Non-linear association between daily dietary folate intake and cognitive performance in elder America: A population-based cross-sectional study

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Abstract

Background

The association between daily dietary folate intake and cognitive performance in older populations is unclear.

Methods

This study aimed to investigate whether a dose-dependent association exists between dietary folate levels and cognition performance. The 2011–2014 datasets from the National Health and Nutrition Examination Survey were collected. Data from adults aged ≥ 60 years who completed all three cognitive tests with daily dietary data were analyzed. Weighted smooth curve fitting and multiple linear regression models were applied to study the association between folate intake and cognitive performance. Age, sex, race, education, smoking status, alcohol intake, body mass index, hypertension, stroke, diabetes, and depression were adjusted using a weighted multiple regression model.

Results

Data from 1,255 participants were analyzed. The mean age of the study population was 69.3 years. Males accounted for a weighted 48.8% of the total population. Daily dietary folate was not significantly associated with delayed recall (per 10 mcg/day increment, β 0.003, 95% CI -0.002–0.009, P = 0.23). Below the cut-off of 250 mcg/day, dietary folate intake was positively associated with immediate recall (per 10 mcg/day increment, β 0.01, 95% CI 0.00–0.02, P = 0.05) and animal fluency test score (per 10 mcg/day increment, β 0.02, 95% CI 0.00–0.03, P = 0.05). However, above this cut-off, the association was not significant. Dietary folate intake was not significantly associated with an increase in the digit symbol substitution test score until dietary the folate intake reached 250 mcg/d (per 10mcg/d increment, β 0.29, 95% CI 0.05-0.53, P = 0.04).

Conclusion

Daily dietary folate intake was non-linearly associated with cognitive performance in the older American population.

Introduction

We are entering an aging era worldwide. It is estimated that, by 2030, people aged >65 years would accumulate to 71 million, with 35 million older people in 2000 in America [1]. Age-associated cognitive decline is common in the older population and affects the quality of life [2]. Nutritional conditions are associated with degenerative cognitive impairment [3, 4]. As a feasible monitoring and modifying

lifestyle, understanding the association between dietary nutrients and cognition performance could help improve the quality of life of the older population.

As a cofactor in one-carbon metabolism, folate acid may be involved in cognition-related mechanisms. A lack of folate intake causes detrimental gene expression alterations in the hippocampus of mice [5] and memory impairment. In rats with Alzheimer's disease (AD), folate deficiency has been related to memory impairment, with impaired gut microbiota and hippocampal insulin signaling [6]. Dietary folate may play a role in amyloid-β protein (Aβ) metabolism; Aβ is a biomarker of cognitive impairment. Tian et al. [7] found that folate supplementation decreased Aβ deposition by downregulating the expression of β-secretase (β-site amyloid precursor protein-cleaving enzyme 1) and γ-secretase complex catalytic component (presenilin 1) in mice. In vitro, folic supplementation was found to decrease Aβ deposition via stimulation of DNA methyltransferase (DNMT) activity [8]. Folate supplementation also showed dose-dependent stimulation of DNMT activity in AD transgenic mice [9]. High serum homocysteine (HHCY) level is commonly secondary to folate deficiency. This secondary metabolic alteration has also been reported to increase tau protein phosphorylation and enhance tau oligomerization and aggregation, leading to AD progression in mice [10].

However, the association between dietary folate intake and cognitive performance remains unclear [11, 12]. Evidence on the dose-dependent association between dietary folate and cognitive performance is relatively limited. Thus, in this study, we collected population-based data of older Americans to investigate whether a dose-dependent association exists between dietary folate levels and cognitive performance.

Materials And Methods

Data collection

The National Health and Nutrition Examination Survey (NHANES) has been a continuous program since 1999, conducted by the National Center for Health Statistics (NCHS). It has a complex, multistage, probability cross-sectional design. 5000 nationally representative American residents are screened each year. Demographic, dietary, physical, health-related, and laboratory information are released in a two-year cycle. The NHANES datasets are available at https://www.cdc.gov/nchs/nhanes/Default.aspx. All participants provided written informed consent. The Research Ethics Review Board of the National Center for Health Statistics approved the NHANES protocol (Protocol #2011-17).

We collected data from the 2011–2012 and 2013–2014 NHANES survey cycles. Trained medical professionals interviewed participants aged ≥ 60 years for cognitive assessment. We collected data from the participants who fully completed three cognition tests. Participants with available dietary information were also collected, as shown in Figure 1.

