

Vitamin B₆, B₉, and B₁₂ Intakes and Cognitive Performance in Elders: National Health and Nutrition Examination Survey, 2011–2014

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Purpose: This research intended to investigate vitamin B₆, B₉, and B₁₂ consumption in relation to the risk of low cognitive performance (LCP) among elderly adults.

Patients and Methods: We analyzed data of 2421 participants retrieved from the National Health and Nutrition Examination Survey (NHANES) 2011–2014 database in this cross-sectional study. Cognitive performance was evaluated by the Consortium to Establish a Registry for Alzheimer's disease (CERAD) word learning and recall modules, the animal fluency test (AF), and the digit symbol substitution test (DSST). Participants who scored the lowest 25th percentile were categorized in the LCP group. The Dietary Interview-Total Nutrient Intakes dataset was used to determine the dietary intake of B vitamins in the participants. The low intake group and adequate intake group were differentiated based on the recommended dietary allowance. Subgroup analyses were conducted to assess the relations between 3 B vitamins and cognitive performance among different sex, race, and age groups.

Results: Compared with low vitamin B₆ intake (<1.7 mg/day), adequate vitamin B₆ intake (≥1.7 mg/day) corresponded to a 31.7% decrease in LCP odds in the DSST tests. Participants who consumed adequate B₉ (≥400 mcg/day) were associated with 31.2%, 33.8%, and 46.5% declines in the risk of LCP in the CERAD, AF, and DSST tests in contrast to those having low B₉ intake (<400 mcg/day). Adequate vitamin B₁₂ intake (≥2.4 mcg/day) correlated with a lower LCP occurrence in the CERAD, AF, and DSST tests, with 30.5%, 21.5%, and 33.3% reductions, respectively. Further, the relations between 3 B vitamins and cognitive performance varied across different sex, race, and age groups of people.

Conclusion: Adequate dietary vitamin B₉ and B₁₂ intakes are significantly associated with a better cognitive performance in immediate and delayed memory recall, categorical verbal fluency, processing speed, sustained attention, and working memory among elders assessed in the CERAD, AF, and DSST tests.

Keywords: vitamin B₆, pyridoxine, B₉, folate, B₁₂, cobalamin, cognition, National Health and Nutrition Examination, NHANES, dietary intake

Introduction

The global population of elderly people aged 60 or above is expected to double from 12% to 22%, reaching 2 billion by 2050.¹ As the size of the elder population increases substantially, age-related health conditions have raised considerable concerns. Aging is commonly accompanied by cognitive function declines, such as processing speed, attention, certain memories, language, visuospatial abilities, and executive functioning.² Cognitive changes or deficits that affect one's ability to perform daily activities are considered major neurocognitive disorders. The definition and diagnostic criteria of several cognitive disorders are provided by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).³ According to the World Health Organization, the economic burden of dementia, a cognitive disorder that impacts daily functioning, costs approximately US\$ 818 billion in 2015.⁴

Although current pharmaceutical treatment is limited, studies have shown promising effects of lifestyle change and dietary intervention on slowing the progression of cognitive impairments.^{5–7} Vitamin B complex plays an essential role in maintaining proper physiological functions of cellular energy metabolism, methylation, DNA synthesis and repair, immune system, and steroid hormone activity.⁸ Because of the crucial function vitamin B complex performs in homocysteine metabolism, suboptimal vitamin B levels have been linked to cognitive decline.⁹ Homocysteine, a sulfur-containing amino acid, has established a putative relationship with cognitive decline.¹⁰ The association between elevated plasma homocysteine levels and cognitive impairments may be attributed to mechanisms involving the methylation pathways. It has been proposed that homocysteine is associated with brain atrophy, oxidative stress, DNA damage, increased apoptosis, excitotoxicity, and neurodegeneration.⁹

Vitamin B₆ (Pyridoxine), vitamin B₉ (Folate), and vitamin B₁₂ (Cobalamin) are the three core B vitamins that facilitate homocysteine metabolism. In the process of resynthesizing methionine from homocysteine, vitamin B₉, in the form of tetrahydrofolate, and B₁₂ mainly participate in the remethylation of homocysteine to methionine.¹¹ To be further metabolized in the human body, homocysteine enters the trans-sulfuration pathway to form cysteine, the process of which requires the presence of pyridoxal phosphate, the coenzyme form of vitamin B₆.^{11,12}

The aging-related decrease in satiety predisposes the elderly to vitamin B deficiencies or suboptimal vitamin B levels.¹¹ Thus, the neuro-protective properties of vitamin B may assist the prevention and management of poor cognitive performance among elders to a considerable extent.

Since vitamin B complex is proposed to be a protective factor of cognitive decline,^{9,10,13–15} previous studies focused on three critical B vitamins, vitamin B₆, B₁₂, and B₉,^{16,17} when examining the association between vitamin B and cognitive functions in the elderly. However, there are limited publications on specific cognitive domains affected by vitamin B deficiencies, so this study intended to investigate whether dietary vitamin B₆, B₉, and B₁₂ intakes were in relation to cognitive performance among the elderly, through the Consortium to Establish a Registry for Alzheimer's disease (CERAD) word learning and recall modules, the Animal Fluency test (AF), and the Digit Symbol Substitution Test (DSST) which assessed different cognitive domains. We further performed subgroup analyses to demonstrate if and how the relations between 3 B vitamins and cognitive performance varied across different sex, race, and age groups of elderly people.

Methods

Study Participants

The National Health and Examination Survey (NHANES) collected nation-wide representative data, aiming to assess the health and nutritional status of adults and children in the United States. There were two main parts of the NHANES program, an in-home interview and a physical examination in a mobile examination center (MEC).¹⁸ All protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. Only the NHANES 2011–2012 and 2013–2014 cycles evaluated cognitive functions in both the questionnaire and MEC examination. Thus, we downloaded 2011–2012 and 2013–2014 NHANES public data for analysis in this research. A total of 2937 participants were aged >60 years and completed cognitive assessment. Individuals who had missing data in vitamin B₆, B₉, and B₁₂ intakes, body mass index (BMI), poverty income ratio (PIR), alcohol use, education level, hypertension, and cardiovascular diseases were excluded (n=516). In total, 2421 people were included in this study (Figure 1).

Cognitive Performance Assessment

During the MEC examination, a series of cognitive function assessments were administered to participants aged 60 years or older, including the CERAD word learning and recall modules, AF, and DSST. All the collected data were available in the cognitive functioning questionnaire (CFQ).

The CERAD consisted of learning trials and delayed recall, which examined immediate and delayed memory recall.¹⁹ Participants were visually or auditorily presented with 10 words and instructed to read aloud. Participants recalled as many as possible words immediately after the presentation and after the completion of the AF and DSST. The AF evaluated the categorical verbal fluency by asking the participants to name as many animals as possible in 1 minute.²⁰

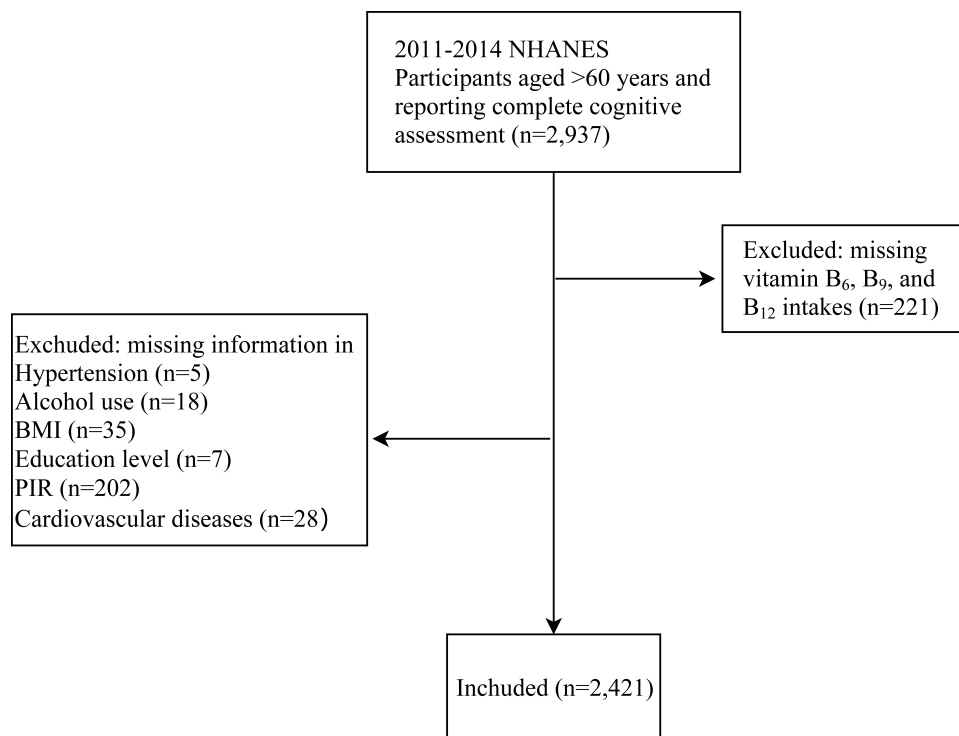


Figure 1 Flow chart of selecting eligible participants.

