Research article

Dietary vitamin B6 intake and stroke are negatively associated in adults: A cross-sectional study from the NHANES

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ABSTRACT

Background: The relationship between dietary vitamin B6 and stroke risk is controversial; thus, we analyzed their correlation using data from the National Health and Nutrition Examination Survey (NHANES).

Method: Data from 2005 to 2018 were collected from the NHANES database. Two 24-h dietary recalls and a standard questionnaire were used to evaluate vitamin B6 intake and stroke prevalence. We used logistic regression models to estimate the association between dietary vitamin B6 intake and stroke risk and investigated the nonlinear relationship between them using a restricted cubic spline (RCS). Sensitivity analysis was conducted using propensity score matching (PSM).

Results: Among 24,214 participants, 921 were patients diagnosed with stroke, while 23,293 were without stroke. The multivariate logistic regression model revealed that individuals in the highest quartile of vitamin B6 consumption had a significantly lower stroke risk than those in the lowest quartile under the fully adjusted model (OR: 0.48, 95 % CI: 0.35–0.66, $P < 0.001$). Subgroup analyses showed that dietary intake of vitamin B6 was a significant protective factor against stroke risk in different populations, with the most pronounced effect in the population engaging in moderate-intensity physical activity (OR: 0.34, 95%CI: 0.20–0.57). The RCS models revealed a non-linear L-shaped relationship (P for nonlinearity = 0.006) between stroke and dietary intake of vitamin B6.

Conclusions: Our study shows that an increased intake of vitamin B6 could be an effective strategy in reducing the risk of stroke.

1. Introduction

Stroke is a prevalent and significant global health concern, representing a major global contributor to both permanent disability and mortality [1,2]. Annually, 13.7 million individuals suffer from stroke, of which 5.5 million die worldwide [3]. Stroke mortality has progressively declined as a result of advancements in prevention and healthcare [4]. However, the prevalence and incidence of stroke are increasing, and the age of onset is decreasing [5,6]. Hypertension, diabetes, coronary artery disease, atrial fibrillation, systemic inflammation, and high homocysteine concentrations have been conclusively identified as factors that contribute to stroke occurrence

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[7–9]. B vitamins are water-soluble vitamins that are essential to human health [10]. B vitamin supplementation reduces high homocysteine levels and may reduce the risk of stroke [11,12]. As an important member of the B-vitamin family, vitamin B6 has anti-inflammatory and homocysteine-lowering properties [13,14]. Vitamin B6 is a coenzyme of cystathionine-γ-lyase, which is involved in the conversion of homocysteine to L-cysteine, which is then catabolized to produce taurine and inorganic sulphates, which are excreted in the urine, thereby reducing homocysteine levels [15]. In addition, the vitamin inhibits the activation of NF-κB, IL-6 and TNF-α [16,17], thereby reducing the inflammation levels in the body. Several studies have explored the link between vitamin B6 intake and stroke risk; however, the results have been inconsistent. For example, Larsson et al. found no significant association between dietary vitamin B6 consumption and stroke [18]. In contrast, Chen et al. reported a negative correlation between stroke and vitamin B6 intake [8]. Considering these conflicting findings, we analyzed cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) between 2005 and 2018 to further examine the relationship between dietary vitamin B6 intake and stroke risk.
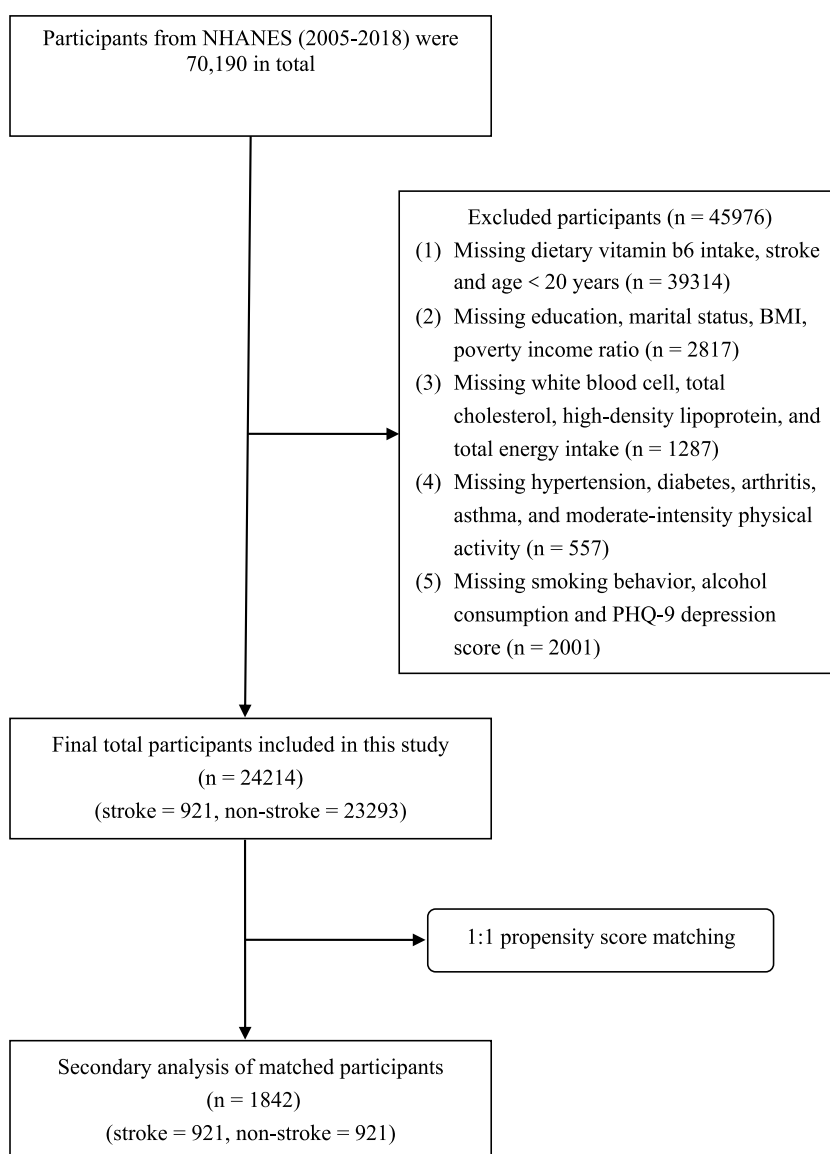

Fig. 1. Study population screening flowchart.

