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Association between vitamin B2 intake and cognitive performance among older adults: a cross-sectional study from NHANES

Kangkang Ji[1,5], Minli Sun[2,5], Li Li[1], Ye Hong[3], Shengkai Yang[1] & Yueju Wu[1,4]✉

The impact of vitamin B2 (riboflavin) intake on cognitive performance among older adults in the United States (US) remains inadequately understood. This study aimed to explore the association between vitamin B2 intake and cognitive performance among non-institutionalized elderly people in the US. Weighted logistic regression was used to evaluate the association between vitamin B2 intake and cognitive performance. Vitamin B2 intake was determined from the mean of two 24-hour dietary recall interviews. Three cognitive ability assessment tests, namely the Immediate Recall Test (IRT), Animal Fluency Test (AFT), and Digit Symbol Substitution Test (DSST), were performed. Participants included all older adults over 60 who underwent cognitive scoring, with cut-offs defined based on the lowest quartile (25th percentile) for each test (the cut-offs for the three scores were 15.625, 12, and 33, respectively). Sensitivity analysis, including dose-response curves, subgroup analyses, interaction effects, per 1 standard deviation (SD), recommended dietary allowance (RDA), and residual energy model analysis, were performed to solidify the solid association between vitamin B2 and cognitive performance. A total of 2893 individuals aged over 60 were included, with a mean age of 69 (7) years, and 46% were men. There was a significant association between vitamin B2 intake and all three cognitive scores (IRT, Odds Ratio = 0.77, 95% confidence interval: [0.65,0.92]; AFT, 0.75, [0.64,0.88]; DSST, 0.72, [0.59,0.88]). Moreover, vitamin B2 intake above the RDA reduced the risk of low cognitive performance (IRT, 0.66, [0.46,0.93]; AFT, 0.83, [0.62,1.11]; DSST, 0.65, [0.45,0.92]) compared to intake below the RDA. Dose-response curves indicated that higher vitamin B2 intake was negatively associated with the risk of low cognitive performance. Physical activity may modify the association between vitamin B2 and cognitive performance. Vitamin B2 intake was positively associated with cognitive performance among older adults. Adequate vitamin B2 intake could help protect cognitive function.

Keywords Vitamin B2, Riboflavin, Cognitive performance, Recommended dietary allowance, Dose-response

With the demographic shift towards older populations occurring in nearly every country, cognitive impairment is emerging as a significant healthcare burden for older society[1,2]. Cognitive impairment is prevalent among older adults[3] and is an essential precursor to dementia[4]. Dementia typically follows a phase of mild cognitive impairment, during which cognitive decline beyond normal aging is evident, though daily function is not yet significantly impaired[5]. Addressing cognitive impairment at the preclinical stage can delay the progression to dementia[6]. Alzheimer's disease and related dementias pose considerable challenges to healthcare systems globally[7]. In 2021, over 50 million people globally lived with dementia, with associated costs exceeding $800 billion[8]. By 2050, it is estimated that two billion people will be aged 60 years or over, with 131 million suffering from dementia[9]. Cognitive impairment, frequently overlooked, profoundly impacts daily life activities[10]. Therefore, prioritizing cognitive health in the older population has significant social and medical implications.

[1]Department of Clinical Medicine Research Centre, Binhai County People's Hospital, Yancheng 224000, China. [2]Department of Geriatrics, Binhai County People's Hospital, Yancheng 224000, China. [3]Department of Clinical Nutrition, Binhai County People's Hospital, Yancheng 224000, China. [4]Department of Neurology, Binhai County People's Hospital, Yancheng 224000, China. [5]These authors contributed equally Kangkang Ji and Minli Sun. ✉email: yuluoweilan@163.com

Improved nutrition is beneficial in preventing cognitive decline[11,12]. Vitamin B2 (riboflavin) is an essential member of the vitamin family, and its intake has been widely associated with cognitive performance[13]. Vitamin B2 improves cognitive function through its anti-oxidative and anti-inflammatory properties[14]. A two-year prospective cohort study suggested that dietary riboflavin improves multidomain cognitive function in a middle-aged and older population[15]. A recent cross-sectional study found that higher vitamin B2 intake correlates with higher cognitive scores[16]. Specifically, the highest quartile of vitamin B2 intake was associated with a 45.1-fold increase in DSST test scores compared to the lowest quartile[16]. Moreover, higher dietary riboflavin intake in midlife has been associated with a reduced risk of cognitive impairment in later life[17]. However, vitamin B2 intake has not been studied in detail, with previous studies not accounting for total energy intake and standardized vitamin B2 levels. There is a notable lack of validated cross-sectional studies examining the effects of vitamin B2 intake above and below the recommended daily allowance (RDA) on cognitive performance. Moreover, there is no report of potential interacting factors influencing the association between vitamin B2 and cognitive performance. Furthermore, no studies have quantified changes in the risk of cognitive impairment due to vitamin B2 intake from a dose-response perspective. Based on these gaps, vitamin B2 intake has been hypothesized to influence cognitive function and intake more than the RDA could reduce the risk of low cognitive performance.

Methods

Data source and study population

This cross-sectional analysis utilized data from two cycles of National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2014. The NHANES survey employs a stratified multistage probability sampling design to ensure the representativeness of the non-institutionalized civilian population in the US. Approximately 10,000 participants are interviewed and tested annually. The data for this study included information from structured home interviews and physical assessments conducted at the Mobile Examination Centre (MEC). The National Center for Health Statistics (NCHS) Research Ethics Review Committee approved the study protocol, and written informed consent was obtained from all participants before enrolment. This study adhered to the STROBE reporting guidelines for strengthening the reporting of observational studies in epidemiology. As the analysis involved secondary data and did not fall under the "human studies" category, further approval from the Centers for Disease Control and Prevention (CDC) Institutional Review Board was not required[18]. This study included 2,893 participants aged $\geq$ 60 years, following the screening and exclusion criteria outlined in the literature (Fig. 1).