The participant gained one point for each animal correctly named. The processing speed, sustained attention, and working memory were evaluated by the DSST.²¹ The DSST was a paper-delivered test composed of a reference at the top and 133 boxes containing the numbers 1–9, in random order, adjoined in rows on a page with an empty box underneath each number. The reference was 9 numerical numbers paired with unique symbols. Participants were asked to match the corresponding symbols in the 133 boxes using the reference in 2 minutes.

Since there is no standard cut-offs for CERAD, AF and DSST to define low cognitive performance (LCP), we categorized participants who scored the lowest 25th percentile in each of the tests into the LCP group and the remaining participants into the normal cognitive performance (NCP) group. This method was consistent with those applied in multiple previous NHANES cognitive studies.^{22–26} Respective cut-off values for CERAD, AF and DSST were 5, 13 and 35.

Dietary Intake Assessment

Dietary intake data from the 24-hour dietary recall interview were collected using a validated USDA Automated Multiple-Pass Method during the MEC examination.²⁷ We obtained vitamin B₆, B₉ and B₁₂ consumption from the Dietary Interview-Total Nutrient Intakes dataset. Vitamin intakes were further categorized into two groups, a group with vitamin intakes equal to or higher than the Recommended Dietary Allowance (RDA) and a group with vitamin intakes lower than the RDA. Vitamin B₆ intake was categorized into a group of <1.7 mg/day and a group of ≥1.7 mcg/day. Vitamin B₉ intake was classified into a group consuming ≥400 mcg/day and a group consuming <400 mcg/day. Vitamin B₁₂ consumption was divided into ≥2.4 mcg/day and <2.4 mcg/day. In all the analyses, the group with intakes lower than the RDA was the reference group.

Potential Covariates

Alcohol use and social-economic status were associated with cognitive functions, and were therefore considered potential covariates in this study.¹⁰ Alcohol consumers were defined using the Alcohol Use Questionnaire (ALQ) question ALQ101: “Had at least 12 alcohol drinks/1 yr?” Participants who answered “Yes” were categorized as alcohol consumers. Social-economic status was evaluated using the PIR available in the Demographic Variables & Sample

Weight (DEMO) as INDFMPIR. PIR is the ratio of family income to poverty, which was calculated by dividing family income by the poverty guidelines. Therefore, we classified $PIR < 1$ as the low-income group.

Medical Conditions

Hypertension patients were determined based on the examination data. The participants were defined as having hypertension if their systolic pressure is ≥ 140 mmHg, and diastolic pressure is ≥ 90 mmHg. Additionally, people who answered “Yes” to the Blood Pressure & Cholesterol Questionnaire (BPQ) question 020, “{Have you/Has SP} ever been told by a doctor or other health professional that {you/s/he} had hypertension, also called high blood pressure?” were classified as having hypertension. Diabetic patients were identified if their plasma fasting glucose level ≥ 126 mg/dL or Hemoglobin A1c $\geq 6.5\%$. In addition, participants who answered “yes” to Diabetes Questionnaire (DIQ) question 010,

The next questions are about specific medical conditions. {Other than during pregnancy, {have you/has SP}/{Have you/Has SP}} ever been told by a doctor or health professional that {you have/{he/she/SP} has} diabetes or sugar diabetes? Were defined as diabetic.

Cardiovascular diseases, including congestive heart failure, coronary heart disease, angina, heart attack, and stroke, were determined based on the Medical Conditions Questionnaire (MCQ) 160b-f:

Has a doctor or other health professional ever told {you/SP} that {you/s/he} had congestive heart failure/coronary (kor-o-nare-ee) heart disease/angina (an-gi-na) (also called angina pectoris)/a heart attack (also called myocardial infarction (my-o-car-dee-al in-fark-shun))/a stroke?

Statistical Analysis

Continuous variables were presented as means and standard deviations (Mean \pm SD), while categorical variables were described as cases and percentages. Baseline characteristics were compared using the independent-*t*-test and Pearson chi-square test. Univariate and multivariate logistic regression models were applied to analyze the association between vitamin B intakes and cognitive performance. Crude model was a univariate model. Model 1 was a multivariate model adjusted for age and gender. Model 2 was a multivariate model adjusted for age, gender, race, education level, PIR, hypertension, heart failure, heart attack, and stroke for the CERAD test, adjusted for age, gender, race, education level, marital status, PIR, alcohol use, hypertension, and stroke for the AF test, and adjusted for age, gender, race, education level, marital status, PIR, alcohol use, diabetes, hypertension, heart failure, heart attack, and stroke for the DSST test. Odds Ratios (ORs), 95% Confidence Intervals (CIs), and *P* value were also acquired using the logistic regression models. Further, we have performed subgroup analyses to demonstrate if and how the relations between 3 B vitamins and cognitive performance varied across different sex, race, and age groups of people. Moreover, we included NHANES sample weights in statistical analysis of this study. All statistical tests were two-sided with a significance level set at 0.05. We used SAS 9.4 (SAS Institute, inc. Cary, NC, USA) for all the statistical analyses and R 4.0.2 for forest plots in this research.

Results

Baseline Characteristics

Of the 2421 participants, 337 were classified into the LCP group based on the CERAD test, 398 into the LCP group according to the AF test, and 563 into the LCP group when assessed by the DSST. Baseline characteristics were compared between the two groups, as shown in [Table 1](#). Means, SDs, and ranges for these cognitive tests are shown in [Supplementary Table 1](#). Across all the three cognitive measures, age, race, education level, PIR, hypertension, stroke, vitamin B₉ intake were significantly different between the NCP and LCP groups.

The LCP group had a higher proportion of participants aged 70–79 years and ≥ 80 years than the NCP group in all the three cognitive tests. Across all the cognitive measures, the LCP group had a higher percentage of the participants with hypertension than the NCP group. The CERAD test revealed a significantly higher proportion of heart failure in the LCP group (13.39%) than the NCP group (5.82%). Similarly, the percentage of individuals with heart failure was significantly

Table 1 Characteristics of n=2421 Study Participants, NHANES 2011–2014

	Total (n=2421)	LCP (n=337)	CERAD		LCP (n=398)	AF		LCP (n=563)	DSST	
			NCP (n=2084)	P		NCP (n=2023)	P		NCP (n=1858)	P
Age (years), n(%)				<0.001			<0.001			<0.001
60–69	1336 (58.25)	125 (33.25)	1211 (61.27)		178 (36.41)	1158 (60.80)		238 (32.82)	1098 (61.98)	
70–79	712 (28.91)	111 (35.09)	601 (28.16)		141 (39.83)	571 (27.63)		196 (37.05)	516 (27.71)	
≥80	373 (12.84)	101 (31.67)	272 (10.57)		79 (23.76)	294 (11.57)		129 (30.13)	244 (10.30)	
Sex, n(%)				0.253			0.686			0.549
Male	1182 (46.54)	196 (50.72)	986 (46.04)		187 (44.95)	995 (46.73)		315 (48.29)	867 (46.29)	
Female	1239 (53.46)	141 (49.28)	1098 (53.96)		211 (55.05)	1028 (53.27)		248 (51.71)	991 (53.71)	
Race, n(%)				0.034			<0.001			<0.001
Mexican American	204 (3.12)	34 (4.78)	170 (2.92)		27 (4.07)	177 (3.01)		74 (8.82)	130 (2.28)	
Other Hispanic	235 (3.27)	41 (5.47)	194 (3.00)		55 (7.19)	180 (2.81)		101 (10.74)	134 (2.17)	
Non-Hispanic White	1216 (81.29)	153 (75.31)	1063 (82.01)		127 (60.88)	1089 (83.67)		174 (57.33)	1042 (84.80)	
Non-Hispanic Black	567 (7.81)	91 (11.04)	476 (7.42)		147 (19.50)	420 (6.44)		194 (20.69)	373 (5.92)	
Other races	199 (4.52)	18 (3.40)	181 (4.65)		42 (8.36)	157 (4.07)		20 (2.42)	179 (4.82)	
Education level, n(%)				0.002			<0.001			<0.001
Less than 9th grade	243 (4.96)	73 (11.59)	170 (4.16)		71 (11.87)	172 (4.16)		187 (24.95)	56 (2.03)	
9–11th grade	323 (9.51)	55 (11.97)	268 (9.21)		87 (18.51)	236 (8.46)		122 (20.42)	201 (7.91)	
High school graduate	563 (21.41)	90 (29.79)	473 (20.40)		116 (32.00)	447 (20.17)		131 (26.26)	432 (20.69)	
Some college	708 (32.62)	67 (28.37)	641 (33.13)		77 (22.07)	631 (33.85)		88 (20.31)	620 (34.43)	
College graduate or above	584 (31.50)	52 (18.28)	532 (33.09)		47 (15.55)	537 (33.36)		35 (8.06)	549 (34.94)	
Marital status, n(%)				0.091			0.043			<0.001
Married	1349 (63.71)	181 (60.93)	1168 (64.05)		199 (52.39)	1150 (65.03)		262 (48.24)	1087 (65.98)	
Widowed	443 (15.43)	80 (22.03)	363 (14.64)		94 (25.84)	349 (14.22)		147 (27.68)	296 (13.64)	
Divorced	362 (12.91)	38 (9.70)	324 (13.30)		58 (12.49)	304 (12.96)		74 (12.14)	288 (13.03)	
Separated	66 (1.16)	11 (1.51)	55 (1.11)		15 (2.29)	51 (1.02)		33 (3.96)	33 (0.74)	
Never married	136 (4.18)	15 (3.75)	121 (4.23)		23 (4.69)	113 (4.12)		31 (5.28)	105 (4.02)	
Living with partner	65 (2.60)	12 (2.08)	53 (2.66)		9 (2.29)	56 (2.64)		16 (2.69)	49 (2.59)	
PIR, n(%)				0.006			<0.001			<0.001
<1	387 (8.31)	75 (14.05)	312 (7.61)		105 (18.76)	282 (7.09)		174 (23.96)	213 (6.01)	
≥1	2034 (91.69)	262 (85.95)	1772 (92.39)		293 (81.24)	1741 (92.91)		389 (76.04)	1645 (93.99)	
BMI (kg/m²), n(%)				0.120			0.157			0.515
<25	637 (25.69)	90 (29.31)	547 (25.25)		112 (30.93)	525 (25.07)		153 (27.87)	484 (25.36)	
25–30	851 (36.22)	137 (40.06)	714 (35.76)		139 (34.79)	712 (36.39)		194 (33.55)	657 (36.61)	
≥30	933 (38.09)	110 (30.63)	823 (38.99)		105 (18.76)	282 (7.09)		216 (38.58)	717 (38.02)	
Alcohol use, n(%)				0.078			<0.001			<0.001
Yes	1679 (73.72)	227 (68.53)	1452 (74.35)		247 (62.24)	1432 (75.06)		353 (59.41)	1326 (75.82)	