2. Methods

2.1. Source of data and study population

The NHANES database holds data on the health and nutritional status of the American population and comprises five components: demographics, dietary intake, examinations, laboratory tests, and questionnaires [19]. The NHANES survey design can be accessed at http://www.cdc.gov/nchs/nhanes/index.html. Before data collection, the ethical oversight commission of the National Center for Health Statistics obtained informed consent from all participants. The study used data retrieved from the NHANES database for the years 2005–2018. The exclusion criteria for the study population were as follows: (1) missing dietary vitamin b6 intake, stroke and age < 20 years (n = 39314); (2) missing education, marital status, BMI, poverty income ratio (PIR) (n = 2817); (3) missing white blood cell (WBC), total cholesterol (TC), high-density lipoprotein (HDL) and energy (n = 1287); (4) missing hypertension, diabetes, arthritis, asthma, and moderate-intensity physical activity (MIPA) (n = 557); and (5) missing smoking behavior, alcohol consumption and PHQ-9 depression score (n = 2001). The final cohort for the cross-sectional analyses included 24,214 participants. The process of study population selection is illustrated in Fig. 1.

2.2. Assessment of dietary vitamin B6 intake

Each participant was interviewed twice for dietary recall. The first interview was held face–to–face at the Mobile Examination Center, and the subsequent interview was conducted via phone 3–10 days later. The total amounts of nutrients and food constituents in all foods were determined and subsequently submitted to the NHANES database, using the United States Department of Agriculture's Food and Nutrition Database for Dietary Studies [20]. This study evaluated the average intake of vitamin B6 through two 24-h dietary recalls. Based on previous research studies [20] and the distribution of vitamin B6 intake in our study population, vitamin B6 intake was divided into four quartiles, which revealed more clearly the differences in vitamin B6 intake among the study populations and allowed us to explore more effectively the relationship between different levels of vitamin B6 intake and the incidence of stroke. The first quartile (Q1) was less than 1.290 mg/day, the second quartile (Q2) was between 1.290 and 1.796 mg/day, the third quartile (Q3) was between 1.796 and 2.470 mg/day, and the fourth quartile (Q4) was equal to or greater than 2.470 mg/day.

2.3. Defining disease and related covariates

Stroke diagnosis was established using the Medical Condition Questionnaire. During the interviews, interviewees were asked, "Have you ever been diagnosed with stroke by a physician or other healthcare professional?". Those who responded affirmatively were subsequently classified as having experienced a stroke [21]. Similar criteria were used to diagnose arthritis. The subjects were considered diabetic if any of the following conditions were met: prior diagnosis of diabetes by a doctor or other healthcare provider or receiving diabetic medication to lower blood sugar levels [22]. Identical diagnostic criteria were applied for hypertension and arthritis. Smoking behavior was classified into three categories: never smoked (less than 100 cigarettes smoked in their lifetime), former smoker (smoked >100 cigarettes in their lifetime but quit smoking), and current smoker (smoked >100 cigarettes in their lifetime and still smoked regularly or occasionally) [23]. Alcohol consumption was classified based on the following criteria: never drinkers were those who reported <12 drinks in their lifetime, ever drinkers were those who reported >12 drinks in their lifetime but none in the previous year. Current drinkers were further classified into three categories: heavy, moderate, and mild drinkers. Heavy drinkers were women having ≥3 or men having ≥4 drinks/day, with ≥5 monthly binge-drinking days; moderate drinkers were women having ≥2 or men having ≥3 drinks/day, with 2–4 monthly binge drinking days; and light drinkers did not meet the criteria for moderate or heavy drinkers [24,25]. The PIR was classified into three distinct categories: below 1.5 (<1.5), ranging from 1.5 to 3.5 (1.5–3.5), and over 3.5 (≥3.5) [26]. Symptoms of depression were assessed using the PHQ-9 depression scale, which comprised nine items and yielded a total score ranging from 0 to 27. The sensitivity and specificity of a PHQ-9 total score of 10 or higher for severe depression are both 88 %, according to previous research [27]. Subjects who obtained a PHQ-9 total score of 10 or higher were categorized as having clinically significant depression for the purposes of this research. Based on the NHANES Physical Activity Questionnaire, moderate-intensity physical activity is defined as any activity that causes light sweating or a slight to moderate increase in heart rate and breathing rate that lasts for at least 10 continuous minutes.

We also included various variables of interest basedon prior research. These variables include age, sex, race (Mexican American, non-Hispanic white, non-Hispanic Black, and other races), body mass index (BMI), marital status (unmarried, divorced/separated, widowed, or married), educational level (less than high school, high school, or more than high school), total energy intake, WBC count, TC levels, and HDL levels.

2.4. Statistical analysis

For the NHANES 2005–2018 dataset, we used the sampling weights from all analyses to represent the entire national population. Dietary intake of vitamin B6 was divided into quartiles ranging from the lowest (Q1) to the highest (Q4), with the lowest quartile acting as the reference group. Baseline continuous variables were analyzed using Student's t-test or nonparametric Mann-Whitney U test, reporting the median and interquartile range for each group. Chi-squared or Fisher's exact tests were used to analyze categorical variables among baseline characteristics, reporting frequency, and percentage for each group. In the logistic regression model, significant covariates from the univariate analysis were included to investigate the relationship between stroke and vitamin B6

Table 1

Baseline characteristics of participants categorized into quartiles based on dietary vitamin B6 intake.