Variables

The Cognitive Functioning Module of NHANES 2011–2014 was used to assess the cognitive ability of the participants, as detailed on the NHANES website (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/CFQ_H.htm). Cognitive performance was assessed using three functional tests, namely the Immediate Recall Score Test (IRT), Animal Fluency Test (AFT), and Digit Symbol Substitution Tent (DSST)[19]. All older adults > 60 years participated in the cognitive scoring; the cut-off was defined based on the lowest quartile (25th percentile) of

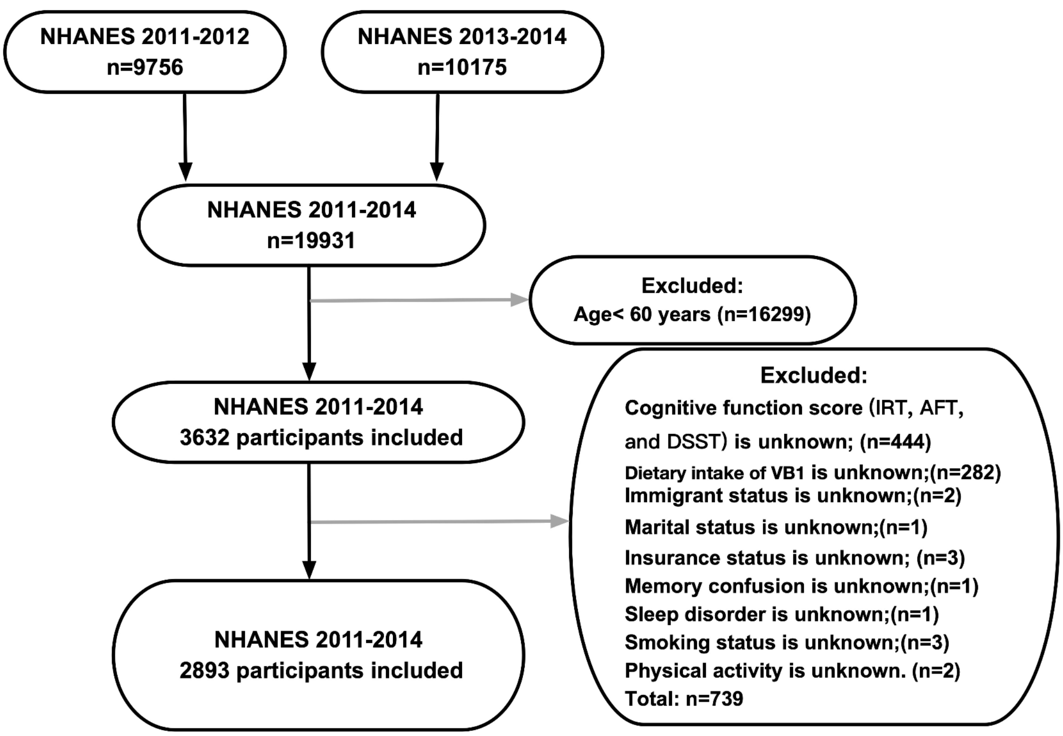

Fig. 1. Flowchart depicting the patient selection in this study.

test scores (the cut-off for the three scores was 15.625, 12, and 33). Finally, using this cut-off, the sub-sample (2893) was categorized into groups with low cognitive and normal cognitive performance. Vitamin B2 intake information was derived from the mean of two 24-hour dietary recall interviews. The mean intake from the first and second days was calculated. Vitamin B2 was divided into quartiles (Q1, 0.114 < vitamin B2 < 1.297 mg/d; Q2, 1.297 ≤ vitamin B2 ≤ 1.779 mg/d; Q3, 1.781 ≤ vitamin B2 ≤ 2.332 mg/d; Q4, 2.333 ≤ vitamin B2 ≤ 13.726 mg/d) for analysis. Several important potential confounders such as age, race, and gender based on recent literature[20–22]. Participants were categorized into three age groups: 60–69, 70–79, and ≥ 80 years. Gender was classified as male or female. Race was categorized according to the US population composition. Education was classified as "below high school (< HS)," "high school diploma," and "college or higher diploma." Immigration status was determined by the question "Born in the United States or not?" The poverty income ratio (PIR) is calculated by dividing family (or individual) income by a specific poverty guideline to the year of the survey and is used as a measure of socio-economic status[23]. In this study, PIR was further categorized as PIR < 1, 1–3, and > 3. Health insurance status was determined based on the response to the question, "Do you have health insurance or any other type of health care plan?" Memory confusion was assessed with the question, "In the past 12 months, have you experienced confusion or memory loss that has occurred more often or has gotten worse?". Sleep disorder was identified based on the question, "Did your physician tell you that you have a sleep disorder" or "Did you tell your physician that you have a sleep disorder?" Alcohol consumption was categorized into four groups: "Never", "Moderate" (≤ 2 drinks/day [men]; ≤1 drink/day [women]), "Heavy" (3–4 drinks/day [men]; 2–3 drinks/day [women]), and "Binge" (≥ 5 drinks/day [men]; ≥4 drinks/day [women])[24–26]. Smoking status was classified as "No" and "Yes". Physical activity was grouped based on the intensity of work or recreational activities: "Sedentary," "Moderate," and "Vigorous." Waist circumference was classified as "Normal" (< 94 cm [men]; < 80 cm [women]), "Moderate" (94–102 cm [men]; 80–88 cm [women]), and "High" (≥ 102 cm [men]; ≥88 cm [women])[27,28].

