

Association Between Dietary Theobromine and Cognitive Function in a Representative Elderly American Population: A Cross-Sectional Study

Lijie Gao

Sichuan University West China Hospital

Chaohua Cui

Sichuan University West China Hospital

Zhengzhou Yuan

Southwest Medical University

Wenjing Ge

Sichuan University West China Hospital

Qian Liu

Sichuan University West China Hospital

Jie Li

Peoples Hospital of Deyang City

Na Liu

Sichuan University West China College of Stomatology

Chunyan Lei

Sichuan University West China College of Ophthalmology Department

Jie Liu (✉ liujie3514@163.com)

Chinese PLA General Hospital

Research

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Abstract

Background: Despite reports on neuroprotective effects of dietary theobromine intake, whether dietary theobromine can exert beneficial effects on cognitive function is unclear. We aimed to investigate the association between dietary theobromine and cognitive function in old American population.

Methods: We collected data from the 2011-2012 and 2013-2014 cycles of the National Health and Nutrition Examination Survey, a cross-sectional survey. Daily dietary theobromine was treated as a continuous variable and a log transform. Cognitive function was measured by four tests: Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning tests, CERAD delayed recall test, animal fluency test, and digit symbol substitution test (DSST). We conducted linear regression analyses and subgroup analyses to study the association between theobromine intake and cognitive performance. Basic characteristics, lifestyle factors, disease history, and nutritional intake were adjusted in these models.

Results: A total of 2,845 participants were included in this study. Daily theobromine intake was not significantly different between the 2011-2012 and 2013-2014 cycles. The CERAD-immediate and delayed recall scores were significantly different between these two cycles, but not the animal fluency score or digital symbol score. The daily dietary theobromine intake in log form was positively associated with immediate recall score (β , 95% CI, P : 0.661, 0.222-1.101, <0.01), delayed recall score (β , 95% CI, P : 0.232, 0.016-0.449, 0.04), and DSST score (β , 95% CI, P : 1.395, 0.140-2.649, 0.03) in the fully adjusted model, but not with the animal fluency score (β , 95% CI: 0.001, -0.122-0.907, 0.13). Sensitive analyses showed that L-theobromine intake was linearly associated with cognitive performance.

Conclusions: Daily theobromine intake was associated with cognitive performance in a large national representative population. However, further research is needed in order to corroborate our findings.

Background

Age-related cognitive decline, characterized by impairment of episodic memory, working memory, and attention, can affect the quality of life (1). Nutritional conditions are reported to be involved in this degenerative cognitive impairment (2, 3). Since previous studies have reported a protective effect of chocolate (4, 5), and theobromine is one of its main active components (6), it could also be associated with cognitive function.

In animal experiments, dietary theobromine is suggested to exert cognitive protection. Theobromine intake is reported to be capable of crossing the blood-brain barrier in mice(7), which provide theobromine chance to interact directly with brain tissue. Further, theobromine is estimated to exert protective effects through neurotransmitter regulation. For example, Mendiola-Precoma et al. (8) found that theobromine intake could improve A1 receptor expression. Theobromine might play a role in phosphodiesterase inhibitors to enhance motor learning skills (9).

Despite this evidence, few clinical trials have investigated the association between dietary theobromine and cognitive function. Therefore, we included a large, representative sample of ≥ 60 -year-old American participants from the cross-sectional National Health and Nutrition Examination Survey (NHANES) dataset to study the association between daily theobromine intake and cognitive performance. We hypothesized that daily theobromine intake would be positively associated with cognitive performance.

Methods

Study population

The NHANES survey was a complex stratified, multistage sampling designed cross-section survey conducted by the Centers for Disease Control and Prevention of USA to assess the American health and nutritional status (10). A survey cycle has been running every 2 years since 1999. In this study, we collected data from the 2011–2012 and 2013–2014 cycles. Participants > 60 years were eligible for cognition test. A total of 3,632 participants were eligible for the cognitive function questionnaire. A total of 508 participants did not answer the cognitive function questionnaire; 269 participants were not available for dietary theobromine intake data. Finally, 2,854 participants were analyzed (Fig. 1). Ethics review board of National Center for Health Statistics approved survey protocol of NHANES, including ethic protocol.

Nutritional intake

The 24-hour dietary questionnaire from the 2011–2012 and 2013–2014 cycles was used to obtain American daily theobromine intake data. All NHANES surveyors were eligible for dietary interviews. Trained interviewers used an automated data collection system under the guidance of an examination protocol (11). Based on previous studies, we also collected data on nutrients reported to be associated with cognitive function, including total energy intake (12), protein (13, 14), lutein (15), zeaxanthin (15), folic acid (16–18), vitamin B12 (17, 19), added vitamin B12 (17, 19), vitamin D (20, 21), magnesium (22), iron (23), zinc (23), copper (23), selenium (23), alcohol, and caffeine (24, 25). Dietary theobromine and other potential confounding dietary nutrients were treated as continuous variables.

Cognitive function

In the 2011–2014 NHANES cycles, survey participants aged ≥ 60 years and qualified to understand English, Spanish, Korean, Vietnamese, traditional or simplified Mandarin, or Cantonese were eligible for cognitive function examination. Three cognition tests were employed: the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word learning and recall test, the animal fluency test, and digit symbol substitution test (DSST). These tests have validated reliability in evaluating cognitive function in Americans (26–28). Participants completed a cognitive test using online tests. The CERAD word learning and recall tests assess immediate and delayed learning ability for new verbal information, respectively (28). The animal fluency test evaluates a component of executive function, categorical verbal fluency (29). DSST is a performance module from the Wechsler Adult Intelligence Scale that evaluates processing speed, sustained attention, and working memory (30). Bad cognitive performance was defined as the lowest quartile of these four scores (31).

