumi and H. Arai, Dietary amino acid intake and sleep duration are additively involved in future cognitive decline in Japanese adults aged 60 years or over: a community-based longitudinal study, *BMC Geriatr.*, 2023, **23**, 653.

24 K. M. Park and V. L. Fulgoni, The association between dairy product consumption and cognitive function in the National Health and Nutrition Examination Survey, *Br. J. Nutr.*, 2012, **109**, 1135–1142.