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as numerical values (percentages). Baseline characteristics were noted according to the three cognitive tests and compared using chi-square tests, analyses of variance (ANOVA), and Tukey's tests, as appropriate. Weighted logistic regression analysis was conducted to assess the association between vitamin B2 intake and the three cognitive test scores, with effect values expressed as "odds ratios (ORs) + 95% confidence intervals (CIs)". Stratified and interaction analyses were performed using baseline characteristics as moderators to assess potential differences in the impact of vitamin B2 intake on cognitive performance among different subgroups. A nutrient residual energy model was constructed to determine the precise effect of vitamin B2 on cognitive performance. A simple linear regression model was created with total energy intake as the independent variable and vitamin B2 intake as the dependent variable to calculate the energy-corrected residuals for vitamin B2. Subsequently, the predicted value of vitamin B2 corresponding to the mean energy intake of the total population was added to the residuals for each individual to obtain their adjusted vitamin B2 intake. The multivariable logistic regression model included adjusted vitamin B2 intake and total energy as independent variables.

In this study, cross-sectional analyses were conducted using nationally representative data from NHANES to explore the association between vitamin B2 intake and cognitive performance in the older population. The effects of standardized vitamin B2 intake (per 1 standard deviation [SD]) on cognitive performance were examined. The study was focused on validating the impact of vitamin B2 intake above and below the RDA on cognitive performance. Subgroup and interaction analyses were employed to determine which groups are more likely to benefit from vitamin B2 intake regarding cognitive performance. Moreover, potential trends in the effect of vitamin B2 intake on the risk of low cognitive function were explored using dose-response curves, and the association was further examined using a nutritional residual energy adjustment model. This approach provides a framework for optimizing vitamin B2 intake to improve cognitive health in older adults. Three models were constructed in this study. Model 1 adjusted for age and gender; Model 2 adjusted for age, gender, race, education level, marital status, PIR, and immigrant status; and Model 3 adjusted for all variables in Model 2 with additional adjustments for waist circumference, physical activity, alcohol consumption, and memory confusion. For the nutrition residual energy model, total energy intake was adjusted based on the existing adjustment variables. All statistical analyses were performed using R version 4.2.1 (R statistical computing program) and Stata SE. Statistical significance was set at $P < 0.05$ (bilateral). In doing the different test analyses, we have adjusted for multiple comparisons and used the adjusted p-value as the basis for statistical significance.

Sensitivity analysis

Several sensitivity analyses were conducted. First, the validity of the association was assessed by analyzing the data in different forms (vitamin B2 quartiles). Second, the data were standardized by introducing 1 SD (0.897 mg) unit to evaluate the stability of the association. Third, subgroup analyses were performed to determine which groups were more likely to benefit from vitamin B2 intake regarding cognitive performance. Moreover, restricted cubic spline curves (RCS) were used to investigate the dose-response association between dietary vitamin B2 intake and the risk of cognitive impairment, adjusted for multiple covariates, including age, gender, race, education level, marital status, PIR, immigrant status, waist circumference, physical activity, alcohol consumption, and memory confusion. Furthermore, the RDA (recommended dietary allowance) parameter to categorize vitamin B2 based on the RDA thresholds (men: 1.3 mg/d, women 1.1 mg/d): (1) VB intake < RDA and (2) VB2 intake ≥ RDA. The effects of these two different VB2 intake levels on cognitive performance were assessed by comparison. Finally, the association between vitamin B2 and cognitive performance was further analyzed using nutritional (vitamin B2) energy residuals.

Results

Population characteristics

A total of 2,893 participants aged ≥ 60 years were included in this study, representing approximately 57.08 million individuals in the US with similar characteristics. The ratio of participants with average cognitive performance to those with low cognitive performance, as assessed by the three cognitive tests, was approximately 3:1 (IRT, Normal vs. Low = 2198 vs. 695; AFT, 2193:700; DSST, 2198:695). The median weighted age of the participants was 69 (7) years, with 46% being men. Non-Hispanic whites constituted the majority, comprising 78% of the study population. The majority of participants were U.S.-born residents, with only 11% being immigrants. Over 90% of the participants were non-poor (PIR < 1). Regarding waist circumference, 67% of older adults were classified as obese. Moreover, individuals with poor cognitive performance tended to have confused memories (IRT, Normal vs. Low = 22% vs. 10%; AFT, 23% vs. 11%; DSST, 23% vs. 11%), engaged in little physical activities (Sedentary, IRT, Normal vs. Low = 49% vs. 36%; AFT, 57% vs. 35%; DSST, 60% vs. 35%) and had a low total energy intake (IRT, Normal vs. Low = 1698 vs. 1902; AFT, 1627 vs. 1912; DSST, 1581 vs. 1911) (Table 1).

Association between vitamin B2 intake and low cognitive performance

Multivariable logistic regression was performed on all potential confounders to examine further the association between vitamin B2 and cognitive performance among older adults. Forest plots displayed the ORs and 95% Cl of each variable's effect on cognitive performance (Fig. 2, Table S1). The impact of total energy intake on cognitive performance was almost negligible (OR value = 1.0), although it was substantial. Cross-sectional modeling investigated the association between vitamin B2 and cognitive performance, adjusting for candidate variables other than total energy intake. In the final adjusted model, vitamin B2 intake showed a considerable association (IRT, OR = 0.77, 95% CI: [0.65, 0.92], $P = 0.004$; AFT, 0.75, [0.64, 0.88], $P < 0.001$; DSST, 0.72, [0.59, 0.88], $P = 0.001$) with cognitive performance (Table 2).