Covariates

Demographic variables, including age, sex, race, education, marital status, home status, employment status, smoking status, body mass index (BMI), history of disease, hypertension, diabetes, sleep disorder, and depression were also noted. Age was treated as a continuous variable and split into three subgroups ($> 60, \leq 70; < 70, \geq 80; < 80$) in stratified analyses. Race was categorized as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other races including multi-racial. Education was classified as less than 9th grade, 9-11th grade (including 12th grade with no diploma), high school graduate or equivalent, some college degree, and college graduate or above. Marriage was categorized as married/living with partner, widowed/divorced/separated, and never married. Home status refers to whether participants owned their living house or other arrangements. Smoking status was defined as never ("never smoked or smoked < 100 cigarettes in their life"), previous smoker ("smoked ≥ 100 cigarettes in their life and currently no longer smoking"), and current smoker ("smoked ≥ 100 cigarettes in their life and currently smoking"). BMI was classified as underweight (< 18.9 kg/m²), healthy or normal weight ($\geq 18.9, < 25$ kg/m²), overweight ($\geq 25, < 30$ kg/m²), or obese (≥ 30 kg/m²). If participants were diagnosed with asthma, anemia, psoriasis, celiac, arthritis, emphysema, liver condition, chronic bronchitis, cancer, or malignancy, the history of disease was binary recorded as yes, or no. Heart disease was positively recorded with previous congestive heart failure, coronary heart disease, angina pectoris, and heart attack medically confirmed. Hypertension, diabetes, and sleep disorders were defined by a previous medical diagnosis. Depression was defined as a patient health questionnaire-9 (PHQ-9) score > 5 (32).

Statistical methods

All analyses were weighted according to 2011–2016 NHANES analytical guidelines (33). The 2-year dietary weight was calculated as a new weight to combine the 2011–2012 and 2013–2014 cycles. Continuous variables are presented as weighted mean \pm SE, and categorical variables as unweighted number and weighted percent. Mean levels of continuous variables were compared by Student's t-test, and categorical variables by chi-square tests among the 2011–2012 and 2013–2014 cycles. As shown in Supplementary Table 1, the distribution of daily theobromine was not normal. Thus, we applied a log transformation in later association analysis. We applied linear regression analyses to study the association between theobromine intake and cognitive scores and bad cognitive performance, adjusting for age, sex, race, education, marital status, home status, employment, smoking status, BMI, history of disease, heart disease, history of stroke, hypertension, diabetes, depression, sleep disorder, and dietary nutrients (including energy, protein, lutein, zeaxanthin, folic acid, vitamin B12, vitamin B12, vitamin D, magnesium, iron, zinc, copper, selenium, and caffeine). Daily theobromine intake was analyzed as a continuous variable and a log transform was employed in these analyses. We also conducted subgroup analysis to study the association between theobromine intake and cognition function scores by basic characteristics using multiple linear regression analysis with adjusted variables in the full model, except for the subgroup variable. $P < 0.05$ was considered statistically significant. All analyses were performed using R 4.0.0.

Results

The recruited participants completed a cognitive questionnaire together with the first questionnaire from the 2011–2012 and 2013–2014 NHANES surveys. As shown in Fig. 1, this study included 2,854 elderly American participants.

The mean age of study participants was 69.4 years. Study participants had a mean score of 19.0 for the CERAD word list learning test, 5.9 for the CERAD recall test, 16.7 for the animal fluency test, and 46.2 for the digital symbol test. The mean CERAD word list learning test score was 1.7 points higher in the 2013–2014 cycle than in the 2011–2012 cycle, while the mean CERAD recall test was 0.7 points higher. The animal fluency test and digital symbol test were not significantly different in the 2011–2014 two cycles. Mean theobromine intake was 81.8 mg/d. Theobromine intake did not significantly vary between the 2011–2012 and 2013–2014 cycles. The characteristics of other covariates are presented in Table 1.

Table 1
Study population characteristics by survey cycle

	Total ¹	2011–2012 Cycle ¹	2013–2014 Cycle ¹	<i>P</i> value
Age, yr, mean ± SE	69.4 ± 0.2	69.3 ± 0.3	69.5 ± 0.2	0.90
Male,	9859 (46.0)	4856 (45.5)	5003 (46.4)	0.62
Race				0.09
Mexican American	3085 (3.7)	1355 (2.9)	1730 (4.4)	
Other Hispanic	2036 (3.9)	1076 (4.5)	960 (3.4)	
Non-Hispanic White	6647 (78.0)	2973 (78.2)	3674 (77.9)	
Non-Hispanic Black	4950 (8.9)	2683 (8.5)	2267 (9.2)	
Other races including multi-racial	3213 (5.5)	1669 (5.9)	1544 (5.2)	
Education				0.07
Less than 9th grade	1005 (6.2)	550 (7.5)	455 (5.0)	
9-11th grade (includes 12th grade with no diploma)	1573 (10.4)	782 (10.8)	791 (10.0)	
High school graduate	2472 (22.4)	1169 (22.4)	1303 (22.5)	
Some college	3427 (31.1)	1657 (29.9)	1770 (32.2)	
College graduate or above	2840 (29.8)	1397 (29.4)	1443 (30.2)	
Marriage status				0.73
Married/living with partner	2300 (4.4)	1188 (4.6)	1112 (4.3)	
Widowed/divorced/separated	6505 (64.9)	3123 (65.4)	3382 (64.4)	
Never married	2514 (30.7)	1242 (30.0)	1272 (31.3)	
Home status				0.46
Owned or being bought	10553 (83.5)	5003 (84.3)	5550 (82.9)	
Rented	8703 (14.5)	4434 (14.1)	4269 (14.9)	
Other arrangement	482 (2)	259 (1.7)	223 (2.2)	
Employment				0.39
Employed	6101 (69.6)	3085 (68.8)	3016 (70.3)	
Unemployed	6530 (30.4)	3087 (31.2)	3443 (29.7)	
Smoking Status				0.11
Never	6716 (49.7)	3184 (49.7)	3532 (49.7)	
Previous	2606 (39.6)	1259 (38.4)	1347 (40.7)	
Current	2340 (10.7)	1108 (11.9)	1232 (9.7)	
BMI				0.24
Underweight	3640 (1.4)	1833 (1.1)	1807 (1.6)	
Normal or healthy weight	5471 (25.2)	2669 (26.6)	2802 (34.0)	
Overweight	6603 (58.7)	3214 (58.5)	3389 (58.9)	
Obese	1943 (14.8)	886 (13.8)	1057 (15.6)	
History of disease	6438 (68.5)	3114 (64.0)	3324 (72.5)	< 0.01