Daily dietary total folate intake

The Agriculture Department of the U.S. and the Department of Health and Human Services collaborated to obtain dietary information among all participants of the NHANES. Dietary data were collected using the automated multiple pass method, a five-step interview. This computerized method helps provide precise dietary intake information in a large survey. The 24-h (before the interview) dietary intake recall was collected. Two datasets of daily dietary information were collected. The first dataset was collected through in-person interviews at the Mobile Examination Center. The second was collected by telephone 3–10 days after the first visit. The average total folate intake of the two sets was applied in this study.

Cognition performance

Participants aged ≥ 60 years who understood English, Spanish, Chinese, Korean, or Vietnamese were eligible for cognition tests. Participants requiring proxy formants were not eligible. The 2011–2012 and 2013–2014 NHANES cycle applied Consortium to Establish a Registry for Alzheimer's Disease (CERAD), animal fluency test (AFT), and digit symbol substitution test (DSST) to assess cognitive performance. The reliability of these tests has been validated in Americans [13–15]. The CERAD evaluates both immediate and delayed word learning capacity, a domain of memory [14]. Three consecutive tests required the recall of ten words per minute. One word was counted for each score. The CERAD-immediate recall score is a summary of these tests. A delayed recall of words was tested after the AFT and DSST or 8–10 min after beginning. Naming as many animals as the participants can in 1 min was performed in the AFT [16]. Each animal named was given a score of one. The AFT assesses categorical verbal fluency, an aspect of executive function. The DSST is a part of the Wechsler Adult Intelligence Scale [17]. Participants were required to match the ruled number and symbol from 133 boxes. Each right match was given a score of one. Participants were excluded if they could not complete each task independently. This test evaluated processing speed, sustained attention, and working memory.

Covariates

Age, sex, race, and education were collected from demographic datasets. Participants aged ≥ 80 years were recorded as 80 years old. Education was classified as less than 9th grade, 9th–11th grade (including 12th grade with no diploma), high school graduate or equivalent, college degree, college graduate or above. Smoking status was classified as never (“never smoked or smoked <100 cigarettes in life”), previous (“smoked ≥100 cigarettes in life and currently no longer smoking”), and current smoker (“smoked ≥100 cigarettes in life and currently smoking”). Demographic information was collected at home. Trained interviewers used the computer-assisted personal interview system in the NHANES. Participants could use English, Spanish, or an interpreter in this interview. Body mass index (BMI) was calculated as the sum of weight(kg)/square of height(m). Underweight referred to BMI <18.9 kg/m^2; normal weight, to BMI ≥18.9 and <25 kg/m^2; overweight, to BMI≥25 and <30 kg/m^2; and obese, to BMI≥30 kg/m^2. Daily alcohol intake was the average of the first and second total daily nutrient intake. Modeled on the U.S. National Health Interview Survey, disease history was obtained from self-reported interviews. If participants reported a diagnosis of hypertension, stroke, or diabetes, the history of disease was recorded as yes. If a participant’s health questionnaire-9 (PHQ-9) score >5, depression was recorded as yes [18].

Statistical analysis

Continuous variables are presented as mean ± standard error (SE), while categorical variables are presented as percentages. Among quartile subgroups of daily folate intake, Kruskal-Wallis rank-sum tests and chi-square tests were used for continuous variables and categorical variables, respectively. Regression analyses were performed to study the association between daily dietary folate intake and cognitive function. Daily dietary folate intake was counted as per 10 mcg/day and split into quartiles in regression models. Smooth fitting analyses were then applied to study the non-linear relationship between dietary intake and cognitive function. We further used 250 μg/day as the threshold to render the dietary folate intake dichotomous to study non-linear associations in stepwise regression models. Age, sex, race, education, smoking status, alcohol intake, BMI, and the presence of hypertension, stroke, diabetes, and depression were adjusted in regression models, smooth fitting analyses, and stepwise regression models.

Weighted clinical characteristics are presented as mean ± standard error (SE) for continuous variables and as percentages for categorical variables according to different survey cycles. They were used to assess differences in clinical characteristics.

All analyses were weighted according to the NHANES analytical guidelines. Statistical significance was set at a P-value < 0.05. R software (http://www.R-project.org, The R Foundation) and Free Statistics Version 1.3 were used for analysis.