Subgroup and interaction analyses

Subgroup analyses were performed to explore further which groups are more likely to benefit from vitamin B2 intake regarding cognitive function. For IRT, individuals aged 60–69 years (OR and 95% Cl: 0.67 [0.48, 0.92]), non-Hispanic Black individuals (0.52 [0.37, 0.73]), those with < HS (0.69 [0.52, 0.93]), individuals with PIR > 3 (0.69 [0.52, 0.90]), average waist circumference (0.61 [0.40, 0.95]), and those who never drank alcohol (0.60 [0.44, 0.82]) were more likely to benefit from vitamin B2 intake. For AFT, the benefiting groups were those aged ≥ 80 years of age (0.63 [0.45, 0.88]), men (0.67 [0.55, 0.81]), non-Hispanic Black individuals (0.69 [0.51, 0.92]), those with < HS (0.59 [0.45, 0.77]), individuals with a PIR > 3 (0.64 [0.45, 0.92]), moderate waist circumference (0.64 [0.43, 0.93]), and moderate drinkers (0.66 [0.48, 0.92]). For DSST, the benefitting groups included those aged 70–79 years of age (0.63 [0.44, 0.89]), non-Hispanic Whites (0.69 [0.52, 0.92]), individuals with a college education (0.57 [0.40, 0.81]), non-married individuals (0.65 [0.51, 0.84]), those with a PIR > 3 (0.51 [0.31, 0.82]), those with no memory confusion (0.67 [0.54, 0.83]), those who never drank alcohol (0.56 [0.39, 0.80]), and those engaged in moderate physical activity (0.67 [0.49, 0.92]) (Fig. 3 and Table S2). Interestingly, for all three cognitive tests, physical activity was identified as a potential interaction variable (P for interaction was < 0.001, < 0.001, and 0.004 for IRT, AFT, and DSST, respectively) that may modify the association between vitamin B2 intake and cognitive performance (Fig. 3 and Table S2).

Sensitivity analysis

Several sensitivity analyses were conducted to ensure the accuracy of the findings. First, a quartile analysis of vitamin B2 intake was performed (Q1 [0.114, 1.297 mg], Q2 [1.297, 1.779 mg], Q3 [1.781, 2.332 mg], and Q4 [2.333, 13.73 mg]). A significant association was found between vitamin B2 intake and cognitive performance for the AFT and DSST tests (AFT, Q2 vs. Q1: OR [95% Cl], 0.81 [0.51, 1.30], Q3 vs. Q1: 0.75 [0.47, 1.19], and Q4 vs. Q1: 0.58 [0.32, 1.03], $P = 0.006$; DSST, Q2 vs. Q1: 0.74 [0.45, 1.22], Q3 vs. Q1: 0.76 [0.51, 1.13], and Q4 vs. Q1: 0.45 [0.28, 0.74], $P < 0.001$). Trend analyses indicated that higher vitamin B2 intake was associated with a lower risk of low cognitive performance (P for trend was 0.005, 0.004, and 0.001 for IRT, AFT, and DSST, respectively). Secondly, the data for vitamin B2 intake were standardized, and standard error values were calculated (1 SD = 0.897 mg), determining that the association remained solid (IRT, OR [95% Cl] P, 0.79 [0.68, 0.93] 0.004; AFT, 0.77 [0.67, 0.89] < 0.001; DSST, 0.74 [0.62, 0.89] 0.001). The RDA was introduced; an intake greater than or equal to the RDA was observed to be more beneficial in protecting cognitive function in older adults (IRT, ≥RDA vs. < RDA, OR [95% Cl] P, 0.66 [0.46, 0.93] 0.017; DSST, 0.65 [0.45, 0.92] 0.014) (Table 2). Subsequently, the effect of vitamin B2 intake on the risk of low cognitive performance was visualized using a dose-response curve, and a negative association was found between vitamin B2 intake and the risk of low cognitive performance (Fig. 4). Finally, by constructing a nutritional residual energy model, adequate intake of vitamin B2 was found to be possibly associated with low cognitive risk (IRT, OR [95% Cl], 0.92 [0.76, 1.12]; AFT, 0.88 [0.73, 1.05]; DSST, 0.94 [0.75, 1.18]), although the results were not significant (Table 3).

Discussion

This national cross-sectional study used weighted logistic regression and multiple sensitivity analyses to reveal an association between dietary vitamin B2 intake and cognitive performance in older Americans. Vitamin B2 intake above the RDA protects cognitive health and is negatively associated with the risk of low cognitive performance. Subgroup analyses identified which groups, such as the affluent class (PIR > 3), were more likely to benefit from vitamin B2 intake regarding cognitive performance. Interaction analyses indicated that physical activity may influence the association between vitamin B2 intake and cognitive performance. The consistency of the findings was confirmed through several sensitivity analyses.