¹: Categorical variables are presented as unweighted sample size (weighted percentage); Continuous variables as mean ± SE.

Abbreviations: Body Mass Index, BMI; GED; AA; Consortium to Establish a Registry for Alzheimer's disease, CERAD

	Total ¹	2011–2012 Cycle ¹	2013–2014 Cycle ¹	P value
Heart disease	900 (17.9)	428 (17.6)	472 (18.3)	0.63
History of stroke	431 (6.6)	229 (6.0)	202 (7.2)	0.21
Hypertension	4205 (58.8)	2031 (56.2)	2174 (61.1)	0.01
Diabetes				0.00
No	17365 (76.1)	8524 (78.0)	8841 (74.4)	
Borderline	310 (4.3)	125 (3.0)	185 (5.5)	
Yes	1445 (19.6)	708 (19.0)	737 (20.1)	
Sleep disorder	1064 (12.5)	485 (11.8)	579 (13.1)	0.30
Depression	2534 (21.1)	1178 (16.6)	1356 (25.0)	< 0.01
Dietary intake				
Energy, kcal	1839.5 ± 16.9	1833.7 ± 21.3	1844.6 ± 25.7	0.46
Protein, g	72.1 ± 0.7	71.2 ± 1.1	72.9 ± 0.8	0.39
Lutein + Zeaxanthin, mg	1750.1 ± 96.8	1957.0 ± 186.7	1567.3 ± 78.5	0.07
Folic acid, mcg	373.3 ± 5.7	383.9 ± 9.4	364.0 ± 6.8	< 0.01
Vitamin B12, mcg	4.7 ± 0.1	5.0 ± 0.3	4.3 ± 0.1	< 0.01
Added vitamin B12, mcg	0.9 ± 0.0	1.0 ± 0.1	0.8 ± 0.1	0.16
Vitamin D (D2 + D3), mcg	4.7 ± 0.1	4.7 ± 0.2	4.7 ± 0.2	0.80
Magnesium, mg	281.6 ± 3.1	282.5 ± 5.1	280.8 ± 3.9	0.27
Iron, mg	13.8 ± 0.2	14.1 ± 0.3	13.5 ± 0.3	< 0.01
Zinc, mg	9.9 ± 0.1	9.9 ± 0.2	9.9 ± 0.1	0.55
Copper, mg	1.2 ± 0.0	1.3 ± 0.0	1.2 ± 0.0	< 0.01
Selenium, mg	102.0 ± 1.1	99.3 ± 1.4	104.5 ± 1.6	0.05
Caffeine, mg	146.7 ± 4.8	150.9 ± 8.5	142.9 ± 5.1	< 0.01
Theobromine, mg	31.8 ± 1.3	31.0 ± 2.1	33.1 ± 1.4	0.29
CERAD: immediate recall score	19.0 ± 0.2	18.1 ± 0.3	19.7 ± 0.2	< 0.01
CERAD: delayed recall score	5.9 ± 0.1	5.6 ± 0.1	6.3 ± 0.1	< 0.01
Animal fluency score	16.7 ± 0.1	16.5 ± 0.2	16.8 ± 0.2	0.59
Digital symbol score	46.2 ± 0.6	45.4 ± 1.0	46.9 ± 0.8	0.43
¹ : Categorical variables are presented as unweighted sample size (weighted percentage); Continuous variables as mean ± SE.				
Abbreviations: Body Mass Index, BMI; GED; AA; Consortium to Establish a Registry for Alzheimer's disease, CERAD				

Table 2 Weighted regression models evaluating association between dietary theobromine intake and cognitive performance.

CERAD: Immediate Recall Score												
Theobromine intake, mg/d	Non-adjusted ¹			Adjust I ²			Adjust II ³			Adjust III ⁴		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Continuous Form	0.002	(0.000, 0.004)	0.01	0.002	(-0.000, 0.003)	0.07	0.002	(-0.000, 0.003)	0.07	0.001	(-0.001, 0.003)	0.16
Log form	0.588	(0.151, 1.025)	0.01	0.627	(0.228, 1.027)	<0.01	0.672	(0.262, 1.082)	<0.01	0.661	(0.222, 1.101)	<0.01
CERAD: Delayed Recall Score												
Theobromine intake, mg/d	Non-adjusted ¹			Adjust I ²			Adjust II ³			Adjust III ⁴		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Continuous Form	0.001	(-0.000, 0.002)	0.24	0.000	(-0.001, 0.001)	0.48	0.000	(-0.001, 0.001)	0.45	0.000	(-0.001, 0.001)	0.56
Log form	0.172	(-0.041, 0.386)	0.11	0.214	(0.014, 0.413)	0.04	0.207	(0.005, 0.409)	0.05	0.232	(0.016, 0.449)	0.04
Animal Fluency Score												
Theobromine intake, mg/d	Non-adjusted ¹			Adjust I ²			Adjust II ³			Adjust III ⁴		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Continuous Form	0.004	(0.002, 0.006)	<0.01	0.001	(-0.001, 0.004)	0.15	0.002	(-0.001, 0.004)	0.14	0.001	(-0.001, 0.003)	0.3
Log form	0.729	(0.194, 1.264)	<0.01	0.528	(0.063, 0.994)	0.03	0.492	(0.009, 0.976)	0.05	0.393	(-0.122, 0.907)	0.13
Digital Symbol Score												
Theobromine intake, mg/d	Non-adjusted ¹			Adjust I ²			Adjust II ³			Adjust III ⁴		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Continuous Form	0.015	(0.008, 0.022)	<0.01	0.009	(0.004, 0.014)	<0.01	0.009	(0.004, 0.014)	<0.01	0.009	(0.004, 0.015)	<0.01
Log form	1.525	(-0.002, 3.053)	0.05	1.5	(0.320, 2.680)	0.01	1.631	(0.456, 2.806)	0.01	1.395	(0.140, 2.649)	0.03