(Continued)

Table I (Continued).

	Total (n=2421)	LCP (n=337)	CERAD		LCP (n=398)	AF		LCP (n=563)	DSST	
			NCP (n=2084)	P		NCP (n=2023)	P		NCP (n=1858)	P
No	742 (26.28)	110 (31.47)	632 (25.65)		151 (37.76)	591 (24.94)		210 (40.59)	532 (24.18)	
Diabetes				0.248			0.180			<0.001
Yes	561 (19.18)	91 (24.44)	470 (18.54)		115 (25.08)	446 (18.49)		181 (30.90)	380 (17.46)	
No	1746 (76.48)	230 (71.14)	1516 (77.12)		265 (71.14)	1481 (77.10)		358 (65.27)	1388 (78.12)	
Borderline	114 (4.35)	16 (4.41)	98 (4.34)		18 (3.77)	96 (4.41)		24 (3.83)	90 (4.42)	
Hypertension, n(%)				0.046			0.005			<0.001
Yes	1509 (58.38)	221 (64.58)	1288 (57.63)		277 (67.42)	1232 (57.33)		399 (73.98)	1110 (56.09)	
No	912 (41.62)	116 (35.42)	796 (42.37)		121 (32.58)	791 (42.67)		164 (26.02)	748 (43.91)	
Heart failure, n(%)				0.010			0.504			<0.001
Yes	169 (6.63)	37 (13.39)	132 (5.82)		35 (7.86)	134 (6.49)		63 (14.75)	106 (5.44)	
No	2252 (93.37)	300 (86.61)	1952 (94.18)		363 (92.14)	1889 (93.51)		500 (85.25)	1752 (94.56)	
Coronary Heart Disease, n(%)				0.278			0.617			0.439
Yes	218 (9.29)	38 (12.01)	180 (8.96)		37 (8.47)	181 (9.38)		53 (10.67)	165 (9.09)	
No	2203 (90.71)	299 (87.99)	1904 (91.04)		361 (91.53)	1842 (90.62)		510 (89.33)	1693 (90.91)	
Angina, n(%)				0.315			0.657			0.079
Yes	131 (5.80)	20 (7.27)	111 (5.63)		21 (5.11)	110 (5.89)		32 (8.86)	99 (5.36)	
No	2290 (94.20)	317 (92.73)	1973 (94.37)		377 (94.89)	1913 (94.11)		531 (91.14)	1759 (94.64)	
Heart attack, n(%)				0.017			0.353			0.008
Yes	206 (8.45)	34 (13.24)	172 (7.87)		38 (10.14)	168 (8.25)		68 (13.37)	138 (7.73)	
No	2215 (91.55)	303 (86.76)	1912 (92.13)		360 (89.86)	1855 (91.75)		495 (86.63)	1720 (92.27)	
Stroke, n(%)				0.024			0.023			<0.001
Yes	160 (5.96)	35 (9.67)	125 (5.51)		44 (10.89)	116 (5.39)		71 (13.58)	89 (4.84)	
No	2261 (94.04)	302 (90.33)	1959 (94.49)		354 (89.11)	1907 (94.61)		492 (86.42)	1769 (95.16)	
Vitamin B₆ (mg/d), n(%)				0.995			0.061			0.001
<1.7	1254 (49.09)	171 (49.11)	1083 (49.09)		226 (55.37)	1028 (48.36)		326 (59.52)	928 (47.56)	
≥1.7	1167 (50.91)	166 (50.89)	1001 (50.91)		172 (44.63)	995 (51.64)		237 (40.48)	930 (52.44)	
Vitamin B₉ (mcg/d), n(%)				0.019			0.015			<0.001
<400	1551 (61.34)	232 (68.73)	1319 (60.45)		291 (71.34)	1260 (60.17)		409 (73.91)	1142 (59.49)	
≥400	870 (38.66)	105 (31.27)	765 (39.55)		107 (28.66)	763 (39.83)		154 (26.09)	716 (40.51)	
Vitamin B₁₂ (mcg/d), n(%)				0.122			0.037			0.001
<2.4	812 (30.03)	119 (34.26)	693 (29.52)		160 (35.13)	652 (29.44)		230 (38.31)	582 (28.82)	
≥2.4	1609 (69.97)	218 (65.74)	1391 (70.48)		238 (64.87)	1371 (70.56)		333 (61.69)	1276 (71.18)	

Note: P values are in bold for easy identification.

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; AF, animal fluency; DSST, digit symbol substitution test; LCP, low cognitive performance group, consisting of participants score the lowest 25th percentile; NCP, normal cognitive performance group; P, P value obtained from Pearson's chi-square test; n(%), weighted number of cases and percentage; PIR, poverty income ratio.

higher in the LCP group (13.37%) than that in the NCP group (4.84%) in the DSST test. The prevalence of stroke was higher in the LCP group than that in the NCP group across all three tests.

In terms of vitamin B intakes, the LCP group showed a higher percentage of people consuming <1.7 mg/day vitamin B₆ than the NCP group (59.52% vs 47.56%, $P=0.001$) when assessed by the DSST test. In all three cognitive assessments, the proportion of participants consuming vitamin B₉ <400 mcg/day in the LCP group was greater than that in the NCP group. As evaluated by the AF and DSST test, the proportion of low vitamin B₁₂ intake, <2.4 mcg/day, was significantly higher in the LCP group than that in the NCP group.

Vitamin B Intake and Cognitive Performance

To further investigate whether vitamin B₆, B₉, and B₁₂ intakes were associated with cognitive performance, logistic regression models were implemented. In terms of vitamin B intakes, vitamin B₆ intake <1.7 mg/day, vitamin B₉ intake <400 mcg/day, and vitamin B₁₂ intake <2.4 mcg/day were set as the reference groups in all analyses.

When assessing immediate and delayed memory recall by the CERAD test, after controlling for age, gender, race, education level, PIR, hypertension, heart failure, heart attack, and stroke, vitamin B₆ intake was not associated with the risk of LCP ($P=0.659$). Compared with the reference group, higher vitamin B₉ intake (≥ 400 mcg/day) was associated with a 0.312 decrease in the odds of LCP (OR: 0.688, 95% CI: 0.507–0.934, $P=0.018$). Similarly, higher vitamin B₁₂ consumption was also associated with a lower risk of LCP (OR: 0.695, 95% CI: 0.522–0.924, $P=0.014$) (Table 2, Figure 2).