Variables	Overall *N*[1] = 2893	IRT			AFT			DSST		
		Normal	Low	*P*[2]	Normal	Low	*P*[2]	Normal	Low	*P*[2]
Age (years, mean, sd)	69 (7)	68 (6)	73 (7)	**< 0.001**	69 (7)	72 (7)	**< 0.001**	69 (7)	73 (7)	**< 0.001**
Male, n (%)	1421 (46)	1007 (44)	414 (54)	**0.003**	1089 (47)	332 (42)	0.2	1031 (46)	390 (47)	0.6
Race, n (%)				**0.005**			**< 0.001**			**< 0.001**
Hispanic	547 (7.6)	381 (6.5)	166 (13)		405 (6.8)	142 (12)		333 (5.4)	214 (21)	
Non-His White	1385 (78)	1081 (79)	304 (71)		1153 (81)	232 (59)		1183 (82)	202 (53)	
Non-His Black	703 (9)	533 (8.6)	170 (11)		452 (6.9)	251 (19)		459 (6.9)	244 (22)	
Non-His Asian	213 (3.8)	169 (3.6)	44 (4.3)		149 (3.1)	64 (7.3)		185 (3.8)	28 (3.3)	
Others	45 (1.8)	34 (1.8)	11 (1.6)		34 (1.7)	11 (2.3)		38 (2)	7 (0.5)	
Education level, n (%)				**< 0.001**			**< 0.001**			**< 0.001**
< HS	768 (17)	456 (13)	312 (33)		469 (13)	299 (35)		373 (12)	395 (49)	
HS diploma	665 (22)	509 (21)	156 (26)		484 (21)	181 (28)		508 (22)	157 (25)	
College/AA	1458 (61)	1232 (65)	226 (41)		1240 (66)	218 (37)		1317 (66)	141 (26)	
Immigrant, (yes, n, %)	675 (11)	482 (10)	193 (17)	**0.003**	459 (9)	219 (23)	**< 0.001**	416 (8.7)	259 (27)	**< 0.001**
Married (vs. others)	1654 (65)	1283 (66)	371 (58)	**0.002**	1303 (67)	351 (53)	**< 0.001**	1316 (68)	338 (48)	**< 0.001**
PIR, n (%)				**< 0.001**			**< 0.001**			**< 0.001**
< 1	471 (9)	312 (7.2)	159 (17)		299 (7.2)	172 (18)		270 (6.6)	201 (23)	
1 to 3	1179 (37)	874 (35)	305 (46)		874 (35)	305 (47)		849 (34)	330 (53)	
> 3	1022 (48)	851 (52)	171 (31)		864 (52)	158 (27)		921 (53)	101 (16)	
Insurance (yes, n, %)	2659 (95)	2031 (95)	628 (94)	0.8	2019 (95)	640 (95)	0.7	2044 (95)	615 (93)	0.056
Memory confusion (yes, n, %)	421 (13)	258 (10)	163 (22)	**< 0.001**	271 (11)	150 (23)	**< 0.001**	276 (11)	145 (23)	**< 0.001**
Sleep disorder (yes, n, %)	952 (35)	738 (35)	214 (35)	> 0.9	715 (35)	237 (37) 0.2	0.2	735 (35)	217 (38) 0.4	0.4
Alcohol consumption, n (%)				**< 0.001**			**< 0.001**			**< 0.001**
Never	1082 (32)	777 (29)	305 (44)		752 (29)	339 (46)		741 (28)	341 (53)	
Moderate	971 (41)	787 (43)	184 (32)		799 (43)	172 (29)		847 (44)	124 (20)	
Heavy	313 (12)	255 (13)	58 (8.2)		253 (13)	60 (7.2)		253 (13)	60 (6.8)	
Binge	493 (15)	364 (15)	129 (15)		364 (15)	129 (17)		339 (14)	154 (18)	
Smoking (yes, n, %)	1467 (50)	1122 (51)	345 (46.8)	0.4	1116 (49)	351 (52) 0.7		1103 (50)	364 (51)	0.3
Physical activity, n (%)				**< 0.001**			**< 0.001**			**< 0.001**
Sedentary	1242 (38)	869 (36)	373 (49)		844 (35)	398 (57)		847 (35)	395 (60)	
Moderate	1134 (40)	890 (40)	244 (39)		901 (41)	233 (33)		896 (41)	238 (33)	
Vigorous	517 (22)	439 (24)	78 (12)		448 (24)	69 (10)		455 (25)	62 (7.2)	
Waist circumference (cm), n (%)				**< 0.001**			**< 0.001**			**< 0.001**
Normal	404 (12)	299 (12)	105 (14)		303 (12)	101 (13)		294 (12)	110 (13)	
Moderate	528 (17)	378 (15)	150 (23)		406 (17)	122 (18)		389 (17)	139 (18)	
High	1819 (67)	1439 (69)	380 (56)		1410 (68)	409 (58)		1430 (68)	389 (59)	
Total energy (kcal, mean, sd)	1865 (674)	1902 (678)	1698 (629)	**< 0.001**	1912 (672)	1627 (630)	**< 0.001**	1911 (667)	1581 (646)	**< 0.001**

Table 1. Baseline characteristics of all participants categorized by three cognitive tests. *IRT* Immediate recall test, *AFT* animal fluency test, *DSST* digit symbol substitution test, *Unweighted n* other analysis is weighted. [1]N not Missing (unweighted). [2]Wilcoxon rank-sum test for complex survey samples; chi-squared test with Rao & Scott's second-order correction. Data were shown as number (percentage) or mean (sd). Significant values are in bold.

Previous studies have examined the association between various vitamins, including vitamin B2, and cognitive performance. A meta-analysis suggested that different vitamins may help maintain cognitive function and delay the onset of dementia[29]. Jiang et al. reported that individuals who regularly consumed vitamins (folic acid, B vitamins, vitamin D, and coenzyme Q10) had a lower rate of cognitive impairment[30]. Moreover, a follow-up study found that daily multivitamin supplementation for three consecutive years improved overall cognitive performance, episodic memory, and executive function in older adults[31]. Zhou et al. found that older adults who consumed more vitamin B2 were likely to perform better in certain aspects of cognitive function[16]. Nguyen et al. concluded that increasing the daily intake of mixed B vitamins through regular meals might minimize the risk of dementia[32]. Despite using distinct cross-sectional data and analytical methods, these findings align with one of our study's main conclusions that focusing on adequate vitamin B2 intake in the daily diet may protect cognitive function in the older population.