¹Adjusted non-variables: Age, sex, race, education, marital status, home status, employment, smoking status, BMI, history of disease, heart disease, history of stroke, hypertension, diabetes, depression, sleep disorder, and sex were adjusted.

²Adjusted model I for sex, age, race, education, marriage, home status, and employment.

³Adjusted for sex, age, race, education, marriage, home status, employment, smoking status, BMI, history of disease, heart disease, history of stroke, hypertension, diabetes, depression, and sleep disorder.

⁴Adjusted model III for sex, age, race, education, marriage, home status, employment, smoking status, BMI, history of disease, heart disease, history of stroke, hypertension, diabetes, depression, sleep disorder, and dietary nutrients (including alcohol, energy, protein, lutein, zeaxanthin, folic acid, vitamin B12, vitamin B12, vitamin D, magnesium, iron, zinc, copper, selenium, and caffeine).

Abbreviations: Consortium to Establish a Registry for Alzheimer's disease, CERAD.

Figure 2 presents a weighted distribution of daily theobromine intake in log form with respect to quartiles of immediate recall score, delayed recall score, animal fluency score, and DSST score. Daily theobromine intake was not significantly different among these quartile subgroups. As shown in Supplementary Fig. 1, daily theobromine intake did not follow a normal distribution. However, the log transformation distribution did. Thus, we used a continuous form and a log transform of daily theobromine intake to analyze the association between dietary theobromine and cognitive performance, as shown in Table 3. In the initial model, log transformation of daily theobromine intake was significantly associated with

immediate recall test score (β , 95%CI, P value: 0.588, 0.151–1.025, 0.01), animal fluency test score (β , 95%CI, P value: 0.729, 0.194–1.264, < 0.01), and DSST score (β , 95%CI, P value: 1.525, -0.002-3.053, 0.05), but not with the delayed recall test (β , 95%CI, P value: 0.172, -0.041-0.386, 0.11). In the fully adjusted model, dietary theobromine intake was positively associated with immediate recall score (β , 95% CI, P : 0.661, 0.222–1.101, < 0.01), delayed recall score (β , 95% CI, P = 0.232, 0.016–0.449, 0.04), and DSST score (β , 95%CI, P value: 0.009, 0.004–0.015, < 0.01). Daily theobromine intake was not associated with the poor cognitive function measured by the four indexes, independent of whether confounding variables were adjusted or not.

To study the association between theobromine intake and cognitive performance we performed subgroup analyses. Theobromine was significantly positively associated with immediate recall score in those who never-smoked (β , 95%CI, P value: 0.006, 0.003–0.010, < 0.01), had hypertension (β , 95%CI, P value: 0.004, 0.001–0.008, 0.02), but not depression (β , 95%CI, P value: 0.005, 0.002–0.008, < 0.01), the 3rd quartile of daily energy (β , 95%CI, P value: 0.002, 0.002–0.011, < 0.01), and protein (β , 95%CI, P value: 0.006, 0.001–0.010, 0.01) intake.

Daily theobromine intake was negatively associated with delayed recall test scores in males (β , 95%CI, P value: -0.002, -0.004-0.000, 0.02), age > 80 (β , 95%CI, P value: -0.004, -0.008-0.000, 0.03), and the 3rd quartile of Lutein + Zeaxanthin (β , 95%CI, P value: -0.004, -0.006- -0.001, < 0.01). However, it was positively associated with delayed recall test scores in the 2nd quartile of Lutein + Zeaxanthin (β , 95%CI, P value: 0.004, 0.001–0.007, 0.01).

Theobromine intake was positively associated with animal fluency score in never-smokers (β , 95%CI, P value: 0.006, 0.002–0.011, < 0.01), normal BMI (β , 95%CI, P value: 0.010, 0.004 – 0.0015, < 0.01), non-depression (β , 95%CI, P value: 0.004, 0.000-0.007, 0.04), the 2nd quartile of Lutein + Zeaxanthin (β , 95%CI, P value: 0.008, 0.002–0.015, 0.01), and the highest quartile of vitamin D2 + D3 (β , 95%CI, P value: 0.008, 0.002–0.015, 0.01) subgroups.