Results

Weighted clinical characteristics of study participants

A total of 199,931 participants were surveyed in the 2011–2012 and 2013–2014 NHANES cycles. A total of 16,299 participants were not eligible for the cognition function tests. A total of 509 participants did not complete all three cognitive tests. A total of 1,766 participants did not complete the 1st day dietary interview, while 1,868 did not fulfill that of the 2nd day. In total, 1,255 participants were finally included in this study, as shown in Figure 1.

As presented in Table 1, the weighted average age of the study participants was 69.3 years. Males accounted for 48.8% of the total study population. Sex, race, education, smoking status, BMI, hypertension, and high serum folate levels were significantly different among persons classified into the different quartiles of daily folate intake. The lowest dietary folate intake was <240.0 mcg/day, the 2nd was ≥240.0 and <341.0 mcg/day, the 3rd was ≥341.0 and <472.5 mcg/day, and the highest was ≥472.5 mcg/day.

Table 1
Weighted characteristics of study participants divided by quantile of folate intake.

	Dietary folate intake*, mcg					
	Total N**=1,255	Q1 N** =281	Q2 N** =356	Q3 N** =321	Q4 N** =297	*P* value
Age, yr, mean ± SE	69.3±0.3	69.5±0.5	69.7±0.4	69.3±0.5	68.8±0.3	0.72
Male, N%	48.8	37.7	44.9	48.4	63.9	<0.01
Race, N%						<0.01
Mexican American	6.0	4.5	5.1	5.7	8.5	
Other Hispanic	11.3	12.5	10.8	13.1	9.2	
Non-Hispanic White	46.2	36.6	49.4	47.5	49.7	
Non-Hispanic Black	27.3	40.4	27.3	22.3	21.1	
Other race including multi-racial	9.1	6.0	7.4	11.5	11.6	
Education, N%						<0.01
Less than 9th grade	13.0	18.1	13.4	12.7	8.2	
9-11th grade	15.0	23.8	14.5	11.5	11.6	
High school graduate or equivalent	22.2	21.5	27.6	21.3	17.3	
College degree	27.6	25.7	25	29.6	30.3	
College graduate or above	22.2	10.9	19.6	24.8	32.7	
Smoking status, N%						<0.01
Never	49.5	49.1	52.6	51.6	43.9	
Previous	38.0	32.8	34.9	39.2	45.2	
Current	12.5	18.1	12.5	9.2	10.9	
Alcohol, gm, mean ± SE	5.49±0.4	3.6±0.6	5.1±0.8	6±1.1	7.8±1.4	0.16
BMI, kg/m^2, N%						<0.01

*: Quantile of daily folate intake was cut by 240.0, 341.0, and 472.5 mcg.

**: Unweighted number of participants in each group.

Abbreviations: BMI, body mass index; CERAD, Consortium to Establish a Registry for Alzheimer's disease; AFT, animal fluency test; DSST, digit symbol substitution test; VB, Vitamin B.

	Dietary folate intake*, mcg					
Underweight	1.3	2.6	0.6	0.6	1.7	
Normal or healthy weight	25.6	26.8	23.9	27.1	24.8	
Overweight	57.7	52.1	59.9	54.1	63.9	
Obese	15.4	18.5	15.6	18.2	9.5	
Hypertension, N%	61.9	68.7	60.5	61.1	58.2	0.03
Stroke, N%	7.0	9.8	7.1	6.1	5.4	0.07
Diabetes, N%						0.21
No	24.0	27.5	25.9	22.9	19.7	
Yes	72.5	69.8	71.3	72.6	76.2	
Borderline	3.5	2.6	2.8	4.5	4.1	
Depression, N%	16.6	19.7	17.0	15.3	14.9	0.53
Low serum VB12, N%	2.3	1.6	2.8	3.3	1.1	0.26
High serum folate, N%	35.3	26.2	31.8	41.2	41.3	<0.01
CERAD: immediate recall score	18.3±0.3	17.5±0.4	18.4±0.3	18.5±0.3	18.5±0.3	0.04
CERAD: delayed recall score	5.7±0.1	5.5±0.1	5.7±0.2	5.8±0.1	5.7±0.1	0.15
AFT score	16.6±0.2	15.5±0.4	16.4±0.3	16.8±0.2	17.8±0.3	0.03
DSST score	45.8±1	39.7±1.3	46.5±1.3	47.0±1.5	49.3±0.8	<0.01
*: Quantile of daily folate intake was cut by 240.0, 341.0, and 472.5 mcg.						
**: Unweighted number of participants in each group.						
Abbreviations: BMI, body mass index; CERAD, Consortium to Establish a Registry for Alzheimer's disease; AFT, animal fluency test; DSST, digit symbol substitution test; VB, Vitamin B.						