Variable	Total Subjects (N = 24214)	Dietary Vitamin B6 Intake Quartile, mg/day				P-value
		Q1(<1.290)	Q2(1.290-)	Q3(1.796-)	Q4(≥2.470)	
Age (y), Mean (SD)	47.45(0.27)	48.23(0.37)	48.70(0.36)	48.03(0.41)	45.15(0.41)	<0.0001
Sex (%)						<0.0001
Female	12333(51.23)	4183(72.74)	3554(60.55)	2834(48.74)	1762(28.02)	
Male	11881(48.77)	1853(27.26)	2509(39.45)	3230(51.26)	4289(71.98)	
Race (%)						<0.0001
Mexican American	3565(8.09)	846(7.65)	911(8.08)	883(8.07)	925(8.46)	
Non-Hispanic Black	4927(10.20)	1496(13.74)	1279(10.92)	1132(9.13)	1020(7.72)	
Non-Hispanic White	11264(69.76)	2613(66.36)	2743(68.93)	2899(70.99)	3009(72.07)	
Other races	4458(11.95)	1081(12.24)	1130(12.07)	1150(11.81)	1097(11.75)	
Education (%)						<0.0001
High school	5575(23.08)	1509(26.36)	1413(23.86)	1335(21.52)	1318(21.22)	
Less than high school	5262(13.78)	1676(18.65)	1366(14.70)	1130(11.34)	1090(11.34)	
More than high school	13377(63.14)	2851(54.99)	3284(61.44)	3599(67.14)	3643(67.44)	
PIR (%)						<0.0001
<1.5	8401(24.13)	2558(31.63)	2122(24.86)	1894(20.40)	1827(20.94)	
1.5–3.5	7961(31.25)	1992(32.50)	2059(31.82)	1955(31.08)	1955(29.91)	
≥3.5	7852(44.62)	1486(35.86)	1882(43.32)	2215(48.52)	2269(49.16)	
Marital status (%)						<0.0001
Divorced/Separated	3471(12.81)	1088(16.31)	877(12.64)	757(11.53)	749(11.33)	
Married	14753(63.85)	3269(57.13)	3705(64.93)	3920(67.09)	3859(65.26)	
Unmarried	4175(17.99)	1075(18.52)	982(16.58)	961(16.37)	1157(20.31)	
Widowed	1815(5.36)	604(8.03)	499(5.85)	426(5.01)	286(3.11)	
Smoking behavior (%)						<0.0001
Former	6110(24.95)	1328(21.35)	1523(24.98)	1607(25.61)	1652(27.22)	
Never	13273(55.57)	3226(52.74)	3447(56.89)	3388(57.61)	3212(54.76)	
Now	4831(19.48)	1482(25.91)	1093(18.13)	1069(16.78)	1187(18.02)	
Alcohol consumption (%)						<0.0001
Former	4019(13.38)	1214(16.19)	1039(14.03)	917(12.25)	849(11.60)	
Heavy	4734(21.06)	1021(19.20)	1067(18.74)	1165(20.32)	1481(25.31)	
Mild	8437(37.22)	1823(32.12)	2091(36.53)	2283(39.90)	2240(39.41)	
Moderate	3828(17.82)	949(19.08)	993(18.38)	963(17.98)	923(16.18)	
Never	3196(10.52)	1029(13.41)	873(12.32)	736(9.56)	558(7.51)	
BMI, kg/m2, Mean (SD)	29.11(0.09)	29.56(0.14)	29.30(0.14)	29.13(0.16)	28.55(0.15)	<0.0001
WBC count (1000 cell/μL)	7.29(0.03)	7.45(0.05)	7.34(0.05)	7.27(0.05)	7.14(0.05)	<0.001
TC, mg/dl, Mean (SD)	194.98(0.52)	196.39(0.88)	195.98(0.88)	194.88(0.85)	193.04(0.83)	0.03
HDL, mg/dl, Mean (SD)	53.35(0.21)	54.61(0.39)	54.15(0.34)	53.33(0.39)	51.66(0.29)	<0.0001
Energy, kcal	4219.07(18.70)	2966.41(21.51)	3768.38(25.73)	4402.48(25.60)	5454.14(34.96)	<0.0001

Variable	Total Subjects (N = 24214)	Dietary Vitamin B6 Intake Quartile, mg/day				P-value
		Q1(<1.290)	Q2(1.290-)	Q3(1.796-)	Q4(≥2.470)	
MIPA (%)						<0.0001
No	13115(49.16)	3577(54.05)	3375(50.39)	3282(50.59)	2881(42.77)	
Yes	11099(50.84)	2459(45.95)	2688(49.61)	2782(49.41)	3170(57.23)	
Hypertension (%)						<0.001
No	13836(62.53)	3200(59.72)	3409(61.48)	3506(62.50)	3721(65.75)	
Yes	10378(37.47)	2836(40.28)	2654(38.52)	2558(37.50)	2330(34.25)	
Diabetes (%)						<0.0001
No	20881(89.90)	5057(88.65)	5133(88.40)	5278(90.24)	5413(91.89)	
Yes	3333(10.10)	979(11.35)	930(11.60)	786(9.76)	638(8.11)	
Arthritis (%)						<0.0001
No	17389(73.97)	4031(69.28)	4311(72.52)	4433(74.84)	4614(78.20)	
Yes	6825(26.03)	2005(30.72)	1752(27.48)	1631(25.16)	1437(21.80)	
Asthma (%)						0.003
No	20691(85.53)	5036(83.37)	5205(85.42)	5246(86.51)	5204(86.44)	
Yes	3523(14.47)	1000(16.63)	858(14.58)	818(13.49)	847(13.56)	
PHQ.9 depression score (%)						<0.0001
No	22131(92.18)	5294(87.75)	5529(91.91)	5649(93.50)	5659(94.76)	
Yes	2083(7.82)	742(12.25)	534(8.09)	415(6.50)	392(5.24)	
Stroke (%)						<0.0001
No	23293(97.21)	5700(95.74)	5825(96.72)	5854(97.55)	5914(98.50)	
Yes	921(2.79)	336(4.26)	238(3.28)	210(2.45)	137(1.50)	

Notes: SD, standard deviation. **Abbreviations:** BMI: body mass index; PIR: family poverty income ratio; MIPA: Moderate-intensity physical activity; PHQ: patient health questionnaire; WBC: white blood cell; TC: total cholesterol; HDL: high-density lipoprotein. In the study, consideration was given to the examination weights were considered.