Another significant finding of this study is that physical activity may modify the association between vitamin B2 intake and cognitive performance. Physical activity and exercise have been found to improve cognitive function[33] and reduce the risk of dementia[34]. Chen et al. proposed that bodily adaptations made to enhance

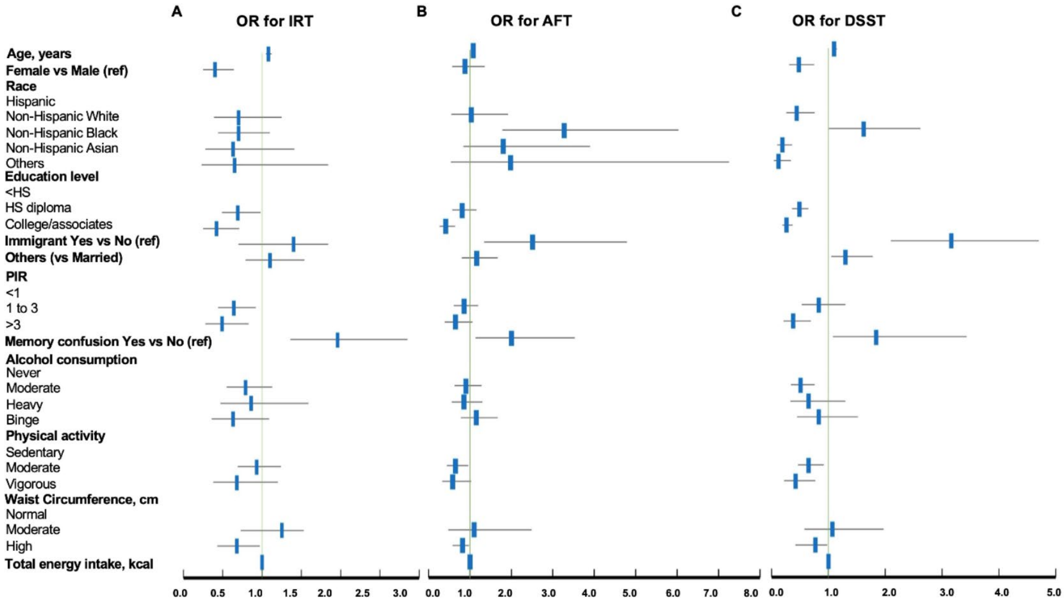

Fig. 2. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) illustrating the association between three cognitive tests and various covariates in multivariable analysis.

exercise performance also benefit the brain and contribute to improved cognition. These adaptations include the release of growth factors, anti-inflammatory cytokines, neurotransmitters, lactic acid production, increased mitochondrial biogenesis, and antioxidant enzyme activity[35]. An assessment of vitamin B2 nutritional status in young people with different levels of physical activity found that the effects of physical activity levels on vitamin B2 intake and nutritional status were not well-established[36]. Physically active people who limit their energy intake or make poor dietary choices are most likely to have poor riboflavin status[37]. Although physical activity can theoretically enhance the nutrient absorption function of the gut, it can accelerate nutrient depletion and loss. The complex relationship between physical activity and nutrient levels requires further investigation; however, these findings suggest a significant association between the two. This key finding in our study provides insight into the relationship between physical activity and vitamin B2 intake, though the underlying mechanisms remain unclear.

While the exact mechanism is poorly understood, the current study suggests vitamin B2 (riboflavin) may ameliorate cognitive impairment through its anti-oxidative stress and anti-inflammatory properties[14]. B-vitamins are involved in numerous neurochemical pathways related to neuromodulatory (noradrenergic, serotonergic, dopaminergic, and cholinergic systems), glutamate, and gamma-aminobutyric acid (GABA), and neurotransmitter systems[32,38,39]. Bioinformatics analysis identified the IL-18 signaling pathway and apoptosis as fundamental molecular mechanisms for the cognitive improvement associated with mixed B vitamins, with NFKB1, ATF3, and NR3C1 being important transcription factors[32]. However, these findings are at the bioinformatics level, and specific mechanisms need to be validated at the molecular and biochemical levels. In the future, large-scale, multicenter, and high-quality studies are required to confirm these findings and further elucidate the molecular mechanisms underlying the effects of vitamin B2 on cognitive performance in older adults.

Strengths and limitations

This research has two key strengths. Firstly, a nationally representative sample from the NHANES database was used, which is known for its ability to identify associations and provide generalizable results with satisfactory statistical power. Secondly, various sensitivity analyses were employed to determine the stability of the findings, including the introduction of RDA and residual energy models, standardization of the data, and dose-response curves. However, the study also has limitations. First, as a cross-sectional study, it has a temporal bias and cannot establish a causal association between vitamin B2 intake and cognitive decline. Second, participants with low cognitive performance might have difficulty accurately recalling and reporting their baseline information, including vitamin B2 intake, which could introduce bias and affect data reliability. Third, cognitive ability scores may have inherent measurement errors. Finally, the study relied on the average of two days of 24-hour dietary recall interviews to assess vitamin B2 intake, which may be subject to recall bias.

This study comprehensively assessed the association between vitamin B2 intake and cognitive function in an older population. A positive association was observed between vitamin B2 intake and cognitive function, confirmed through multiple sensitivity analyses. Physical activity may be an interaction factor influencing the effect of vitamin B2 intake on cognitive performance. The study also identified populations more likely to benefit from vitamin B2 intake in terms of cognitive function. Given the global increase in the prevalence of cognitive impairment and dementia, this hypothesis may pave the way for future interventional studies to determine the effect of vitamin B2 intake on cognitive performance.