Male participants accounted for 37.7%, 44.9%, 48.4%, and 63.9%, respectively, in terms of belonging to the folate intake quartiles from the lowest to the highest. In Mexican-Americans, non-Hispanic Caucasians, and other races, including multi-racial, the highest quartile of daily dietary folate intake ranked the highest weighted percentage (Mexican-Americans 8.5%, non-Hispanic Caucasians 49.7%, and other races including multi-racial 11.6%). In other Hispanic races, the 3rd quartile had the highest weighted percentage at 13.1%. In non-Hispanic African participants, the lowest quartile was the highest at 40.4%. In participants educated to less than the 9th grade and with education to the 9–11th grade education level, the lowest quartile rated the highest weighted percentage with 18.1% and 23.8%, respectively. In high school graduates or those with equivalent degrees, 27.6% of the 2nd quartile was the highest. For college

degree or above, the highest quartile rated the highest (college degree 30.3%, college graduate or above 32.7%). Current smokers accounted for 12.5% of total population, among whom 18.1% accounted for the lowest quartile of folate intake, 12.5% for the 2nd quartile, 9.2% for the 3rd quartile, and 10.9% for the highest quartile. Of the overweight participants, 57.7% accounted for 63.9% of the study participants in the highest quartile. In participants with hypertension, 68.7% accounted for the lowest quartile of folate intake, 61.1% for the 2nd, 58.2% for the 3rd, and 61.9% for the highest quartile. The weighted percentage of patients with high serum folate levels was 35.3% (26.2% for the lowest quartile of folate intake, 31.8% for the 2nd, 41.2% for the 3rd, and 41.3% for the highest quartile). Age; daily alcohol intake; presence of stroke, diabetes, and depression; and low serum VB12 levels were not significantly different in the quartiles classified based on daily dietary folate intake.

The mean score of CERAD-immediate recall was 18.3 in the entire study population (17.5 in the lowest quartile of folate intake, 18.4 in the 2nd, 18.5 in the 3rd, 18.5 in the 4th quartile). The mean score of CERAD-delayed recall was 5.7 among all participants (5.5 in the lowest quartile of folate intake, 5.7 in the 2nd, 5.8 in the 3rd, 5.7 in the 4th). For the AFT score, the total participants were 16.6 (the lowest quartile of folate intake was 15.5, the 2nd was 16.4, the 3rd was 16.8, the 4th was 17.8). For the DSST score, there were 45.8 (the lowest quartile of folate intake was 39.7, the 2nd was 46.5, the 3rd was 47.0, the 4th was 49.3). The CERAD-immediate recall, AFT, and DSST scores were significantly different among the quartiles of daily dietary folate intake.

Weighted linear association between daily dietary folate intake and cognitive performance in old Americans

In unadjusted weighted linear regression models, when daily dietary folate intake was treated as a continuous variable, every 10 mcg increment was associated with a 0.023 increase in the CERAD immediate recall score (95% CI 0.010–0.036, P <0.01), 0.043 increase in AFT score (95% CI 0.025–0.060, P < 0.01), and 0.123 increase in DSST score (95% CI 0.056–0.189, P < 0.01). However, daily dietary folate intake was not significantly associated with the CERAD delayed recall score (β 0.007, 95% CI -0.001-0.014, P = 0.08). In multiple weighted linear regression models, each 10 mcg increment was associated with a 0.015 increase in the CERAD immediate recall score (95% CI 0.007-0.023, P = 0.02) and a 0.017 increase in AFT score (95% CI 0.006-0.028, P = 0.03). Dietary folate intake was not significantly associated with delayed recall (β 0.003, 95% CI -0.002–0.009, P = 0.23) or DSST(β 0.036, 95% CI -0.017–0.089, P = 0.24).