consumption. Model 1 was not adjusted, whereas Model 2 included demographic variables such as age, sex, and race. Model 3 was further adjusted to include BMI, PIR, marital status, educational level, smoking behavior, alcohol consumption, MIPA, PHQ-9 depression score, hypertension, diabetes, asthma, arthritis, total energy intake, WBC count, TC levels, and HDL levels, all based on Model 2. In model 3, all covariates with P < 0.05 in univariate analyses were included as potential confounders, allowing a more accurate assessment of the role of vitamin B6 in stroke disease. We reported the odds ratios (ORs) and 95 % confidence intervals (95 % CIs) for each model to evaluate the strength of the association. To determine whether the association between vitamin B6 intake and stroke risk varied with age, sex, race, smoking behavior, alcohol consumption, hypertension, diabetes, asthma, MIPA, PHQ-9 depression score, or arthritis, we conducted a subgroup analysis. In addition, we used a restricted cubic spline (RCS) model with four knots and took the dietary vitamin B6 intake value corresponding to an OR of 1 as the reference to further explore the nonlinear correlation between vitamin B6 intake and stroke risk. Propensity score matching (PSM) reduces selection bias in observational studies and thus improves the reliability of research arguments [28]. In this study, a 1:1 nearest neighbor PSM algorithm was used to balance the covariate differences between the stroke group and the non-stroke group. Matching propensity scores were performed for age, sex, race, education, BMI, PIR, marital status, smoking behavior, alcohol consumption, WBC count, TC levels, HDL levels, MIPA, hypertension, diabetes, arthritis, asthma, and PHQ-9 depression score to ensure that the stroke and non-stroke groups had similar covariate distributions. Subsequently, to further validate the results, the study population was re-analyzed post PSM implementation. The PSM was executed using R software. RStudio (version 4.2.2) and GraphPad Prism (version 9.5) software were used for the data analysis and figure design. Statistical significance was set at *P* < 0.05.

3. Results

3.1. Participant characteristics

We studied 24,214 individuals ranging from 20 to 85 years old. The average age was 47.45 years, with a standard deviation of 0.27 years. Among them, 51.23 % were women, 69.76 % were not of Hispanic white origin, 63.14 % had completed education beyond high school, and 63.85 % were married. As shown in Table 1, the participants' weighted characteristics were sub-classified based on vitamin B6 intake quartiles. Compared with the low vitamin B6 intake group (the first and second quartiles), the high vitamin B6 intake group (the third and fourth quartiles) had the following characteristics: a higher proportion of males; PIR ≥3.5; never smokers; low alcohol consumption; participants in MIPA; higher total energy intake; had no medical history of hypertension, diabetes, arthritis, and asthma; PHQ-9 depression scores <10; lower incidence of stroke; and relatively lower WBC counts, TC levels, and HDL levels.

After PSM, a total of 1842 participants remained in this study, including 921 participants with stroke and without stroke (Fig. 1). Table S1 shows the baseline characteristics of participants categorized into quartiles based on dietary vitamin B6 intake after PSM. Consistent with before matching, participants with high vitamin B6 intake (third and fourth quartiles) had a lower incidence of stroke.

3.2. The correlation between vitamin B6 consumption and stroke risk

The study findings indicate that, compared with individuals without a history of stroke, a higher proportion of stroke patients have a daily vitamin B6 intake below 1.290 mg and a lower proportion have an intake of 2.470 mg or more, as shown in Fig. S1. The results of the multivariate logistic regression analysis, which summarized the association between vitamin B6 intake and stroke risk, are shown in Fig. 2. We created three weighted logistic regression models with progressive levels of adjustment: Model 1 remained un-adjusted; Model 2 included adjustments for age, sex, and race; and Model 3 incorporated all the covariates outlined in Table 1. In the
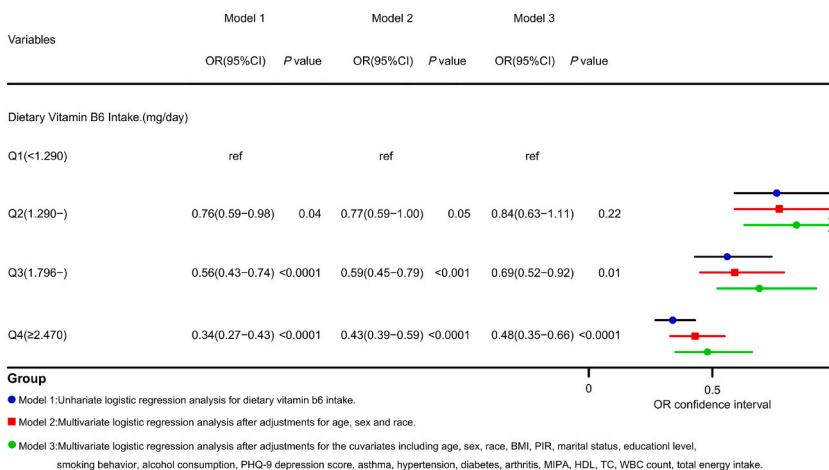

Variables	Model 1		Model 2		Model 3	
	OR(95%CI)	*P* value	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Dietary Vitamin B6 Intake.(mg/day)						
Q1(<1.290)	ref		ref		ref	
Q2(1.290−)	0.76(0.59−0.98)	0.04	0.77(0.59−1.00)	0.05	0.84(0.63−1.11)	0.22
Q3(1.796−)	0.56(0.43−0.74)	<0.0001	0.59(0.45−0.79)	<0.001	0.69(0.52−0.92)	0.01
Q4(≥2.470)	0.34(0.27−0.43)	<0.0001	0.43(0.39−0.59)	<0.0001	0.48(0.35−0.66)	<0.0001

Group
- Model 1:Unhariate logistic regression analysis for dietary vitamin b6 intake.
- Model 2:Multivariate logistic regression analysis after adjustments for age, sex and race.
- Model 3:Multivariate logistic regression analysis after adjustments for the cuvariates including age, sex, race, BMI, PIR, marital status, educationl level, smoking behavior, alcohol consumption, PHQ-9 depression score, asthma, hypertension, diabetes, arthritis, MIPA, HDL, TC, WBC count, total energy intake.