The results were similar in the AF tests, with vitamin B₆ consumption not being associated with the risk of LCP while vitamin B₉ and vitamin B₁₂ intake relating to the odds of LCP. No significant relationship was observed between vitamin B₆ consumption and the risk of low categorical verbal fluency ($P=0.214$). Adequate vitamin B₉ intake was linked to a 33.8% lower risk of LCP (OR: 0.662, 95% CI: 0.445–0.986, $P=0.043$), in contrast to the reference group. Compared with the reference group, the odds of LCP decreased by 21.5% when people consumed ≥ 2.4 mg vitamin B₁₂ per day (OR: 0.785, 95% CI: 0.626–0.984, $P=0.036$) (Table 3, Figure 3).

The relationship between vitamin consumptions and the performance of processing speed, sustained attention, and working memory was evaluated using the DSST test. In model 2, controlling for age, gender, race, education level, marital status, PIR, alcohol use, diabetes, hypertension, heart failure, heart attack, and stroke, adequate vitamin B₆ intake (≥ 1.7 mg/day) was associated with a 31.7% lower risk of LCP (OR: 0.683, 95% CI: 0.505–0.925, $P<0.001$) compared with low vitamin B₆ intake (<1.7 mg/day). Similarly, higher B₉ consumption (≥ 400 mcg/day) was linked to a 0.465 decrease in the odds of LCP (OR: 0.535, 95% CI: 0.363–0.789, $P=0.003$). Compared with vitamin B₁₂ intake <2.4 mcg/day, vitamin B₁₂ intake ≥ 2.4 mcg/day indicated a 0.333 decrease in the odds of LCP (OR: 0.667, 95% CI: 0.521–0.855, $P=0.002$) (Table 4, Figure 4).

Table 2 Logistic Regression Models-CERAD Test

	OR ^a	95% CI	P	OR ^b	95% CI	P	OR ^c	95% CI	P
Vitamin B₆ (mg/d)									
<1.7	Ref			Ref			Ref		
≥ 1.7	0.999	0.724–1.378	0.995	0.941	0.660–1.343	0.731	1.080	0.760–1.535	0.659
Vitamin B₉ (mcg/d)									
<400	Ref			Ref			Ref		
≥ 400	0.695	0.512–0.945	0.022	0.655	0.482–0.889	0.008	0.688	0.507–0.934	0.018
Vitamin B₁₂ (mcg/d)									
<2.4	Ref			Ref			Ref		
≥ 2.4	0.804	0.610–1.059	0.116	0.721	0.541–0.962	0.027	0.695	0.522–0.924	0.014

Notes: ^aCrude model, unadjusted. ^bModel 1, adjusted for age and gender. ^cModel 2, adjusted for age, gender, race, education level. PIR, hypertension, heart failure, heart attack, and stroke. P values are in bold for easy identification.

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; PIR, poverty income ratio; OR, odds ratio; 95% CI, 95% confidence interval.

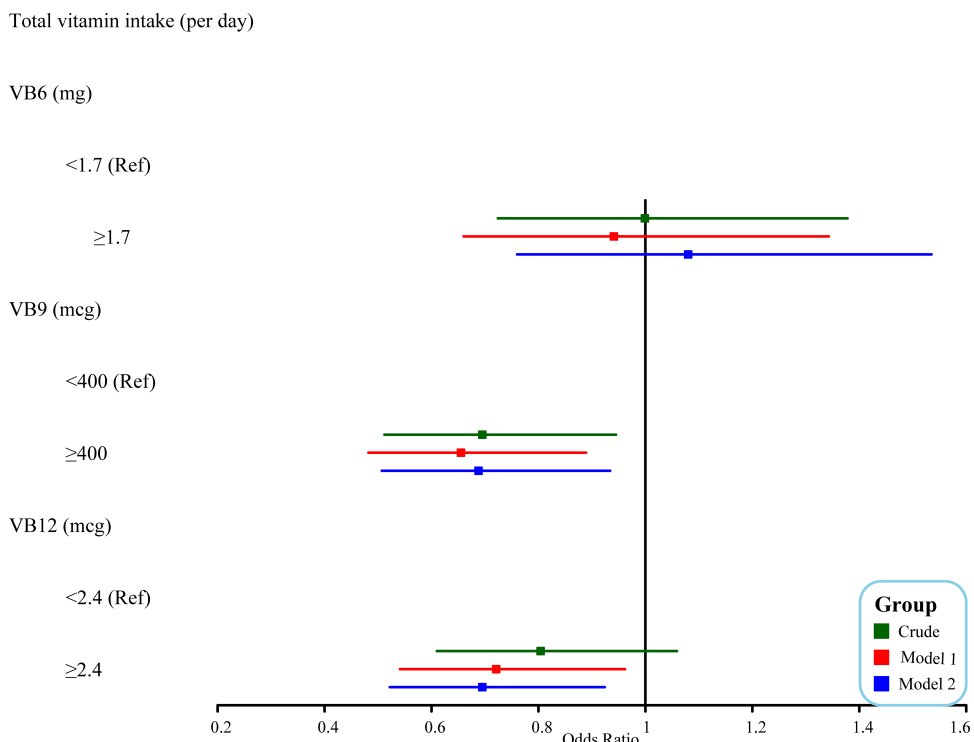


Figure 2 Forest plot of the CERAD test.

Abbreviations: CERAD, consortium to establish a registry for Alzheimer’s disease; PIR, poverty income ratio; VB6, vitamin B₆; VB9, vitamin B₉; VB12, vitamin B₁₂.

Vitamin B Intake and Cognitive Performance Across Different Sex, Race, and Age Groups

Subgroup analyses were performed to demonstrate if and how the relations between 3 B vitamins and cognitive performance varied across different sex, race, and age groups of the elderly. After covariate adjustment, under the CERAD test, adequate intake of vitamin B₆ was associated with lower odds of LCP than low vitamin B₆ intake among older adults aged 60–69 years (OR: 0.545, 95% CI: 0.364–0.816, *P*=0.004) and of non-Hispanic black race (OR: 0.652, 95% CI: 0.431–0.988, *P*=0.044), while it was not significantly related to the risk of LCP for people of other ages, both sexes, and other races (all *P*> 0.05). The inverse association between vitamin B₉ intake and odds of LCP was significant for people aged 60–69 years (OR: 0.362, 95% CI: 0.219–0.599, *P*<0.001), older men (OR: 0.568, 95% CI: 0.349–0.924, *P*=0.024) and women (OR: 0.532, 95% CI: 0.352–0.804, *P*=0.004), and the elderly of non-Hispanic white (OR: 0.502, 95% CI: 0.345–0.730, *P*<0.001). Older people of

Table 3 Logistic Regression Models-AF Test

	OR ^a	95% CI	<i>P</i>	OR ^b	95% CI	<i>P</i>	OR ^c	95% CI	<i>P</i>
Vitamin B₆ (mg/d)									
<1.7	Ref			Ref			Ref		
≥1.7	0.755	0.560–1.018	0.065	0.737	0.543–1.001	0.051	0.838	0.631–1.113	0.214
Vitamin B₉ (mcg/d)									
<400	Ref			Ref			Ref		
≥400	0.607	0.398–0.926	0.022	0.601	0.403–0.896	0.014	0.662	0.445–0.986	0.043
Vitamin B₁₂ (mcg/d)									
<2.4	Ref			Ref			Ref		
≥2.4	0.770	0.602–0.985	0.038	0.735	0.574–0.939	0.016	0.785	0.626–0.984	0.036

Notes: ^aCrude model, unadjusted. ^bModel 1, adjusted for age and gender. ^cModel 2, adjusted for age, gender, race, education level, marital status, PIR, alcohol use, hypertension, and stroke. *P* values are in bold for easy identification.

Abbreviations: AF, animal fluency; PIR, poverty income ratio; OR, odds ratio; 95% CI, 95% confidence interval.