In terms of execution ability, theobromine was associated with DSST score among age > 60 and \leq 70 years old (β , 95%CI, P value: 0.011, 0.005–0.017, < 0.01), non-Hispanic white race (β , 95%CI, P value: 0.011, 0.004–0.018, 0.01), collage graduate or above (β , 95%CI, P value: 0.011, 0.003–0.019, 0.01), never-smoker (β , 95%CI, P value: 0.020, 0.010–0.031, < 0.01), overweight (β , 95%CI, P value: 0.010, 0.004–0.016, < 0.01), no history of stroke (β , 95%CI, P value: 0.010, 0.004–0.015, < 0.01), hypertension (β , 95%CI, P value: 0.012, 0.005–0.018, < 0.01), non-diabetes (β , 95%CI, P value: 0.012, 0.005–0.018, < 0.01), and depression (β , 95%CI, P value: 0.016, 0.008–0.024, < 0.01) subgroups. With respect to nutrition subgroups, theobromine was also positively associated with DSST among the 3rd (β , 95%CI, P value: 0.016, 0.002–0.031, 0.02) and 4th (β , 95%CI, P value: 0.009, 0.003–0.015, 0.01) quartile of energy intake. In the highest quartile of protein (β , 95%CI, P value: 0.017, 0.005–0.029, 0.01), lutein + zeaxanthin (β , 95%CI, P value: 0.027, 0.015–0.038, < 0.01), vitamin B12 (β , 95%CI, P value: 0.030, 0.017–0.043, < 0.01), and vitamin D2 + D3 (β , 95%CI, P value: 0.030, 0.016–0.044, < 0.01) subgroups, dietary theobromine and DSST were also associated.

To further analyze any non-linear associations, we conducted a curve fitting analysis between theobromine intake and cognitive performance. A non-linear association was found, as presented in Supplementary Fig. 3.

Discussion

In this study, we found a linear association between daily theobromine intake and DSST score, an indicator of execution ability, in a representative old American population. However, dietary theobromine intake was not significantly associated with the CERAD-immediate/delayed recall score and animal fluency score.

Previous studies have explored different diet patterns affecting cognitive function. Fernández-Fernández et al. (34) reported that an LMN diet, mainly composed of theobromine, could enhance cognitive reserve function in mice. One of the active components of chocolate is methylxanthine, of which theobromine is the main constituent. A randomized controlled trial (RCT) focusing on the psycho-pharmacologically of methylxanthines showed a protective effect on cognitive function (35). In a Portuguese prospective cohort study, 531 participants aged \geq 65 years with normal cognitive function were followed for a median of 48-month to detect the association of chocolate intake and cognition impairment as measured by the Mini-Mental State Examination (4). In this study, researchers reported that long-term chocolate intake was inversely associated with cognitive decline. Another RCT in Japan also investigated the effect of chocolate intake on cognitive function (5). The intervention group was received dark chocolate daily for 30 days. The modified Stroop color word test and digital cancellation test were conducted to test the association between dark chocolate intake and cognitive function, finding that dark chocolate has a beneficial role in cognitive function.

We selected a large, representative elderly American population to further study the association between dietary theobromine and cognitive performance, finding a significant association between daily theobromine intake and DSST score. However, Mitchell et al. reported non-effect of theobromine (700 mg) alone or combination of theobromine (700 mg) and caffeine (120 mg) on DSST scores in 29 female healthy participants (36). In our study, 1000 mg/d theobromine intake was significantly associated with improvement in DSST score, from 4 to 15. Thus, a higher theobromine intake and a larger study sample size might be necessary to observe a positive association between dietary theobromine and DSST scores.

Islam et al. (7) reported that theobromine could improve the working memory of rats through the CaMKII/CREB/BDNF pathway. DSST is a working memory task that reflects execution ability. Thus, more studies will be required to study whether dietary theobromine intake could exert cognitive protection through similar mechanisms.

There are several limitations to our study. First, owing to the intrinsic limitations of the cross-sectional design, our study cannot conclude a causal association between theobromine intake and cognitive performance. Rigorous, prospective cohort studies or RCTs will be required to validate our results. Second, we excluded participants with unavailable daily dietary data or incomplete cognitive test scores, which could have biased our findings. In Supplementary Table 1, we compare the basic characteristics of included and excluded participants, finding that the majority were balanced between these two groups. Third, because of the questionnaire design, we could not analyze side effects related to theobromine intake, such as heart rate and blood pressure. Thus, we cannot estimate the negative impact of theobromine intake. Further research on the use of theobromine in older adults is warranted.

Conclusions

Daily theobromine intake was associated with cognitive performance in a large national representative elderly population. However, further research is needed in order to corroborate our findings.

Abbreviations

NAHNES, National Health and Nutrition Examination Survey

BMI, Body Mass Index

CERAD, Consortium to Establish a Registry for Alzheimer's Disease

DSST, Digit symbol substitution test

RCT, randomized controlled trial

CaMKII, Calcium Calmodulin Dependent Protein Kinase II

CREB, cyclic AMP response element (CRE)-binding protein

BDNF, Brain-Derived Neurotrophic Factor

Declarations

All authors declared no conflict of interest in this study.

Ethics approval and consent to participate

National Center for Health Statistics institutional review board (NCHS IRB/ERB) approved ethic protocol of 2011-2014 NHANES survey (NCHS IRB/ERB Protocol #2011-17).

Consent for publication Not applicable

Availability of data and materials

The dataset(s) supporting the conclusions of this article are available in the NHANES 2011-2012 and 2013-2014 repository in <https://wwwn.cdc.gov/nchs/nhanes/Default.aspx>.

Competing interests

All authors have no competing interest.

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Authors' contributions

Jie Liu, Li Jie Gao, designed the study, Li Jie Gao, Chao Hua Cui, Zheng Zhou Yuan, Wen Jing Ge, Qian Liu, and Jie Li, collected and cleaned the data, Li Jie Gao analyzed the data, Li Jie Gao and Jie Liu analyzed and interpreted the result, Li Jie Gao Na Liu, and Chun Yan Lei written the article. All authors reviewed this manuscript.