Fig. 2. Multivariate logistic regression forest plot showing the relationship between stroke risk and levels of vitamin B6 intake before PSM. (Please print in color).

null model, vitamin B6 intake was negatively correlated with stroke, and patients in Q4 (OR: 0.34, 95 % CI: 0.27–0.43, $P < 0.0001$) had a 66 % lower risk of stroke than patients in Q1. After adjusting for demographic variables, subjects in Q4 (OR: 0.43, 95 % CI: 0.39–0.59, $P < 0.0001$) exhibited a 57 % reduced risk of stroke compared with those in Q1. In the fully adjusted model, vitamin B6 intake was still negatively correlated with stroke, and the risk of stroke was 52 % lower in patients in Q4 (OR: 0.48, 95 % CI: 0.35–0.66, $P < 0.0001$) than in patients in Q1.

After PSM, the same three multivariable logistic regression models as before PSM were developed. In Models 1, 2, and 3, the risk of stroke was reduced by 42 % ($P < 0.0001$), 44 % ($P < 0.0001$), and 47 % ($P < 0.001$), respectively (Fig. 3), when comparing Q4 to Q1.

3.3. Analysis of dietary vitamin B6 intake and stroke risk in subgroups

Stratified analyses assessed the differences in the association between vitamin B6 intake and stroke risk across different stratification variables (Table 2 and 3). Before PSM, this association was more significant in males under 60 years old, Mexican Americans, former smokers, mild drinkers, hypertensive patients, non-diabetic patients, non-asthmatic patients, non-arthritic patients, those engaging in moderate-intensity physical activity, and those with a depression score ≥10 (all $P < 0.05$).

After PSM, this association was more significant in those aged 60 and above, moderate drinkers, diabetic patients, arthritic patients, and those with a depression score <10 (all $P < 0.05$).

Both before and after PSM, there were no significant interactions between vitamin B6 and other variables ($P \geq 0.05$ for all these interaction).

3.4. Nonlinear correlation between dietary vitamin B6 consumption and stroke

We performed RCS analysis to clearly illustrate the association between dietary vitamin B6 intake and stroke risk (Fig. 4A and 4B). Our findings revealed an L-shaped association between vitamin B6 intake and stroke occurrence, both before (Fig. 4A) and after (Fig. 4B) PSM. This relationship was nonlinear ($P = 0.006$ and $P = 0.048$ for nonlinearity): as vitamin B6 consumption increased, the prevalence of stroke decreased.

4. Discussion

This comprehensive retrospective study aimed to investigate the possible association between the dietary intake of vitamin B6 and stroke occurrence. This study utilized a merged dataset from the NHANES between 2005 and 2018 for analysis. Among a cohort of 24,214 individuals who met the eligibility criteria, 921 participants had been diagnosed with stroke. Our investigation revealed a negative correlation between dietary vitamin B6 intake and the risk of stroke. In conjunction with the findings of the RCS analysis, it was postulated that the consumption of dietary vitamin B6 might exhibit a protective effect against stroke.

The discovery of vitamin B6 originated from its ability to treat dermatitis in rats [29]. Vitamin B6 can alleviate oxygen radical damage, reduce lipid peroxide production, participate in inflammation, and protect against vascular endothelial impairment caused by low-density lipoproteins [30–33]. Numerous studies have reported associations between vitamin B6 levels and the incidence of stroke and cardiovascular conditions. Chen et al. found that for every 0.5 mg/day increase in vitamin B6 intake, the risk of stroke decreased by 6 %. Their analysis revealed a markedly negative correlation between vitamin B6 consumption and stroke prevalence in Asian studies, a marginally inverse link in European studies, and an insignificant association in investigations conducted in the US [8]. Yuan et al. found that a higher vitamin B6 status correlated with lower ischemic stroke risk (OR: 0.88, 95 % CI: 0.81–0.97, $P = 0.009$) [34].
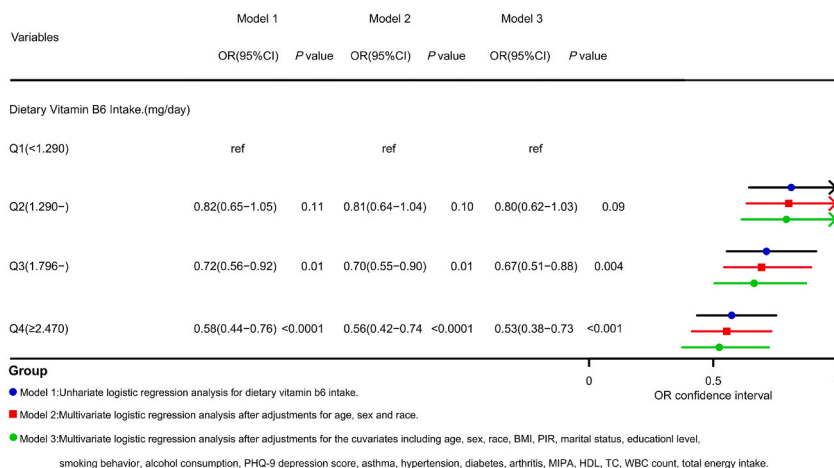

Fig. 3. Multivariate logistic regression forest plot showing the relationship between stroke risk and levels of vitamin B6 intake after PSM. (Please print in color).

Table 2
Subgroup analysis of the connection between the quartile of dietary vitamin B6 consumption and stroke before PSM.