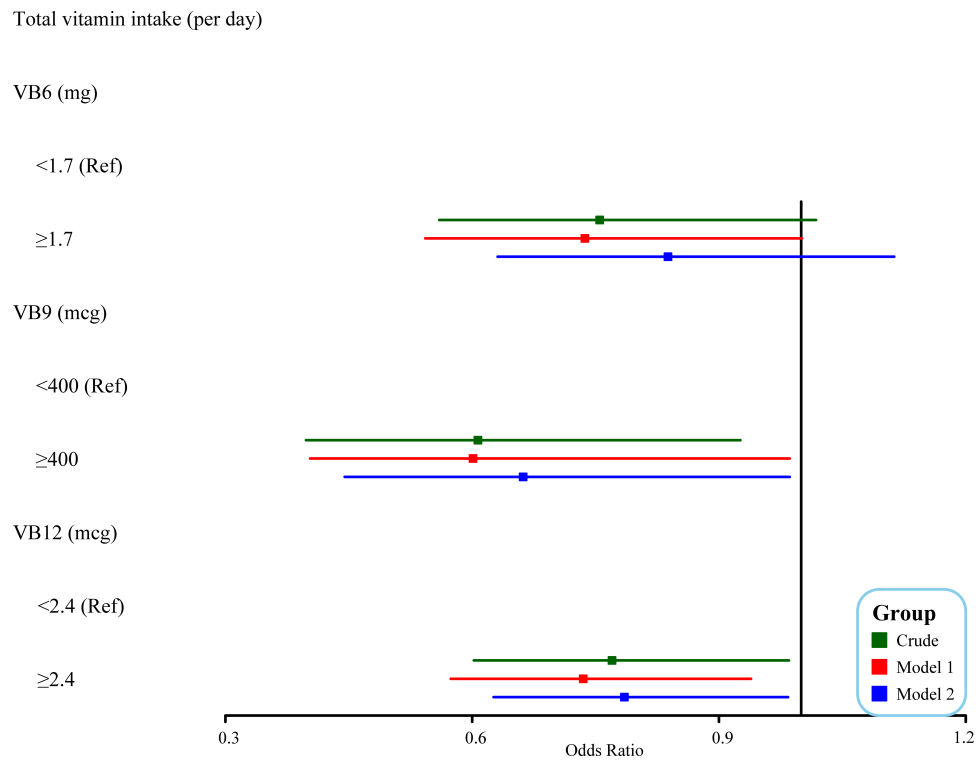


Figure 3 Forest plot of the AF test.

Abbreviations: AF, animal fluency; PIR, poverty income ratio; VB6, vitamin B₆; VB9, vitamin B₉; VB12, vitamin B₁₂.

60–69 (OR: 0.347, 95% CI: 0.214–0.536, $P < 0.001$), 70–79 (OR: 0.603, 95% CI: 0.370–0.981, $P = 0.042$) and ≥ 80 (OR: 0.658, 95% CI: 0.449–0.965, $P = 0.033$) years, of both male (OR: 0.501, 95% CI: 0.369–0.681, $P < 0.001$) and female (OR: 0.547, 95% CI: 0.387–0.773, $P = 0.001$) genders, of non-Hispanic white (OR: 0.501, 95% CI: 0.368–0.681, $P < 0.001$) and non-Hispanic black (OR: 0.578, 95% CI: 0.378–0.883, $P = 0.013$) races with adequate vitamin B₁₂ intake had lower risks of LCP, as compared with those with low vitamin B₁₂ intake (Table 5, Figure 5).

In the AF test, adequate intake of vitamin B₆ was associated with lower odds of LCP than low vitamin B₆ intake among older males (OR: 0.686, 95% CI: 0.488–0.964, $P = 0.031$), and older adults of non-Hispanic white race (OR: 0.515, 95% CI: 0.347–0.765, $P = 0.002$). People of 60–69 (OR: 0.364, 95% CI: 0.218–0.607, $P < 0.001$) and ≥ 80 (OR: 0.303, 95% CI: 0.124–0.737, $P = 0.010$) years, older men (OR: 0.579, 95% CI: 0.376–0.891, $P = 0.015$), and the elderly of non-Hispanic white race (OR: 0.409, 95% CI: 0.242–0.691, $P = 0.002$) having adequate vitamin B₉ consumption had decreased odds of LCP, in

Table 4 Logistic Regression Models-DSST Test

	OR ^a	95% CI	P ^e	OR ^b	95% CI	P	OR ^c	95% CI	P
Vitamin B₆ (mg/d)									
<math>< 1.7</math>	Ref			Ref			Ref		
≥ 1.7	0.617	0.479–0.795	<0.001	0.561	0.415–0.758	<0.001	0.683	0.505–0.925	<0.001
Vitamin B₉ (mcg/d)									
<math>< 400</math>	Ref			Ref			Ref		
≥ 400	0.518	0.370–0.727	<0.001	0.484	0.332–0.707	<0.001	0.535	0.363–0.789	0.003
Vitamin B₁₂ (mcg/d)									
<math>< 2.4</math>	Ref			Ref			Ref		
≥ 2.4	0.652	0.521–0.815	<0.001	0.583	0.459–0.739	<0.001	0.667	0.521–0.855	0.002

Notes: ^aCrude model, unadjusted; ^bModel 1, adjusted for age and gender; ^cModel 2, adjusted for age, gender, race, education level, marital status, PIR, alcohol use, diabetes, hypertension, heart failure, heart attack, and stroke. *P* values are in bold for easy identification.

Abbreviations: DSST, digit symbol substitution test; PIR, poverty income ratio; OR, odds ratio; 95% CI, 95% confidence interval.

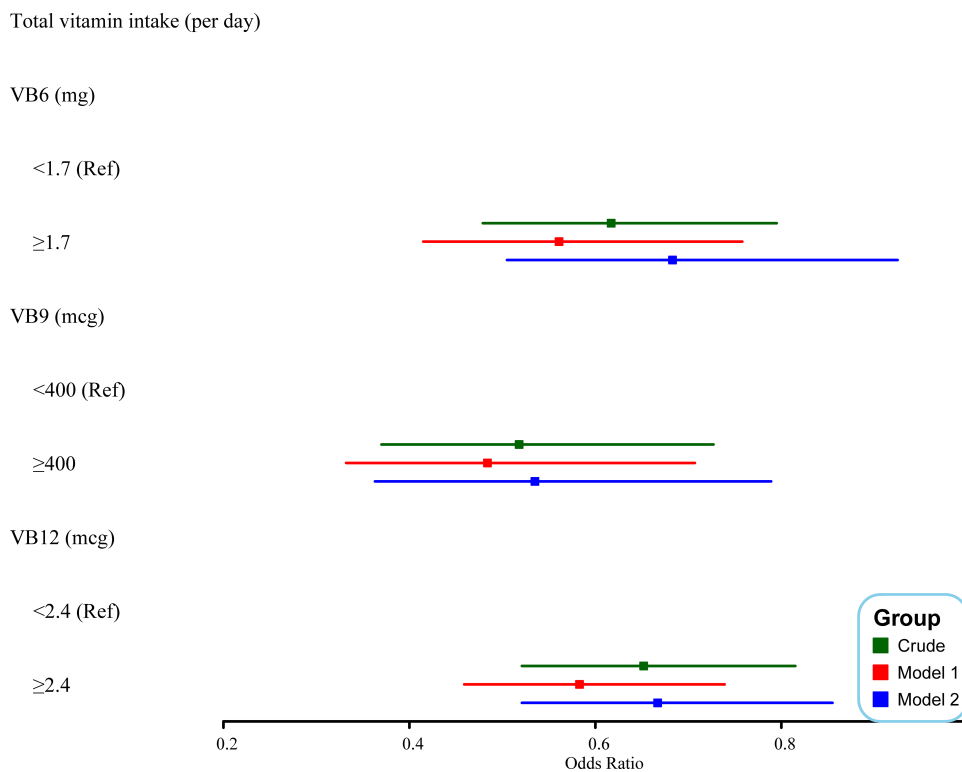


Figure 4 Forest plot of the DSST test.

Abbreviations: DSST, digit symbol substitution test; PIR, poverty income ratio; VB6, vitamin B₆; VB9, vitamin B₉; VB12, vitamin B₁₂.

contrast to those consuming low vitamin B₉. Vitamin B₁₂ intake was negatively correlated with the risk of LCP for individuals of 60–69 years (OR: 0.449, 95% CI: 0.308–0.654, *P*<0.001), elderly males (OR: 0.543, 95% CI: 0.410–0.720, *P*<0.001), the elderly of non-Hispanic white race (OR: 0.533, 95% CI: 0.371–0.766, *P*=0.001) (Table 6, Figure 6).

Table 5 Subgroup Analysis-CERAD Test

	Vitamin B ₆		Vitamin B ₉		Vitamin B ₁₂	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age						
60–69	0.545 (0.364–0.816)	0.004	0.362 (0.219–0.599)	<0.001	0.347 (0.214–0.563)	<0.001
70–79	0.631 (0.374–1.064)	0.082	0.644 (0.358–1.158)	0.137	0.603 (0.370–0.981)	0.042
≥80	1.096 (0.683–1.759)	0.694	0.630 (0.392–1.103)	0.056	0.658 (0.449–0.965)	0.033
Gender						
Male	0.724 (0.471–1.112)	0.135	0.568 (0.349–0.924)	0.024	0.501 (0.369–0.681)	<0.001
Female	0.797 (0.534–1.187)	0.254	0.532 (0.352–0.804)	0.004	0.547 (0.387–0.773)	0.001
Race						
Mexican American	0.652 (0.266–1.595)	0.318	0.896 (0.491–1.636)	0.698	0.861 (0.499–1.486)	0.561
Other Hispanic	0.926 (0.335–2.562)	0.877	0.603 (0.222–1.639)	0.305	0.575 (0.210–1.573)	0.266
Non-Hispanic White	0.725 (0.506–1.039)	0.079	0.502 (0.345–0.730)	<0.001	0.501 (0.368–0.681)	<0.001
Non-Hispanic Black	0.652 (0.431–0.988)	0.044	0.635 (0.330–1.222)	0.167	0.578 (0.378–0.883)	0.013
Other	1.084 (0.306–3.839)	0.895	0.685 (0.184–2.548)	0.555	0.463 (0.147–1.464)	0.179

Notes: Age groups, adjusted for gender, race, education level, PIR, hypertension, heart failure, heart attack, and stroke. Gender groups, adjusted for age, race, education level, PIR, hypertension, heart failure, heart attack, and stroke. Race groups, adjusted for age, gender, education level, PIR, hypertension, heart failure, heart attack, and stroke. *P* values are in bold for easy identification.