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Figures

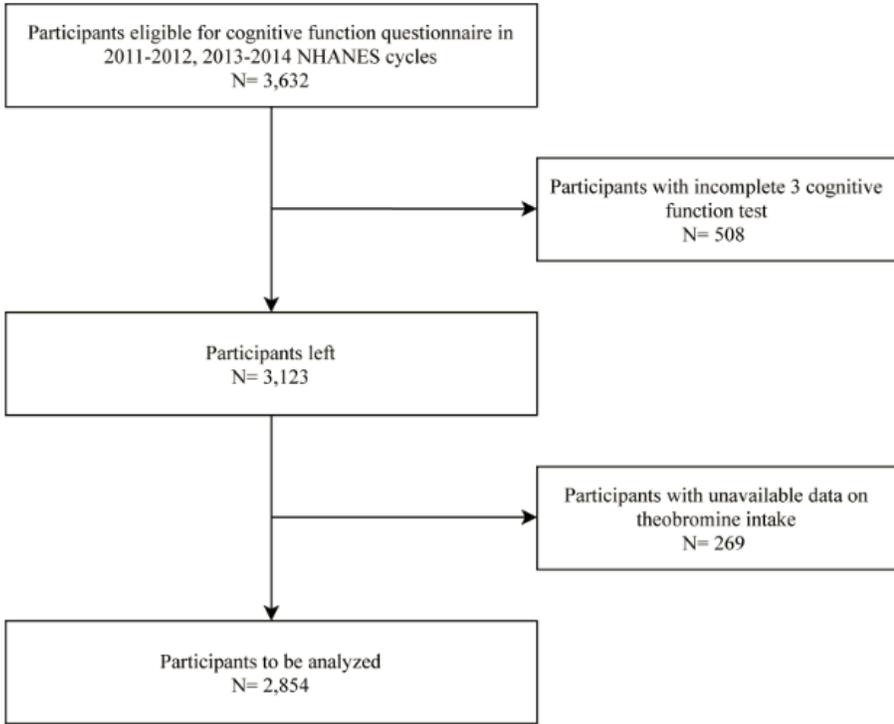


Figure 1
Study Flow Chart

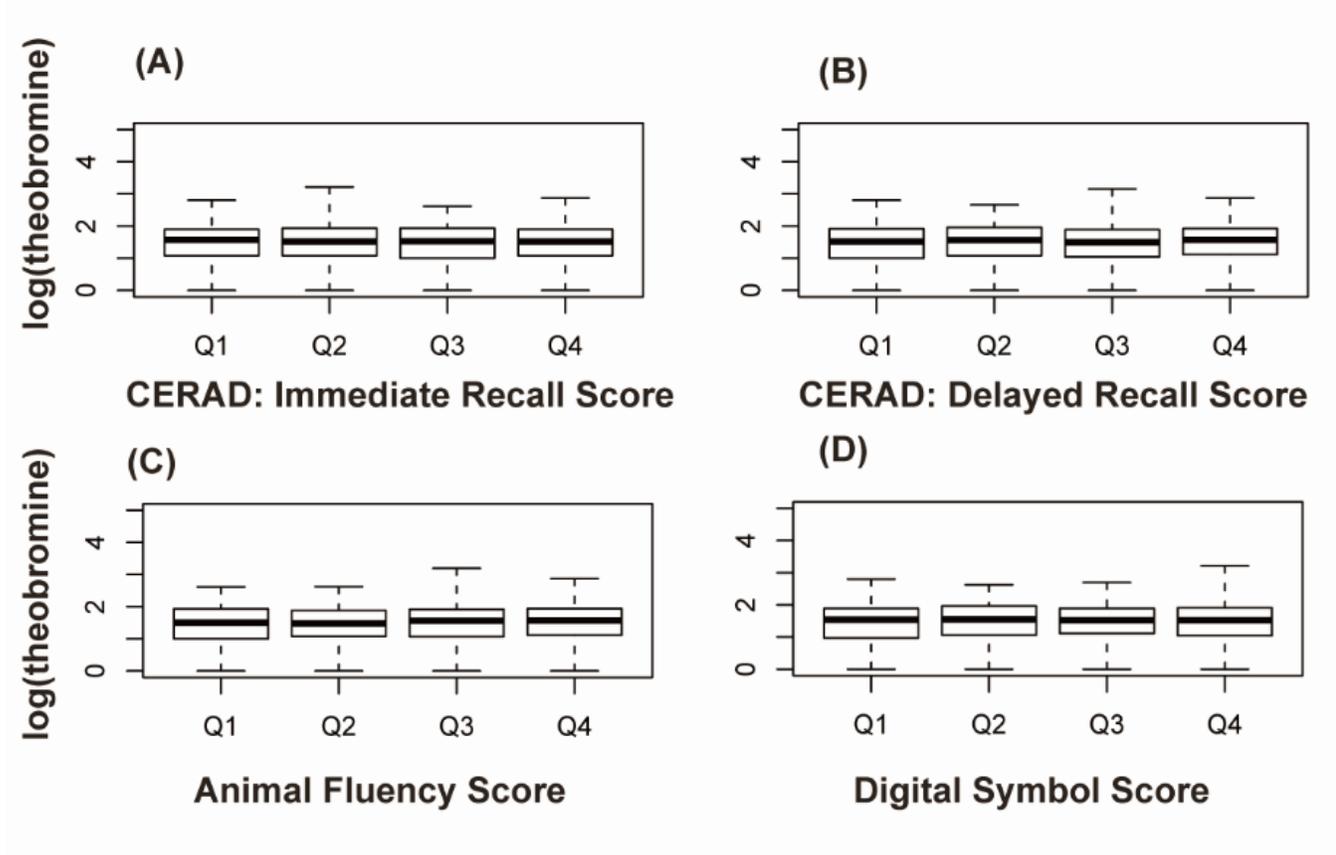


Figure 2
Weighted distribution of daily dietary theobromine intake by quartile subgroups of cognitive performance. $P > 0.05$.