When calculated as a category variable, setting the lowest quartile of daily dietary folate intake (<240.0 mcg/day) as the reference group, the highest quartile group had a 0.77 increase in the CERAD immediate recall score (95% CI 0.03–1.50, P = 0.05) and 1.01 increase in the AFT recall score (95% CI 0.35–1.66, P = 0.05) with potential confounders adjusted. For the DSST score, compared to the lowest quartile of daily dietary folate intake, the 2nd quartile had a 4.22 increase (95% CI 2.60–5.84, P = 0.01), the 3rd had a 3.01 increase (95% CI 0.86–5.16, P = 0.05), and the highest quartile had a 4.19 increase (95% CI 1.69–6.68, P = 0.04). In the four dimensions, the trend from the lowest to the highest quartile of daily dietary folate

intake in the adjusted model existed in CERAD immediate recall (P for trend 0.01), AFT (P for trend <0.01), and DSST (P for trend 0.03) but not in CERAD delayed recall (P for trend 0.57) (Table 2).

Table 2
Weighted association between dietary folate intake and cognitive performance

	Crude*			Model 1**		
	β	95% CI	*P* Value	β	95% CI	*P* Value
CERAD-immediate read						
Dietary folate intake, per 10mcg/d	0.023	(0.010, 0.036)	<0.01	0.015	(0.007, 0.023)	0.02
Dietary folate intake						
Q1(<240.0 mcg/d)	Ref.			Ref.		
Q2(≥240.0, <341.0 mcg/d)	0.95	(0.12,1.77)	0.04	0.70	(-0.05,1.44)	0.16
Q3(≥341.0, <472.5 mcg/d)	1.00	(0.14,1.87)	0.04	0.61	(-0.11,1.32)	0.20
Q4(≥472.5 mcg/d)	1.28	(0.25,2.30)	0.03	0.77	(0.03,1.50)	0.05
P for trend	<0.01			0.01		
CERAD-delayed recall						
Dietary folate intake, per 10mcg/d	0.007	(-0.001,0.014)	0.08	0.003	(-0.002, 0.009)	0.23
Dietary folate intake						
Q1(<240.0 mcg/d)	Ref.			Ref.		
Q2(≥240.0, <341.0 mcg/d)	0.19	(-0.05,0.44)	0.15	0.10	(-0.16,0.36)	0.51
Q3(≥341.0, <472.5 mcg/d)	0.24	(-0.08,0.56)	0.17	0.09	(-0.15,0.33)	0.52
Q4(≥472.5 mcg/d)	0.32	(-0.06,0.69)	0.12	0.13	(-0.16,0.41)	0.44
P for trend	0.97			0.57		
AFT score						
Dietary folate intake, per 10mcg/d	0.043	(0.025, 0.060)	<0.01	0.017	(0.006, 0.028)	0.03
Dietary folate intake						

*: Crude Model adjusted no covariate.

**: Model 1 adjusted age, sex, race, education, smoking status, alcohol intake, BMI, hypertension, stroke, diabetes, and depression.

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's disease; AFT, animal fluency test; DSST, digit symbol substitution test

	Crude*			Model 1**		
Q1(<240.0 mcg/d)	Ref.			Ref.		
Q2(≥240.0, <341.0 mcg/d)	1.01	(0.21,1.81)	0.03	0.32	(-0.46,1.10)	0.48
Q3(≥341.0, <472.5 mcg/d)	1.41	(0.74,2.08)	0.04	0.41	(-0.24,1.05)	0.30
Q4(≥472.5 mcg/d)	2.57	(1.66,3.47)	<0.01	1.01	(0.35,1.66)	0.05
P for trend	<0.01			<0.01		
DSST score						
Dietary folate intake, per 10mcg/d	0.123	(0.056, 0.189)	<0.01	0.036	(-0.017, 0.089)	0.24
Dietary folate intake						
Q1(<240.0 mcg/d)	Ref.			Ref.		
Q2(≥240.0, <341.0 mcg/d)	6.88	(4.74,9.02)	<0.01	4.22	(2.60,5.84)	0.01
Q3(≥341.0, <472.5 mcg/d)	7.13	(4.89,9.37)	<0.01	3.01	(0.86,5.16)	0.05
Q4(≥472.5 mcg/d)	9.62	(6.15,13.08)	<0.01	4.19	(1.69,6.68)	0.04
P for trend	<0.01			0.03		

*: Crude Model adjusted no covariate.

**: Model 1 adjusted age, sex, race, education, smoking status, alcohol intake, BMI, hypertension, stroke, diabetes, and depression.