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; PIR, poverty income ratio; OR, odds ratio; 95% CI, 95% confidence interval.

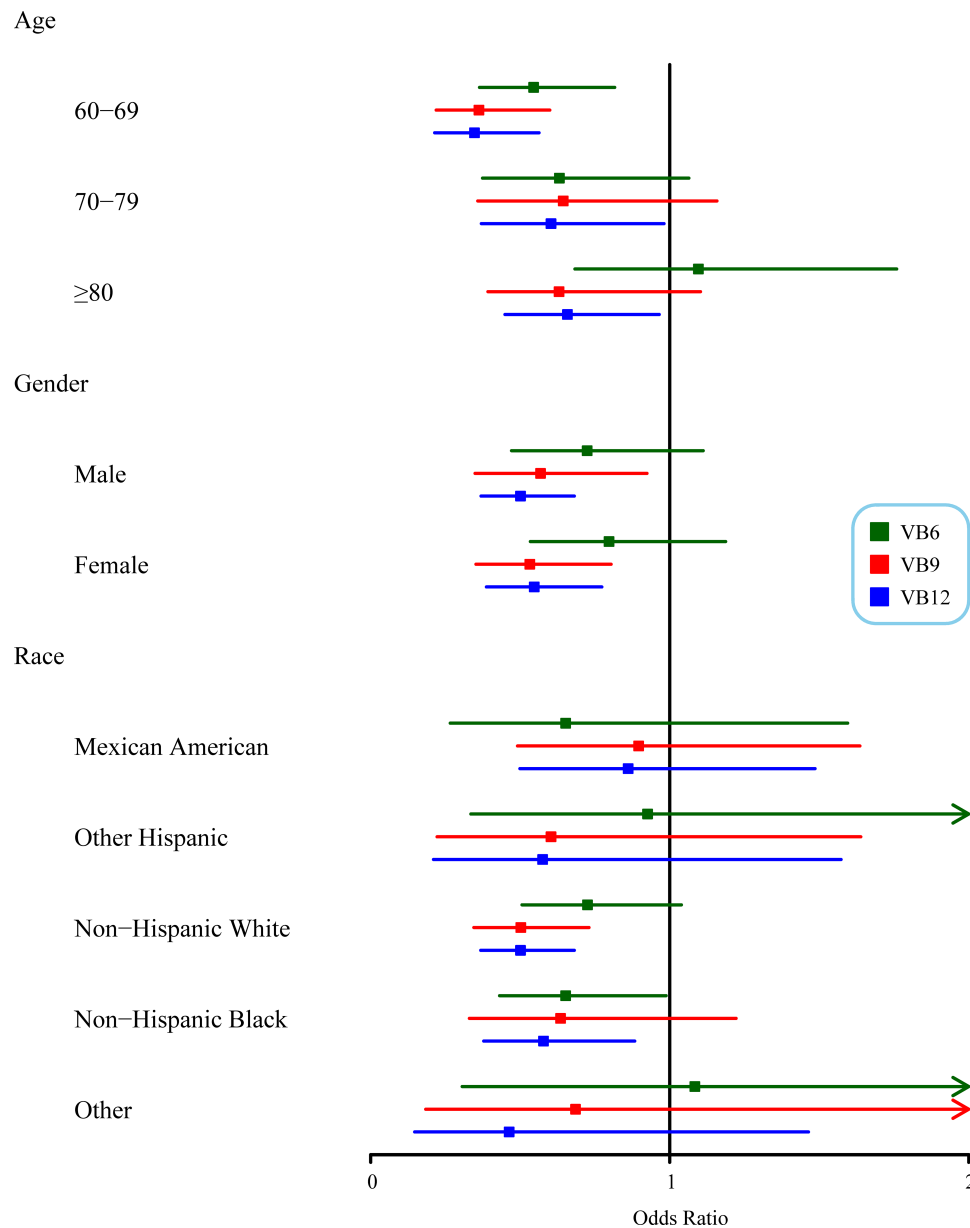


Figure 5 Forest plot of the CERAD test for subgroup analysis.

Abbreviations: CERAD, consortium to establish a registry for Alzheimer's disease; PIR, poverty income ratio; VB6, vitamin B₆; VB9, vitamin B₉; VB12, vitamin B₁₂.

As regards assessment by the DSST test, adequate vitamin B₆ intake was linked to a reduced risk of LCP in older adults of 70–79 years (OR: 0.459, 95% CI: 0.289–0.727, $P=0.002$), male gender (OR: 0.630, 95% CI: 0.412–0.963, $P=0.034$), and non-Hispanic white race (OR: 0.597, 95% CI: 0.389–0.917, $P=0.020$), in comparison with low vitamin B₆ intake. People of 60–69 (OR: 0.543, 95% CI: 0.340–0.868, $P=0.012$), 70–79 (OR: 0.525, 95% CI: 0.287–0.961, $P=0.038$) and ≥ 80 (OR: 0.518, 95% CI: 0.270–0.994, $P=0.048$) years, older men (OR: 0.437, 95% CI: 0.271–0.706, $P=0.001$), and the elderly of non-Hispanic white race (OR: 0.463, 95% CI: 0.257–0.834, $P=0.012$) having adequate vitamin B₉ consumption had lower odds of LCP than those consuming low vitamin B₉. Vitamin B₁₂ consumption was inversely associated with the risk of LCP for elderly people of male sex (OR: 0.573, 95% CI: 0.396–0.830, $P=0.004$) and non-Hispanic white race (OR: 0.650, 95% CI: 0.455–0.926, $P=0.019$) (Table 7, Figure 7).

Table 6 Subgroup Analysis-AF Test

	Vitamin B ₆		Vitamin B ₉		Vitamin B ₁₂	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age						
60–69	0.678 (0.443–1.036)	0.071	0.364 (0.218–0.607)	<0.001	0.449 (0.308–0.654)	<0.001
70–79	0.712 (0.479–1.058)	0.091	1.045 (0.604–1.809)	0.871	0.908 (0.649–1.271)	0.564
≥80	0.627 (0.328–1.198)	0.151	0.303 (0.124–0.737)	0.010	0.675 (0.384–1.187)	0.165
Gender						
Male	0.686 (0.488–0.964)	0.031	0.579 (0.376–0.891)	0.015	0.543 (0.410–0.720)	<0.001
Female	0.702 (0.492–1.001)	0.050	0.560 (0.297–1.056)	0.072	0.823 (0.520–1.302)	0.394
Race						
Mexican American						
Other Hispanic	0.982 (0.476–2.025)	0.959	0.634 (0.221–1.819)	0.379	0.585 (0.318–1.074)	0.081
Non-Hispanic White	0.515 (0.347–0.765)	0.002	0.409 (0.242–0.691)	0.002	0.533 (0.371–0.766)	0.001
Non-Hispanic Black	0.925 (0.578–1.482)	0.738	0.675 (0.431–1.058)	0.084	0.787 (0.542–1.144)	0.200
Other	1.534 (0.662–3.558)	0.302	0.961 (0.413–2.237)	0.924	0.554 (0.289–1.062)	0.073

Notes: Age groups, adjusted for gender, race, education level, marital status, PIR, alcohol use, hypertension, and stroke. Gender groups, adjusted for age, race, education level, marital status, PIR, alcohol use, hypertension, and stroke. Race groups, adjusted for age, gender, education level, marital status, PIR, alcohol use, hypertension, and stroke. P values are in bold for easy identification.

Abbreviations: AF, animal fluency; PIR, poverty income ratio; OR, odds ratio; 95% CI, 95% confidence interval.

Discussion

Our findings suggest that vitamin B₉ and vitamin B₁₂ intakes strongly correlate with cognitive performances among elderly participants. Individuals who consumed adequate vitamin B₉ and vitamin B₁₂ are associated with significantly better cognitive performances across all three cognitive tests, including immediate and delayed memory recall, categorical verbal fluency, processing speed, sustained attention, and working memory. Of the three cognitive tests, adequate vitamin B₉ and vitamin B₁₂ consumption display the greatest protective effects using the DSST test. Furthermore, adequate vitamin B₆ intake is only associated with better cognitive performance when evaluated by the DSST test, implying the prominent role of B vitamins in maintaining normal processing speed, sustained attention, and working memory among elderly people. Further, the relations between 3 B vitamins and cognitive performance vary across different sex, race, and age groups of people.