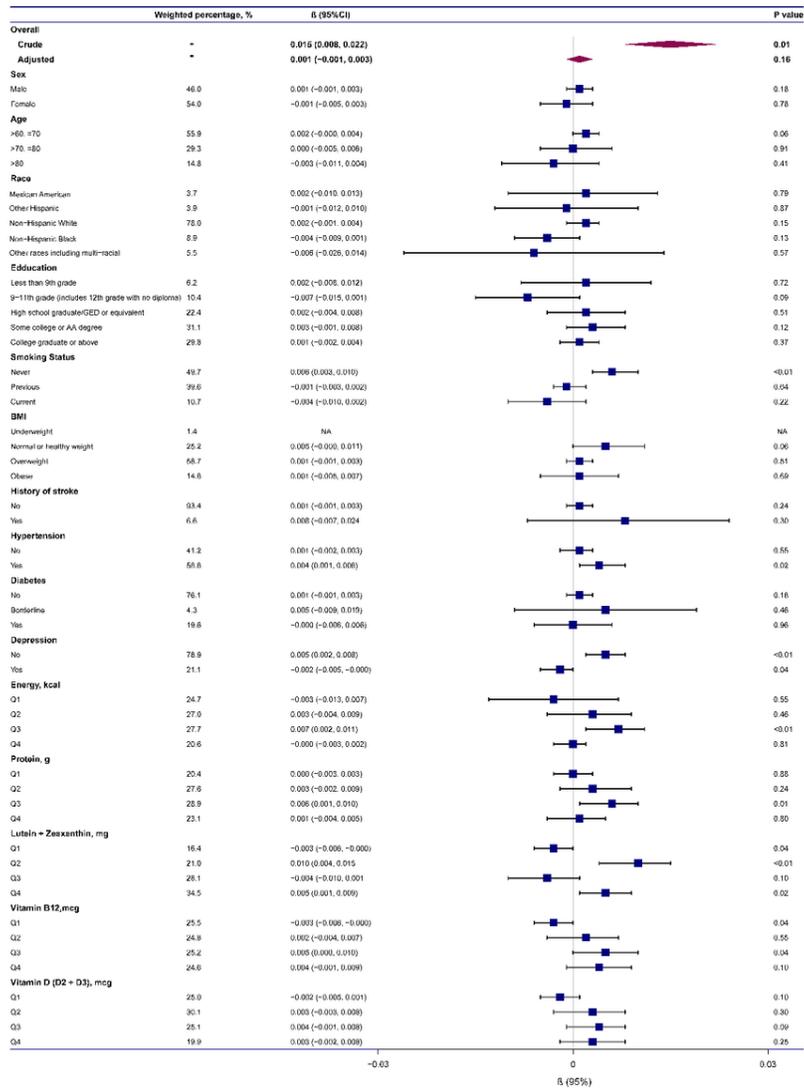


Figure 3

Weighted stratified analyses of the association between dietary theobromine intake and CERAD-immediate recall score according to baseline characteristics.

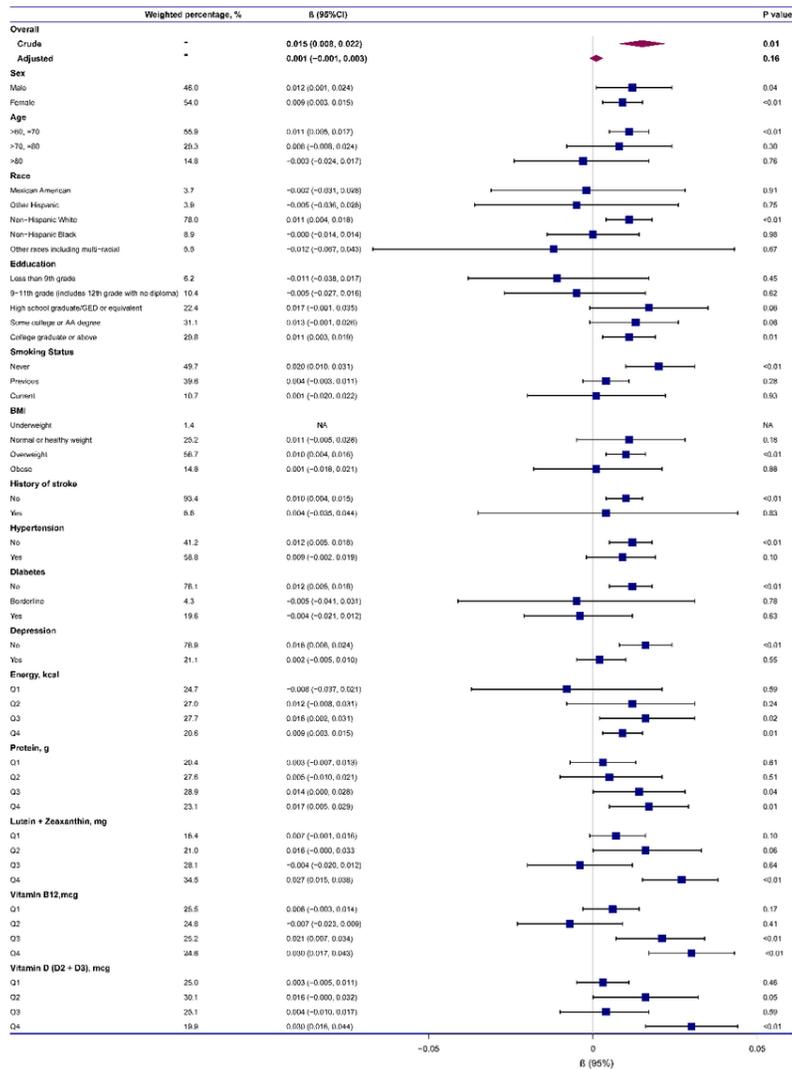


Figure 4
 Weighted stratified analyses of the association between dietary theobromine intake and CERAD-delayed recall score according to baseline characteristics.