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's disease; AFT, animal fluency test; DSST, digit symbol substitution test

Weighted smooth curve fitting of the association between dietary folate intake and cognitive performance in elderly Americans

We used a weighted smooth curve-fitting method to study the association between daily dietary folate intake and cognitive performance. Age, sex, race, education, smoking status, alcohol intake, BMI, hypertension, stroke, diabetes, and depression were adjusted for. As shown in Figures 2A, 2C, and 2D, the association between dietary folate intake and CERAD immediate recall, AFT, and DSST was not linear. However, as shown in Figure 2B, the association between daily dietary folate intake and CERAD delayed recall tended to be linear.

Two-piece logistic regression of the association between dietary folate intake and cognitive performance in elderly Americans

We further conducted a two-piece analysis to measure the non-linear association between daily dietary folate intake and cognitive function. As presented in Table 3, in daily dietary folate intake <250 mcg/day, 10 mcg increase of folate was independently associated with 0.29 (95%CI, 0.05–0.53, P = 0.04) increment of DSST score. However, when daily dietary folate intake was >250 g/day, DSST was not significantly associated with folate intake (β, 0.00; 95% CI, -0.05–0.05; P = 0.98). Nevertheless, every 10 mcg increase in dietary folate intake was associated with a 0.01 increment in CERAD immediate recall (95%CI, 0.00–0.02; P = 0.05) and 0.02 of AFT (95%CI, 0.00–0.03; P = 0.05).

Table 3
Weighted stepwise multivariable logistic regression model evaluating the association between dietary folate intake and cognitive performance*

	Turning Point					
	< 250			> 250		
	β†	95% CI	*P* Value	β†	95% CI	*P* Value
CERAD-immediate read score	0.06	(-0.04,0.15)	0.32	0.01	(0.00,0.02)	0.05
CERAD-delayed recall score	0.02	(-0.03,0.06)	0.5	0.00	(-0.00,0.01)	0.37
AFT score	0.02	(-0.09,0.14)	0.69	0.02	(0.00,0.03)	0.05
DSST score	0.29	(0.05,0.53)	0.04	0.00	(-0.05,0.05)	0.98
*: Age, sex, race, education, smoking status, alcohol intake, BMI, hypertension, stroke, diabetes, and depression were adjusted for.						
†: Coefficients represented quantified variation associated with per 10mcg increase of daily dietary folate intake.						
Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's disease; AFT, animal fluency test; DSST, digit symbol substitution test.						

Discussion

In a representative older American population, daily folate intake was nonlinearly associated with cognitive performance. CERAD immediate recall and AFT scores were significantly associated with daily folate intake, but not until folate intake was >250 μg/day. However, DSST was significantly associated with folate intake until folate intake was <250 g/day. The CERAD-delayed recall was not significantly associated with dietary folate intake.

Dietary pattern enrichment in folate was reported to have a positive association with cognitive function. In a Chinese cohort, participants aged ≥ 60 years with the highest quartile of vegetarian diet had a 28% decrease in cognition in mild cognitive (MCI) risk, compared with those in the lowest quartile [19]. Nutraceutical intervention rich in folate was found to improve cognitive performance in patients with AD

and MCI [20, 21]. A community-based cohort in America also reported that a low intake combination of multiple vitamins, including folate, was associated with larger total brain volume and better cognition functions [22]. Hence, the question of whether dietary folate alone was independently associated with cognitive performance was raised.

A positive association between single dietary folate and cognition performance, similar to the findings of this study, has been reported previously. In a randomized controlled trial (RCT) from China, Fei et al. reported that patients with MCI with dietary folate supplementation of 400 μg/day for 6 months [23] and 24 months [24] had better performance on the Wechsler Adult Intelligence Scale-Revised test ($P < 0.05$) and a lower concentration of serum Aβ-42 ($P < 0.05$), a marker of cognitive impairment. An open-label, multicenter, single-arm study in Japan also found a protective role on cognition in dementia patients with folate deficiency (<3.6 ng/mL) [25]. Dietary folate was administered at 5 mg/day for 28 to 63 days in the control group. The Mini-Mental State Examination (MMSE) score increased from 20.1 ± 4.7 to 22.2 ± 4.3. However, our study was conducted using population-based datasets, which may provide some information on public cognition health management. We further performed a dose-dependent analysis and found a non-linear association between dietary folate and cognition performance.

An adverse association between dietary folate and cognitive performance has also been reported. A Japanese cross-sectional study found that dietary folate intake was not associated with cognitive function measured by Raven's Colored Progressive Matrices in school children [26]. A prospective cohort enrolling a population of older adults with a sample size of 155 also found that dietary folate intake was not related to cognitive decline measured by the MMSE (OR 2.55, 95% CI 0.78–8.41) [27]. This difference may be due to different age groups and sample sizes.