Variable	Vitamin B6 Consumption Quartile, mg/day				P	P for interaction
	Q1(<1.290)	Q2(1.290-)	Q3(1.796-)	Q4(≥2.470)		
Age						0.66
<60	ref	0.84(0.53,1.33)	0.52(0.29,0.94)	0.43(0.25,0.75)	0.001	
≥60	ref	0.82(0.59,1.14)	0.78(0.54,1.13)	0.51(0.32,0.83)	0.01	
Sex						0.97
Female	ref	0.85(0.62,1.18)	0.76(0.49,1.17)	0.51(0.30,0.86)	0.01	
Male	ref	0.92(0.56,1.53)	0.72(0.47,1.11)	0.50(0.32,0.78)	0.001	
Race						0.11
Non-Hispanic Black	ref	0.69(0.44,1.09)	1.05(0.62,1.76)	1.04(0.53,2.06)	0.77	
Non-Hispanic White	ref	0.91(0.64,1.28)	0.77(0.53,1.12)	0.51(0.35,0.76)	0.002	
Other races	ref	1.23(0.52,2.94)	1.09(0.49,2.46)	0.83(0.34,2.03)	0.71	
Mexican American	ref	0.95(0.48,1.89)	0.24(0.10,0.61)	0.12(0.03,0.44)	<0.001	
Smoking behavior						0.98
Never	ref	0.90(0.59,1.37)	0.86(0.56,1.31)	0.69(0.43,1.10)	0.14	
Former	ref	0.86(0.50,1.48)	0.65(0.41,1.04)	0.40(0.22,0.72)	<0.001	
Now	ref	0.91(0.52,1.60)	0.72(0.31,1.67)	0.43(0.22,0.83)	0.05	
Alcohol consumption						0.35
Former	ref	0.93(0.53,1.63)	1.15(0.71,1.87)	0.55(0.32,0.94)	0.22	
Mild	ref	1.08(0.65,1.79)	0.64(0.38,1.06)	0.55(0.35,0.87)	0.003	
Moderate	ref	0.35(0.16,0.77)	0.58(0.28,1.22)	0.28(0.11,0.71)	0.04	
Never	ref	0.60(0.31,1.16)	0.70(0.36,1.36)	0.48(0.22,1.04)	0.11	
Heavy	ref	1.22(0.56,2.69)	0.55(0.23,1.34)	0.61(0.16,2.36)	0.3	
Hypertension						0.78
No	ref	1.23(0.62,2.43)	0.88(0.47,1.65)	0.67(0.29,1.55)	0.22	
Yes	ref	0.79(0.59,1.05)	0.69(0.50,0.96)	0.47(0.32,0.68)	<0.001	
Diabetes						0.38
No	ref	0.92(0.66,1.30)	0.68(0.48,0.98)	0.50(0.35,0.71)	<0.001	
Yes	ref	0.66(0.44,0.98)	0.76(0.44,1.33)	0.46(0.25,0.83)	0.03	
Asthma						0.88
No	ref	0.89(0.65,1.22)	0.73(0.53,1.01)	0.54(0.39,0.75)	<0.001	
Yes	ref	0.90(0.54,1.50)	0.92(0.46,1.86)	0.53(0.29,0.98)	0.15	
Arthritis						0.03
No	ref	1.08(0.72,1.63)	0.59(0.38,0.93)	0.62(0.39,0.97)	0.01	
Yes	ref	0.79(0.55,1.14)	0.96(0.65,1.43)	0.47(0.30,0.73)	0.02	
MIPA						0.52
No	ref	0.87(0.67,1.13)	0.84(0.60,1.18)	0.71(0.48,1.04)	0.08	
Yes	ref	0.91(0.59,1.40)	0.59(0.36,0.98)	0.34(0.20,0.57)	<0.0001	
PHQ-9 depression score						0.98
<10	ref	0.95(0.71,1.29)	0.82(0.59,1.15)	0.59(0.43,0.82)	0.01	
≥10	ref	0.70(0.37,1.30)	0.58(0.32,1.05)	0.39(0.18,0.86)	0.01	

Notes: All covariates were adjusted in this model without adjusting the stratified variable itself. **Abbreviations:** MIPA: Moderate-intensity physical activity; PHQ: patient health questionnaire.

Wei et al. reported that a higher serum concentration of vitamin B6 can mitigate the negative effects of lead exposure on the cardiovascular system [35]. The Norwegian Vitamin Trial demonstrated that high concentrations of vitamin B6 may negatively impact vascular remodeling and myocardial repair, leading to an increase in the incidence of complications and mortality in patients with cardiovascular disease [36]. The Norwegian Vitamin Trial also demonstrated a lack of correlation between vitamin B6 supplementation and protection from myocardial infarction and stroke [35,36]. Differences in the study design and characteristics, stroke subtypes, sample sizes, study populations, as well as differences in dietary habits, lifestyles, and the types and extent of confounding factors adjusted for across different regions and races, may account for the inconsistent findings regarding the association between vitamin B6 and stroke risk. Specifically, Chen et al.'s meta-analysis included multiple populations. Yuan et al.'s Mendelian randomization study and Wei et al.'s retrospective cross-sectional study were both conducted on the US population. On the other hand, the Norwegian Vitamin Trial was a multicenter, prospective randomized controlled trial primarily focused on measuring plasma vitamin B6 concentrations in the Norwegian population. In contrast, Wei et al.' s study focused on dietary vitamin B6 intake. Stroke prevalence differs across geographical areas, with a notably higher occurrence in regions of lower to middle income, including Asia and Africa [37]. The richest sources of vitamin B6 include fish, beef liver and other organ meats, potatoes and other starchy vegetables, and fruit (other than citrus). Given that Asian dietary habits lean towards plant-based foods, while Western dietary preferences might be more inclined towards meat and other animal-derived foods, it's plausible that there could be variations in the intake of Vitamin B6 among these different regional populations. Genetic risk factors for stroke include single-gene disorders (e.g. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), multi-systemic disorders due to single-gene disorders (e.g. sickle-cell anaemia), and genetic variants (e.g. 9p21 mutation) [38]. The relationship between vitamin B6 and the incidence of stroke has some relevance to the study design protocol. Cross-sectional studies lack the ability to determine causality and may introduce bias. Meta-analyses assess intervention effects and disease risk factors but provide average strength of evidence. In contrast, randomized

Table 3

Subgroup analysis of the connection between the quartile of dietary vitamin B6 consumption and stroke after PSM.