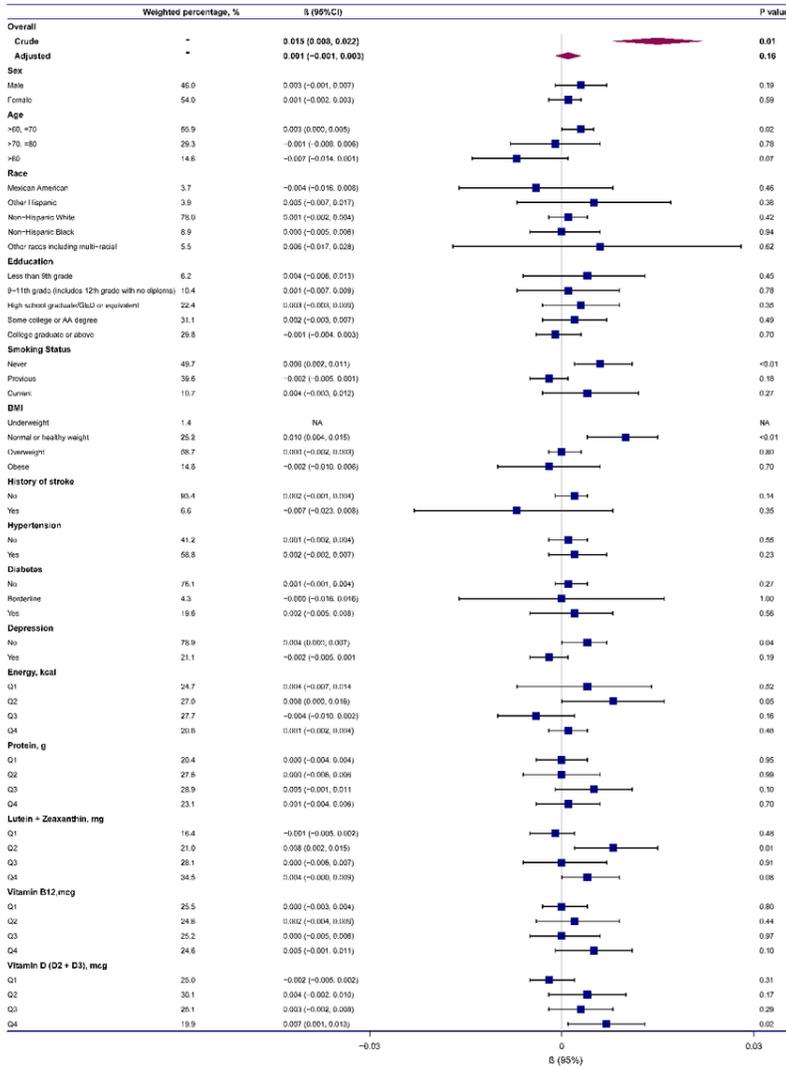


Figure 5

Weighted stratified analyses of the association between dietary theobromine intake and animal fluency score according to baseline characteristics.

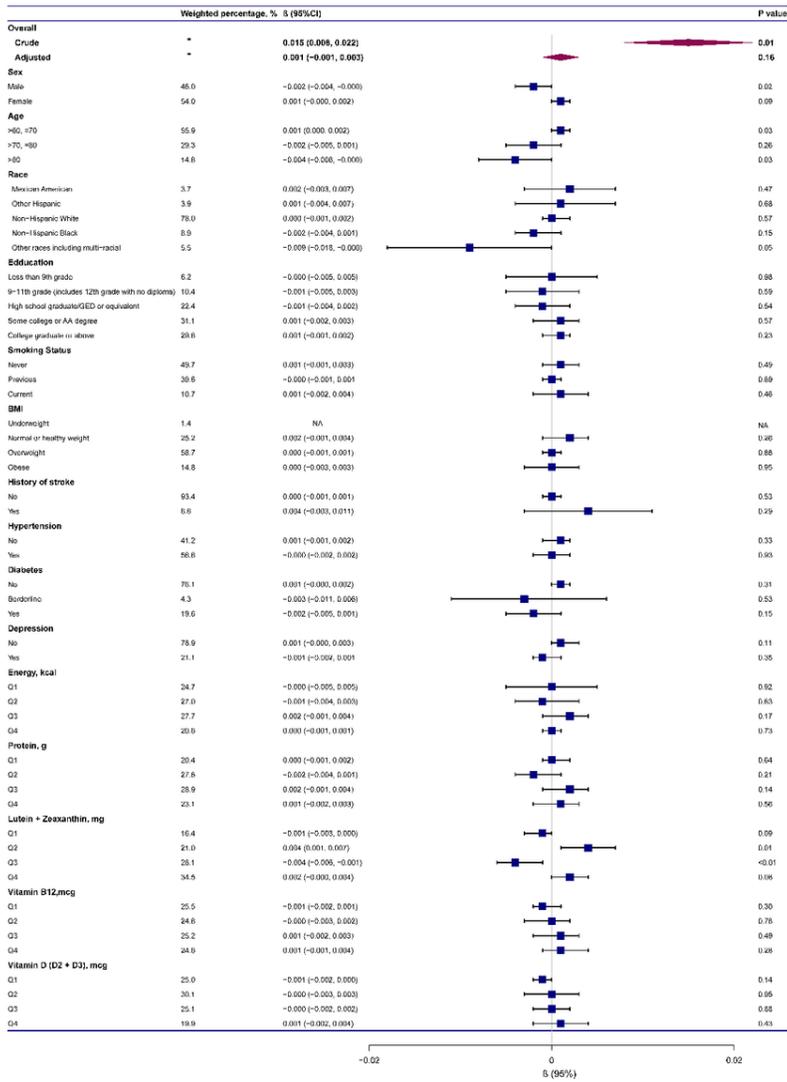


Figure 6

Weighted stratified analyses of the association between dietary theobromine intake and digital symbol score according to baseline characteristics.

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