For vitamin B₆, results from the DSST test demonstrate that sufficient intake (≥1.7 mg/day) decreases the risk of low processing speed, sustained attention, and working memory by 31.7% when comparing to inadequate intake (<1.7 mg/day). When compared with low B₉ intake (<400 mcg/day), adequate B₉ consumption (≥400 mcg/day) is associated with 31.2%, 33.8%, and 46.5% decreases in the risk of low performances in immediate and delayed memory recall, categorical verbal fluency, and impaired processing speed, sustained attention, and working memory, respectively. Adequate vitamin B₁₂ intake also decreases the risk of low immediate and delayed memory recall, low categorical verbal fluency, and low processing speed, sustained attention, and working memory, corresponding to 30.5%, 21.5%, and 33.3% reductions.

The RDA of vitamin B₆, B₉, and B₁₂ intakes is the same among adults, while the RDA of vitamin B₆ is different among elderly males and females.²⁸ To maintain the consistency and simplicity of our analysis, we used ≥1.7 mg/day, the RDA for the elderly male population, as the reference for the adequate vitamin B₆ intake group. Since the RDA for the elderly female population was 1.5 mg/day, the low vitamin B₆ group contained a portion of female participants that consumed adequate vitamin B₆. Nevertheless, a significant reduction in the risk of LCP was still observed when partially including the females with adequate vitamin B₆ consumption in the DSST test, implying the significant protective effect of vitamin B₆ on the processing speed, sustained attention, and working memory among the elderly.

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is unlikely to lead to any risk of adverse health effects to almost all individuals in the general population.²⁸ The ULs of vitamin B₆ and vitamin B₉ are 100 mg/day and 1000 mcg/day, respectively, and no UL has been established for vitamin B₁₂. Excessive intake of B₉ may

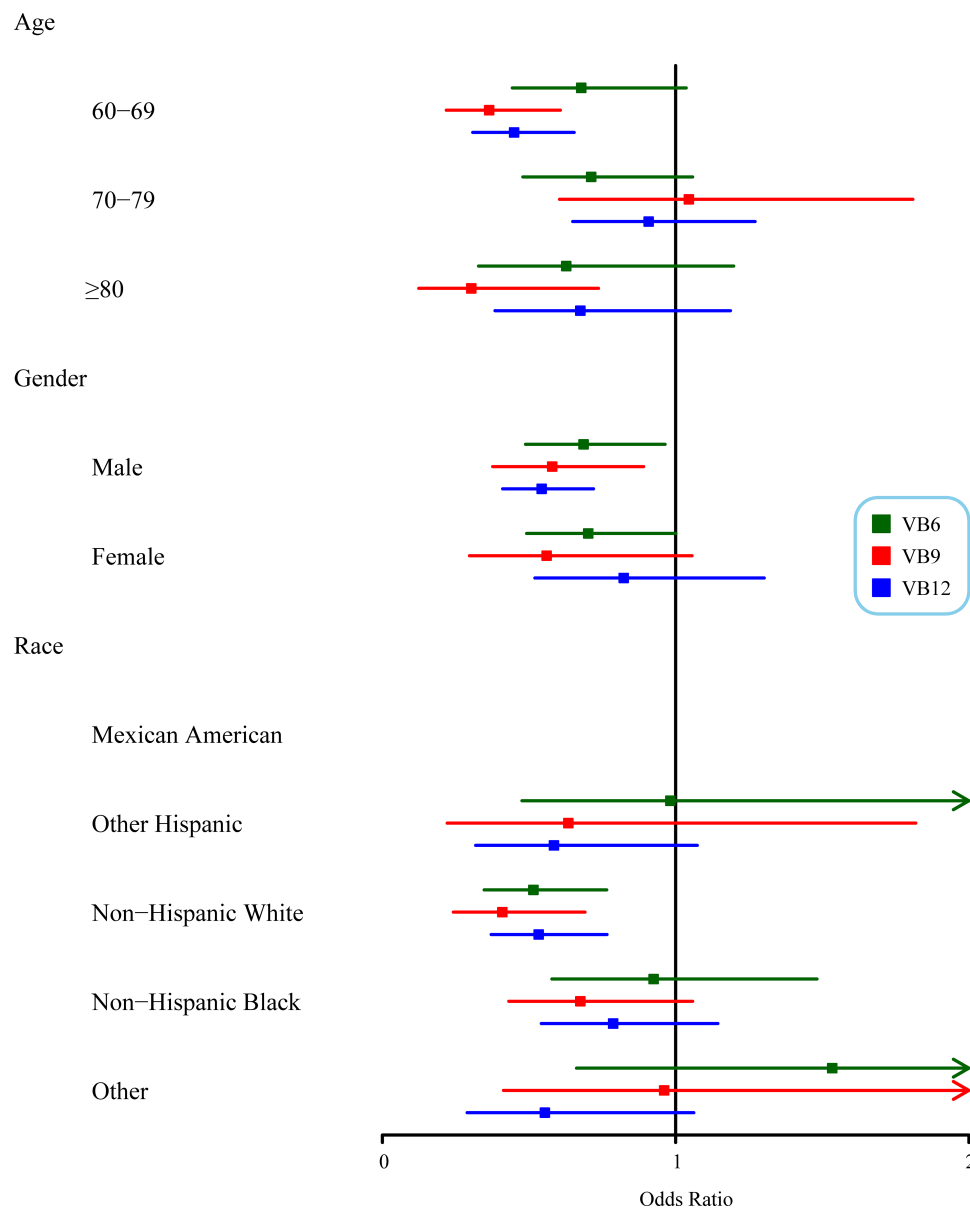


Figure 6 Forest plot of the AF test for subgroup analysis.

Abbreviations: AF, animal fluency; PIR, poverty income ratio; VB6, vitamin B₆; VB9, vitamin B₉; VB12, vitamin B₁₂.

lead to high serum unmetabolized folic acid and result in an unknown effect.²⁹ Therefore, future clinical study is required to determine the ideal range of vitamin B₆, B₉, and B₁₂ intakes for elders.

The strong association observed in our study was allied with previous cross-sectional research among aging men from the Veterans Affairs Normative Aging Study (VANAS).¹⁷ The VANAS study collected baseline plasma level and dietary intake of vitamin B₆, B₉, and B₁₂, and found a significant positive linear association between dietary intake and cognitive performance. A more recent animal study using the wild-type male mice discovered that low B₉ and low vitamin B₆/B₁₂ diets increased neuronal degeneration as compared with the control group,³⁰ implying the crucial impact of dietary B vitamin consumption on cognitive performances.

However, inconclusive results was also detected in studies that examined the effect of dietary or supplement vitamin B₆, B₉, and B₁₂ intakes on cognitive functions. Kado et al examined the plasma vitamin B₆, B₉, and B₁₂ concentrations in relation to cognitive function among community-dwelling elders aged 70–79 years by conducting a cross-sectional and longitudinal analysis, the result of which only revealed an association between plasma B₉ level and cognitive functions

Table 7 Subgroup Analysis-DSST Test

	Vitamin B ₆		Vitamin B ₉		Vitamin B ₁₂	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age						
60–69	0.770 (0.482–1.229)	0.263	0.543 (0.340–0.868)	0.012	0.660 (0.421–1.035)	0.069
70–79	0.459 (0.289–0.727)	0.002	0.525 (0.287–0.961)	0.038	0.709 (0.439–1.143)	0.152
≥80	1.017 (0.579–1.787)	0.951	0.518 (0.270–0.994)	0.048	0.711 (0.427–1.183)	0.181
Gender						
Male	0.630 (0.412–0.963)	0.034	0.437 (0.271–0.706)	0.001	0.573 (0.396–0.830)	0.004
Female	0.768 (0.510–1.158)	0.200	0.702 (0.418–1.180)	0.175	0.800 (0.566–1.130)	0.198
Race						
Mexican American						
Other Hispanic	1.637 (0.678–3.957)	0.258	0.707 (0.336–1.485)	0.342	0.564 (0.252–1.260)	0.153
Non-Hispanic White	0.597 (0.389–0.917)	0.020	0.463 (0.257–0.834)	0.012	0.650 (0.455–0.926)	0.019
Non-Hispanic Black	0.705 (0.458–1.087)	0.109	0.622 (0.349–1.111)	0.105	0.685 (0.465–1.010)	0.056
Other	0.815 (0.260–2.557)	0.713	0.621 (0.202–1.906)	0.387	1.120 (0.475–2.637)	0.787

Notes: Age groups, adjusted for gender, race, education level, marital status, PIR, alcohol use, diabetes, hypertension, heart failure, heart attack, and stroke. Gender groups, adjusted for age, race, education level, marital status, PIR, alcohol use, diabetes, hypertension, heart failure, heart attack, and stroke. Race groups, adjusted for age, gender, education level, marital status, PIR, alcohol use, diabetes, hypertension, heart failure, heart attack, and stroke. P values are in bold for easy identification.