Variable	Vitamin B6 Consumption Quartile, mg/day				*P*	*P* for interaction
	Q1(<1.290)	Q2(1.290-)	Q3(1.796-)	Q4(≥2.470)		
Age						0.96
<60	ref	1.23(0.58,2.58)	0.79(0.40,1.55)	0.59(0.30,1.14)	0.07	
≥60	ref	1.00(0.59,1.71)	0.80(0.49,1.29)	0.50(0.27,0.93)	0.03	
Sex						0.92
Female	ref	1.07(0.65,1.77)	0.90(0.52,1.54)	0.53(0.27,1.07)	0.15	
Male	ref	1.09(0.59,2.00)	0.73(0.46,1.16)	0.55(0.31,0.96)	0.01	
Race						0.41
Non-Hispanic Black	ref	0.64(0.36,1.15)	0.61(0.33,1.12)	0.71(0.34,1.47)	0.19	
Non-Hispanic White	ref	1.18(0.67,2.07)	0.85(0.54,1.35)	0.55(0.31,0.95)	0.03	
Other races	ref	1.09(0.40,2.99)	0.85(0.31,2.30)	0.77(0.25,2.44)	0.59	
Mexican American	ref	0.97(0.25,3.73)	0.79(0.24,2.64)	0.11(0.03,0.42)	0.003	
Smoking behavior						0.93
Never	ref	0.98(0.54,1.77)	0.96(0.56,1.65)	0.56(0.30,1.02)	0.08	
Former	ref	1.06(0.49,2.29)	0.70(0.34,1.41)	0.48(0.20,1.16)	0.08	
Now	ref	1.27(0.56,2.86)	0.64(0.27,1.50)	0.55(0.24,1.25)	0.09	
Alcohol consumption						0.15
Former	ref	0.61(0.31,1.20)	0.78(0.44,1.39)	0.33(0.18,0.61)	0.01	
Mild	ref	1.83(0.90,3.69)	0.93(0.50,1.70)	1.06(0.48,2.36)	0.76	
Moderate	ref	0.44(0.12,1.57)	0.32(0.10,1.06)	0.16(0.04,0.68)	0.02	
Never	ref	0.88(0.35,2.23)	1.14(0.46,2.83)	0.53(0.20,1.40)	0.42	
Heavy	ref	2.44(0.60,9.92)	0.97(0.29,3.17)	0.67(0.14,3.16)	0.43	
Hypertension						0.96
No	ref	1.04(0.43,2.54)	0.96(0.36,2.54)	0.49(0.16,1.52)	0.24	
Yes	ref	1.06(0.66,1.71)	0.76(0.50,1.16)	0.54(0.34,0.86)	0.01	
Diabetes						0.37
No	ref	1.33(0.79,2.22)	0.85(0.56,1.28)	0.57(0.35,0.93)	0.02	
Yes	ref	0.68(0.39,1.21)	0.69(0.39,1.21)	0.46(0.21,1.02)	0.04	
Asthma						0.53
No	ref	1.11(0.71,1.74)	0.78(0.53,1.16)	0.50(0.31,0.79)	0.002	
Yes	ref	0.98(0.45,2.12)	0.88(0.40,1.89)	0.96(0.42,2.20)	0.79	

Variable	Vitamin B6 Consumption Quartile, mg/day				*P*	*P* for interaction
	Q1(<1.290)	Q2(1.290-)	Q3(1.796-)	Q4(≥2.470)		
Arthritis						0.05
No	ref	1.52(0.85,2.72)	0.71(0.40,1.28)	0.82(0.45,1.48)	0.2	
Yes	ref	0.83(0.50,1.36)	0.87(0.54,1.39)	0.36(0.21,0.63)	0.003	
MIPA						0.94
No	ref	1.03(0.66,1.62)	0.84(0.57,1.25)	0.55(0.32,0.94)	0.03	
Yes	ref	1.14(0.59,2.20)	0.73(0.41,1.29)	0.51(0.25,1.02)	0.03	
PHQ-9 depression score						0.98
<10	ref	1.05(0.64,1.75)	0.80(0.52,1.23)	0.53(0.32,0.86)	0.01	
≥10	ref	1.13(0.50,2.59)	0.70(0.33,1.45)	0.56(0.19,1.61)	0.17	

Notes: All covariates were adjusted in this model without adjusting the stratified variable itself. **Abbreviations:** MIPA: Moderate-intensity physical activity; PHQ: patient health questionnaire.

controlled trials provide high-quality evidence, although they can be resource-intensive and require long follow-up periods. Our study revealed a protective link between higher dietary vitamin B6 consumption and lower stroke prevalence, which persisted after adjusting for multiple covariates. Several mechanisms may explain the effect of vitamin B6 on stroke occurrence. Homocysteine (Hcy) is a sulfur-containing, non-protein-derived amino acid [39,40]. Previous studies have demonstrated that S-adenosyl-L-homocysteine can produce homocysteine under the action of S-adenosyl-L-homocysteine hydrolase [41], When vitamin B6 deficiency inhibits the conversion of homocysteine to cysteine, it can lead to hyperhomocysteinemia (HHcy) [42]. In more recent findings, brain inflammation induced by elevated HHcy has been identified as a mechanism in the pathogenesis of Alzheimer's disease [43]. Meanwhile, HHcy is a distinct risk factor for atherosclerosis, hypertension, and stroke [44,45]. Hcy induces chronic inflammation of the arterial wall, promotes the development of atherosclerosis, and causes damage to the blood–brain barrier, which can induce stroke [46–48]. Vitamin B6 is involved in the removal of homocysteine from the body via remethylation to methionine [49–51] and transsulfuration to cysteine, potentially mitigating the risk of stroke. According to meta-analyses, a 19–24 % reduction in stroke incidence is associated with a 3 μmol/L decrease in blood homocysteine levels [18,50,52]. Inflammation plays an important role in stroke pathogenesis. Neutrophils play a crucial role in precipitating ischemic stroke, thrombosis, and atherosclerosis [53–55]. Neutrophils play a crucial role in thrombus formation through various mechanisms. They attach to platelets; break down coagulation factors, such as tissue factor pathway inhibitors and factor X; and secrete substances, such as neutrophil extracellular traps and tissue factors, that promote blood clotting [56]. Furthermore, neutrophils contribute to atherosclerosis and plaque rupture by increasing monocyte infiltration, producing oxidized low-density lipoproteins, and releasing enzymes that weaken the fibrous cap [56]. Muir et al. suggested that patients
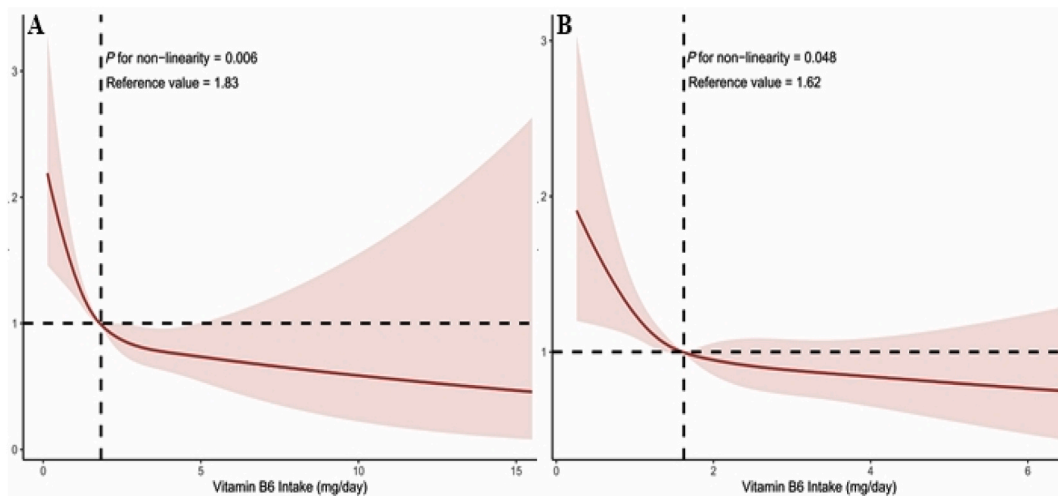
Fig. 4. RCS modeling was utilized to characterize the correlation between dietary vitamin B6 intake levels and stroke risk. Notes: A: RCS before PSM under the fully adjusted model (Model 3); B: RCS after PSM under the fully adjusted model (Model 3). (Please print in color).