Our study had several limitations. First, due to temporality bias, this cross-sectional survey could not conclude a causal association between dietary folate intake and cognitive performance. Second, dietary folate intake was assessed based on a 24-h recall, which suffers from intrinsic methodology limitations [17]. However, we averaged the 2-day dietary recall in this study. Third, serum homocysteine may modify the association between dietary folate and cognitive function [28, 29]. However, in the 2011–2014 NHANES cycle, serum homocysteine levels were not examined. Thus, subgroup analyses for different serum homocysteine levels could not be conducted. Further well-designed RCTs and prospective studies are needed to validate our findings.

Conclusion

In an American population aged ≥ 60 years, dietary folate was not significantly associated with CERAD delayed recall. Dietary folate intake was not linearly associated with immediate CERAD recall, AFT, and DSST scores. Below the cut-off of 250 mcg/day, dietary folate intake was positively associated with immediate recall and AFT. However, this association was not significant. Furthermore, dietary folate intake was not significantly associated with the DSST score increase until dietary folate intake reached 250 mcg/day.

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 atin https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Competing interests

All authors have no competing interests.

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Authors' contributions

LJG initiated ideal of this article and interpreted the results. XHW and CQW collected and cleaned study data. LJG, XHW and WCQ performed data analysis and wrote the original manuscript. All authors read and approved the final manuscript.