Different types of vitamin B2		IRT		AFT		DSST	
		OR (95% Cl)	*P*	OR (95% Cl)	*P*	OR (95% Cl)	*P*
Model1	VB2 (mg)	0.67 (0.57, 0.79)	**< 0.001**	0.57 (0.48, 0.67)	**< 0.001**	0.51 (0.42, 0.62)	**< 0.001**
	Per 0.897 mg (1 SD)	0.70 (0.60, 0.81)	**< 0.001**	0.60 (0.52, 0.69)	**< 0.001**	0.55 (0.46, 0.65)	**< 0.001**
	≥RDA vs. < RDA	0.49 (0.35, 0.68)	**< 0.001**	0.47 (0.36, 0.61)	**< 0.001**	0.35 (0.27, 0.46)	**< 0.001**
Model2	VB2 (mg)	0.75 (0.64, 0.89)	**0.001**	0.72 (0.61, 0.85)	**< 0.001**	0.69 (0.56, 0.85)	**< 0.001**
	Per 0.897 mg (1 SD)	0.78 (0.67, 0.90)	**0.001**	0.75 (0.64, 0.86)	**< 0.001**	0.72 (0.60, 0.86)	**< 0.001**
	≥RDA vs. < RDA	0.62 (0.44, 0.88)	**0.006**	0.75 (0.56, 1.00)	0.053	0.59 (0.41, 0.84)	**0.003**
Model3	VB2 (mg)	0.77 (0.65, 0.92)	**0.004**	0.75 (0.64, 0.88)	**< 0.001**	0.72 (0.59, 0.88)	**0.001**
	Per 0.897 mg (1 SD)	0.79 (0.68, 0.93)	**0.004**	0.77 (0.67, 0.89)	**< 0.001**	0.74 (0.62, 0.89)	**0.001**
	≥RDA vs. < RDA	0.66 (0.46, 0.93)	**0.017**	0.83 (0.62, 1.11) 0.213		0.65 (0.45, 0.92)	**0.014**
	Quartile of vitamin B2	**< 0.001**		**< 0.001**		**< 0.001**	
Model1	1.033 Q1 (0.114, 1.297)	Ref		Ref		Ref	
	1.529 Q2 (1.297, 1.779)	0.65 (0.48, 0.89)		0.57 (0.42, 0.77)		0.49 (0.37, 0.65)	
	2.017 Q3 (1.781, 2.332)	0.59 (0.43, 0.82)		0.49 (0.30, 0.81)		0.44 (0.32, 0.62)	
	2.841 Q4 (2.333, 13.73)	0.41 (0.28, 0.60)		0.31 (0.23, 0.43)		0.23 (0.16, 0.32)	
	P for trend	**< 0.001**		**< 0.001**		**< 0.001**	
	Quartile of vitamin B2	**0.029**		**0.003**		**< 0.001**	
Model2	1.033 Q1 (0.114, 1.297)	Ref		Ref		Ref	
	1.529 Q2 (1.297, 1.779)	0.76 (0.52, 1.10)		0.73 (0.52, 1.02)		0.65 (0.44, 0.98)	
	2.017 Q3 (1.781, 2.332)	0.72 (0.50, 1.04)		0.71 (0.43, 1.16)		0.69 (0.50, 0.95)	
	2.841 Q4 (2.333, 13.73)	0.54 (0.34, 0.85)		0.52 (0.35, 0.76)		0.40 (0.27, 0.61)	
	P for trend	**0.002**		**0.001**		**< 0.001**	
	Quartile of vitamin B2	0.10		**0.006**		**< 0.001**	
Model3	1.033 Q1 (0.114, 1.297)	Ref		Ref		Ref	
	1.529 Q2 (1.297, 1.779)	0.81 (0.51, 1.30)		0.80 (0.53, 1.21)		0.74 (0.45, 1.22)	
	2.017 Q3 (1.781, 2.332)	0.75 (0.47, 1.19)		0.76 (0.41, 1.40)		0.76 (0.51, 1.13)	
	2.841 Q4 (2.333, 13.73)	0.58 (0.32, 1.03)		0.57 (0.37, 0.88)		0.45 (0.28, 0.74)	
	P for trend	**0.005**		**0.004**		**0.001**	

Table 2. Odds ratio (ORs) and corresponding 95% confidence intervals (CIs) representing cognitive performance concerning vitamin B2 intake, as determined by cross-sectional analysis. *RDA* recommended dietary allowance (1.3 mg/d for men, 1.1 mg/d for women). Model 1: Adjusted for age, gender. Model 2: Adjusted for age, gender, race, education level, marital status, PIR, and immigrant. Model 3: Adjusted as model 2 with further adjustments for waist circumference, physical activity, alcohol consumption, and memory confusion. Significant values are in bold.