Abbreviations: DSST, digit symbol substitution test; PIR, poverty income ratio; OR, odds ratio; 95% CI, 95% confidence interval.

but not between vitamin B₆ and B₁₂ levels and cognitive functions.¹⁶ A randomized control trial research studied the efficacy of multivitamin supplementation containing vitamin B₆, folic acid, and vitamin B₁₂ among elderly Asian patients with Alzheimer’s disease. The cognitive function did not change appreciably with B vitamin supplementation.³¹ Because of the inconsistent findings, a previous review study suggested that the short-term benefit of vitamin B₆ in improving cognitive functions was not supported by strong evidence.³²

Several factors may contribute to the discrepancies in research results, including distinct target populations, dissimilar variable measurements, different cognitive evaluation standards, and varied study designs. It is possible that vitamin B₆, B₉, and B₁₂ intakes establish a more robust relationship with cognitive performances among elderly people. Thus, Thus, larger-scale and multi-center studies of high quality are warranted to confirm our findings or further clarify the effects of B vitamins on the cognitive performance of the elderly.

Some potential mechanisms could be considered when interpreting the association between vitamin B₆, B₉ and B₁₂ intakes and particular cognitive domains evaluated by the CERAD, AF and DSST tests among the elderly. Vitamin B₆ consumption can improve memory status by affecting the function of N-methyl-D-aspartate receptors in addition to enhancing the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus.^{33,34} Vitamin B₆ deficiency relates to cognitive deficits and changes in brain structure.³⁵ Greater intake of vitamin B₆ is associated with an increased gray matter volume in the upper frontal gyrus in healthy older adults.³⁶ A positive correlation between vitamin B₆ intake and greater local cortical folds was also found in the inferior frontal gyrus and other parts of the brain region.³⁷ Supplementation with vitamin B₆ may result in better preservation of gray matter in patients with poor cognitive performance. Vitamin B₆ might also relate to the structural integrity of white matter tracts associated with the left middle frontal gyrus, which is linked to processing speed.³⁸ Vitamin B₉ was also shown to be positively associated with processing speed, memory recall and verbal fluency,³⁹ while limited evidence focuses on the underlying mechanisms. In the nervous system, B₁₂ is a coenzyme necessary for myelin synthesis, and its deficiency is linked to attention deficits, memory impairment, and dementia.⁴⁰ Vitamin B₁₂ is involved in acetylcholine synthesis in the brain. Acetylcholine is an essential neurotransmitter for the formation of memory traces and the physiological basis of long-term memory.⁴¹ Vitamin B₁₂ is also involved in the synthesis of monoamine neurotransmitters, which play a role in executive function.⁴² These 3 B vitamins may correlate with the influences of anti-N-Hcy-protein autoantibodies on attention and processing speed.⁴³ More research is underscored to explore more about the association mechanism of vitamin B and different dimensions of cognitive performance. Of note, the DSST was more sensitive to Vitamin B levels than the other

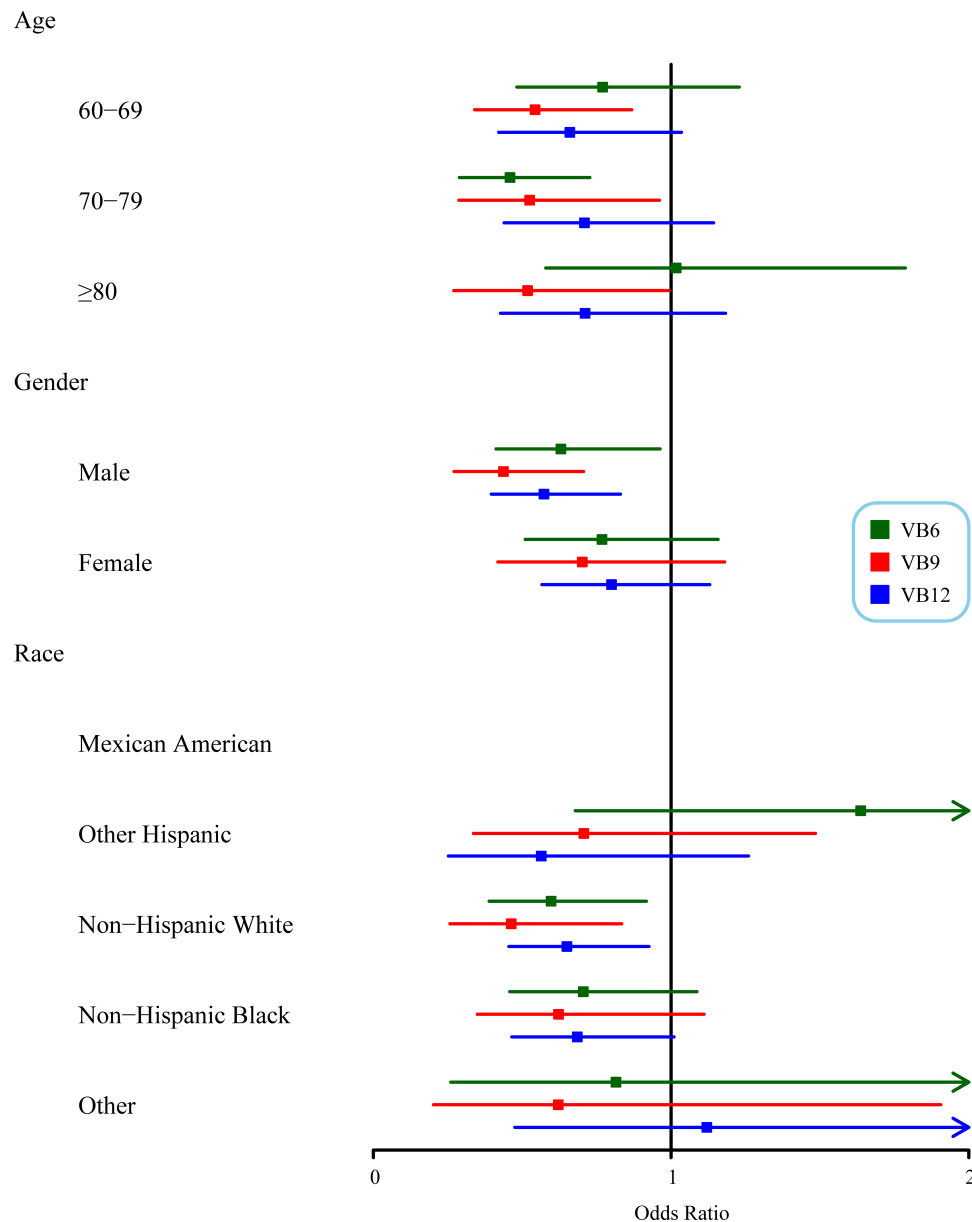


Figure 7 Forest plot of the DSST test for subgroup analysis.

Abbreviations: DSST, digit symbol substitution test; PIR, poverty income ratio; VB6, vitamin B₆; VB9, vitamin B₉; VB12, vitamin B₁₂.

two tests. We hypothesized that this may be attributed to more cognitive domains assessed by the DSST test, and vitamin B₆, B₉ and B₁₂ levels were more significantly associated with cognitive domains in the DSST test than those in the other two tests.

Currently, limited publications focused on specific cognitive domains affected by vitamin B deficiencies, so this study would add to the body of evidence, with a relatively large nationally representative data. Our study uncovered generalizable findings of the therapeutic potential of dietary vitamin B₆, B₉, and B₁₂ intakes in managing LCP among the elderly population. Besides, subgroup analyses exhibited that the relations between 3 B vitamins and cognitive performance vary across different sex, race, and age groups of people. The limitations of our study mainly lied in the cross-sectional design: i) our study could not establish causality between vitamin B intake and cognitive performance; ii) within-person variations of dietary vitamin B intake may exist.

Conclusion

Vitamin B₉ and B₁₂ intakes are strongly associated with LCP odds among elderly participants. Vitamin B₆ consumption is linked with the DSST test that captures processing speed, sustained attention, and working memory. Adequate dietary vitamin B₉ and B₁₂ intakes correlate with lower risk of LCP among elders, corresponding to an approximately 30% reduction in LCP odds when assessed by the CERAD, AF, and DSST tests. Longitudinal studies are needed to show causation between vitamin B₆, B₉ and B₁₂ intakes and cognitive performance.

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Disclosure

The authors reported no conflicts of interest in this work.

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