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Figures

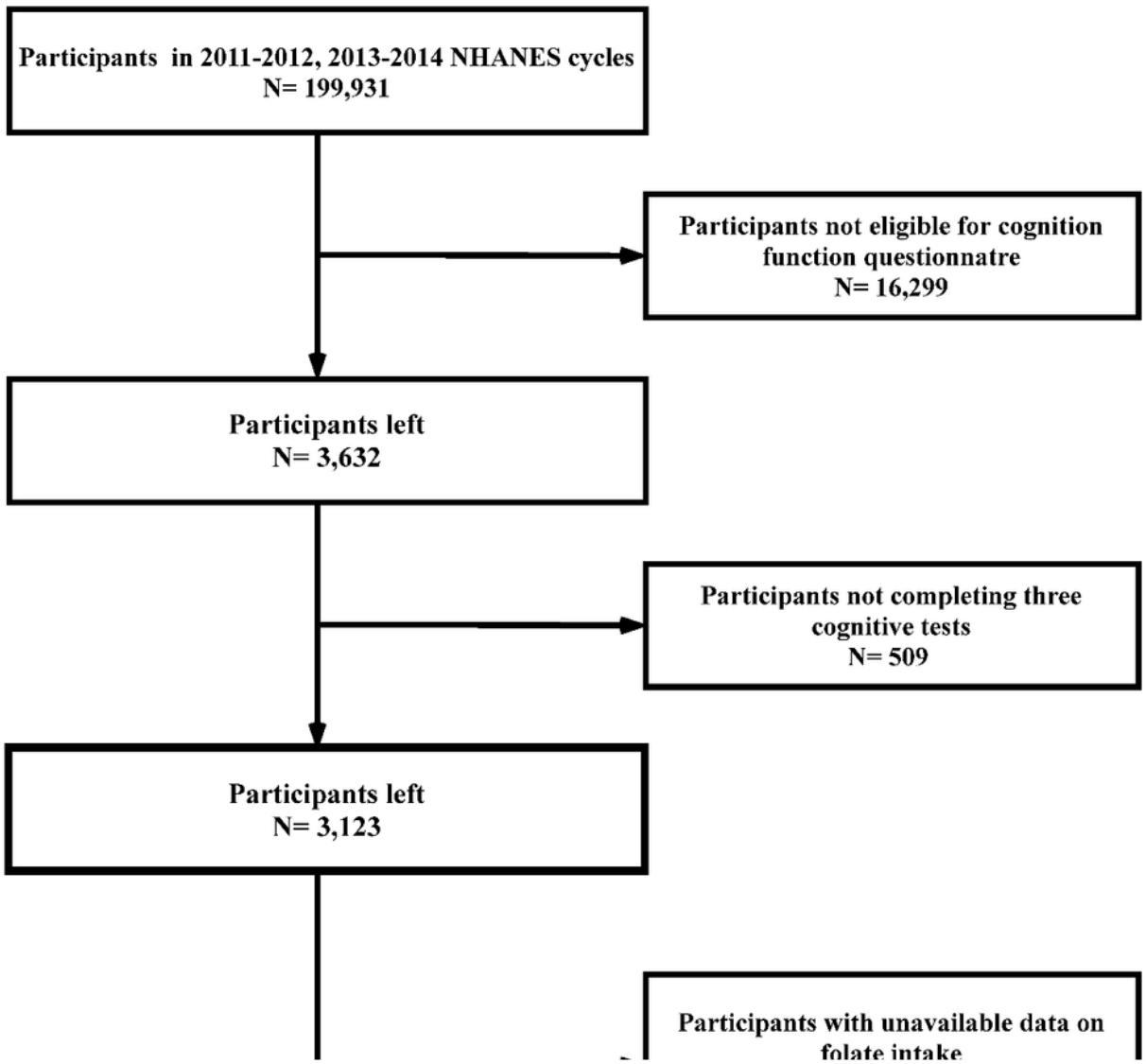

Figure 1

Study flow chart

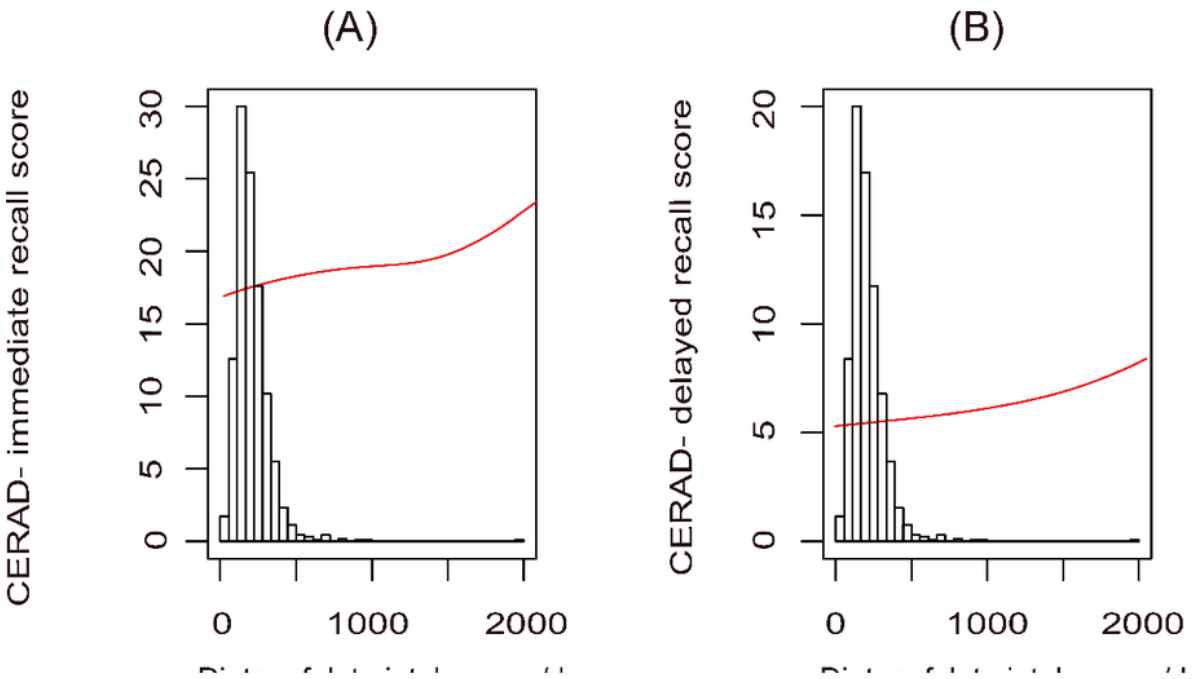

Figure 2

Weighted smooth curve fitting of association between dietary folate intake and (**A)** CERAD-immediate recall score, cognitive performance. Weighted distribution of daily dietary folate intake was also presented. (**B)** CERAD-delayed recall score, (**C)** AFT score, and (**D)** DSST score. Age, sex, race, education, smoking status, alcohol intake, BMI, hypertension, stroke, diabetes, and depression were adjusted for

weighted smooth curve fitting. Red line represented fitted association between folate intake and cognition performance. Columns showed weighted distribution of daily dietary folate intake.

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's disease; AFT, animal fluency test; DSST, digit symbol substitution test.