with elevated C-reactive protein (CRP) levels are at a higher risk of stroke [57]. An animal study showed that vitamin B6 attenuated neutrophil infiltration in the lungs and liver and produced anti-inflammatory effects [58]. Shan et al. recently reported that administering vitamin B6 significantly suppressed systemic inflammation and acute pneumonia induced by LPS in mice [59]. Vitamin B6 improves immunity, leading to increased antibody production and enhancing communication between cytokines and chemokines [60]. Another study showed that pretreatment of RAW cells with vitamin B6 (pyridoxal) inhibited LPS-induced expression of inducible nitric oxide synthase and COX-2 at both mRNA and protein levels [16]. It also inhibited the nuclear translocation of the LPS-induced pro-inflammatory transcription factor NF-κB, thereby exerting an anti-inflammatory effect [16]. Interleukin-1β (IL-1β) is an inflammatory regulatory factor that, when activated, can lead to an inflammatory response [61]. Vitamin B6 has been shown to reduce IL-1β production by inhibiting the NLRP3 inflammasome's response to various NLRP3 inflammasome stimuli, thereby mitigating inflammatory reactions [62]. Morris et al. found that dietary vitamin B6 consumption was negatively correlated with CRP levels [63]. Therefore, inhibition of neutrophil-mediated inflammatory responses and reduction of CRP levels may be one of the mechanisms by which vitamin B6 reduces the incidence of stroke. In addition, vitamin B6 may also reduce systemic inflammation and thus reduce the risk of stroke by inhibiting the expression of pro-inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) and inhibiting NF-κB activation. However, more research is needed to further confirm the role of vitamin B6 in stroke prevention through these anti-inflammatory effects.

The benefits of vitamin B6 to the human body are obvious. However, certain medications interfere with the metabolism and status of vitamin B6, which may increase the risk of stroke. Some studies have shown that certain anti-epileptic drugs, including valproic acid, carbamazepine, and phenytoin, can increase the rate of vitamin B6 degradation, leading to decreased plasma pyridoxal 5′-phosphate (PLP) concentrations and hyperhomocysteinemia. This may potentially increase the risk of stroke [64,65]. Plasma concentrations of PLP are usually low in patients treated with theophylline, which may lead to theophylline-related neurological and central nervous system side effects, including seizures [66,67]. Therefore, when supplementing with vitamin B6, we should be aware of drug interactions and the possible effects of co-medication.

Despite providing robust evidence of the association between dietary vitamin B6 consumption and stroke risk, our study has some limitations. The study's stroke inclusion criteria relied on self-reported medical history without specifying subtype or staging. Nonetheless, the questionnaire used has been utilized in multiple previous studies to assess stroke [20,68]. Furthermore, the dietary vitamin B6 consumption in the research study was obtained via two 24-h recalls, possibly introducing bias in recall, and not precisely reflecting the typical vitamin B6 intake of the individual. However, several studies have demonstrated that two 24-h recalls may be adequate for assessing daily dietary consumption [20,69]. Because this was an observational study, we could not establish a causal link between vitamin B6 intake and the risk of stroke. Further randomized controlled trials are required to confirm this association and examine its mechanisms.

5. Conclusions

We analyzed the NHANES database to investigate the association between vitamin B6 intake and stroke risk. These results indicate that individuals with higher vitamin B6 intake have a lower risk of experiencing a stroke. Furthermore, our study found that the benefits of higher vitamin B6 intake in reducing stroke risk were consistent across various subgroups, including different age groups (<60 and ≥60 years), genders (male and female), ethnicities (non-Hispanic whites and Mexican Americans), former smokers, mild-to-moderate drinkers, hypertensive patients, those without diabetes, those without asthma, those with and without arthritis history, individuals engaging in moderate-intensity physical activity, and those with PHQ-9 depression scores <10 and ≥ 10.

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Ethical statement

The National Center for Health Statistics Ethics Review Board approved the NHANES survey protocols, and the participants provided written informed consent.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Data availability statement

The datasets used in this study were extracted from the NHANES (http://www.cdc.gov/nchs/nhanes.htm).

CRediT authorship contribution statement

Chao Wang: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Bo Li:** Methodology, Data curation, Conceptualization. **Qian Zhu:** Software, Methodology, Conceptualization. **Qikeng Zhang:** Visualization, Software. **Zhenyan Xie:** Investigation, Data curation, Conceptualization. **Huixi Xie:** Methodology, Data curation. **Xuesong Li:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31125.

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