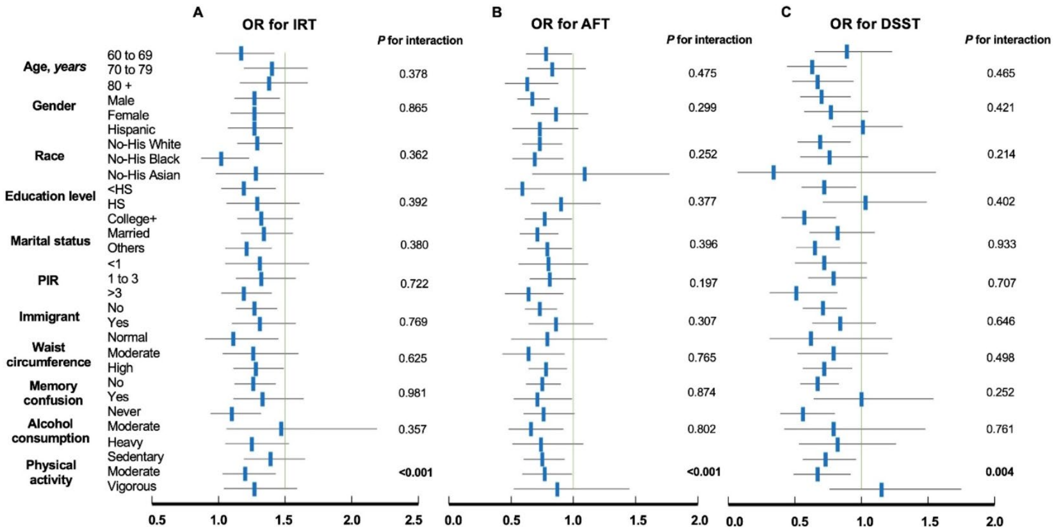

Fig. 3. Examination of the correlation between vitamin B2 and cognitive function across different demographic and health-related factors, including age, gender, race, education level, marital status, poverty-income ratio (PIR), immigrant status, waist circumference, memory confusion, alcohol consumption, and physical activity.

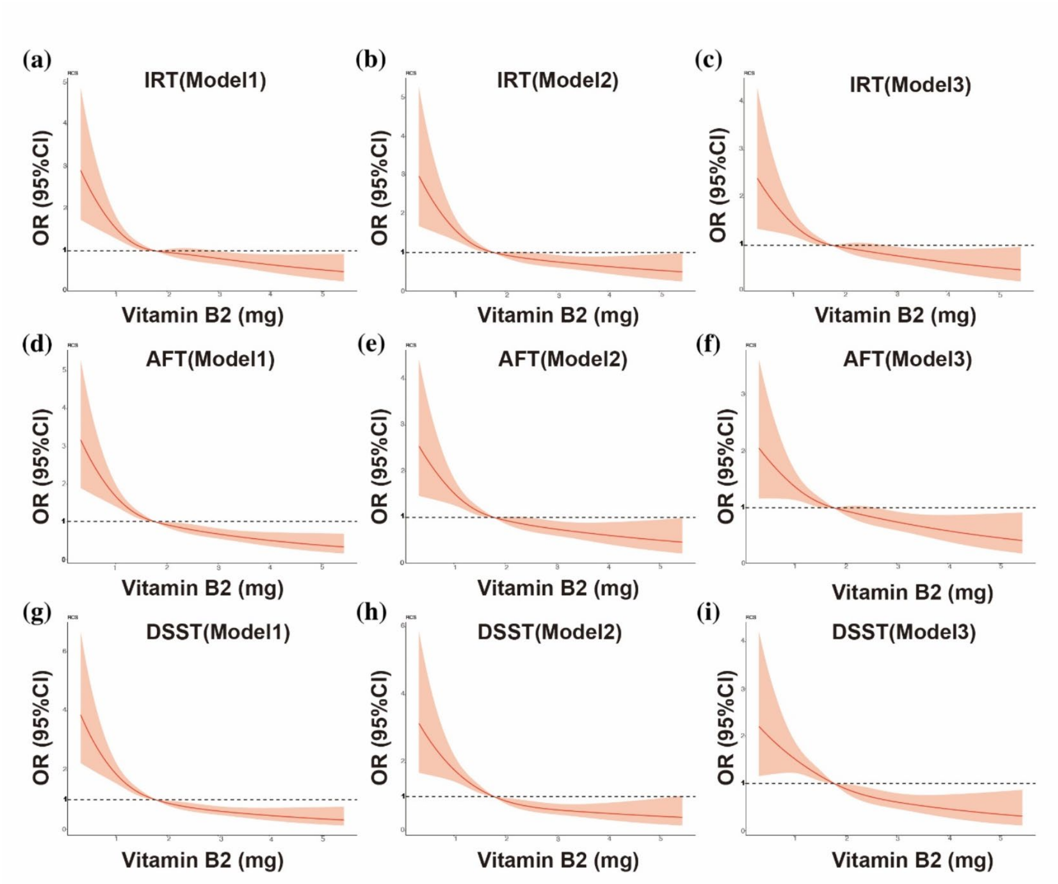

Fig. 4. Association between dietary vitamin B2 intake and the odds ratios of low cognitive performance. The red line and orange shading indicate predicted values and 95% confidence intervals, respectively. Age, gender, race, education level, marital status, PIR, immigrant, waist circumference, physical activity, alcohol consumption, and memory confusion were adjusted.

	IRT	AFT	DSST
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Model 1	0.85 (0.71, 1.00)	0.72 (0.60, 0.85)	0.74 (0.61, 0.88)
Model 2	0.91 (0.76, 1.09)	0.87 (0.73, 1.04)	0.95 (0.77, 1.16)
Model 3	0.92 (0.76, 1.12)	0.88 (0.73, 1.05)	0.94 (0.75, 1.18)

Table 3. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of three cognitive tests by residual vitamin B2 in the residual energy model. Model 1: Adjusted for age, gender. Model 2: Adjusted for age, gender, race, education level, marital status, PIR, and immigrant. Model 3: Adjusted as model 2 with further adjustments for waist circumference, physical activity, alcohol consumption, memory confusion, and total energy intake.

Data availability

The data used in this study were available in the NHANES public database: https://www.cdc.gov/nchs/nhanes/index.htm.

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Declarations

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Y.W.