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Association of dietary vitamin K1 intake with epilepsy in adults in US: a cross-sectional study of National Health and Nutrition Examination Survey 2013–2018

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Abstract

Objective Information regarding the relationship between epilepsy and vitamin K1 remains unclear. We aimed to assess the association between dietary vitamin K1 intake and epilepsy.

Methods Data was obtained from the National Health and Nutrition Examination Survey (NHANES) conducted from 2013 to 2018. The study enrolled participants aged ≥ 18 years that provided complete information on their dietary vitamin K1 intake and epilepsy status. Weighted multivariable regression and subgroup analyses were performed to detect the association between dietary vitamin K1 intake and epilepsy.

Results In total, 10 137 participants (mean age, 48 years) were enrolled. Among them, 84 (0.83%) participants were identified as having epilepsy, whereas 10 053 (99.17%) were included in the non-epilepsy group, with an average dietary vitamin K1 intake of 67.2 ± 6.9 and 105.5 ± 1.5 μg/d, respectively. Each unit (10 μg/d) increase in vitamin K1 intake was associated with a 7% decrease in the odds of epilepsy (odds ratio = 0.93, 95% confidence interval: 0.88–0.98, $p = 0.011$). Multivariate logistic regression analysis revealed that participants in the higher quartile had lower odds of epilepsy than those in the first quartile of vitamin K1 intake. Subgroup analysis showed a stable and consistent inverse association between dietary vitamin K1 intake and epilepsy.

Conclusion Higher dietary vitamin K1 intake was associated with lower incidence of epilepsy. Our study did not establish a cause-and-effect relationship. Further large-scale prospective studies and randomized trials are warranted to confirm our findings.

Keywords Vitamin K1, Epilepsy, NHANES, Cross-sectional study, Adults

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Introduction

Epilepsy is one of the most common neurological disorders, affecting an estimated 70 million people worldwide [1, 2]. Despite the wide range of available antiseizure drug treatments, 30% of patients with epilepsy remain poorly controlled; moreover, antiseizure drugs can incur a variety of adverse effects such as teratogenesis, pancreatitis, and liver failure [3, 4]. The identification of dietary ingredient intake beneficial for epilepsy may help affected individuals to better control their seizures through dietary modifications.

Vitamin K serves as a cofactor for the enzyme γ-glutamyl carboxylase, which activates various vitamin K-dependent proteins essential for neuronal survival and function. Among these proteins, Gas6 and Protein S play significant roles in numerous cellular processes, such as cell growth, survival, and apoptosis [5, 6]. Vitamin K is important in regulating inflammation and its potential antioxidant properties may influence inflammatory processes, alleviate inflammation and promote overall metabolic health. Inadequate levels of vitamin K can result in neurological disorders [7–11]. Moreover, recent research has investigated the direct anticonvulsant effects of vitamin K analogs in animal models. Novel vitamin K compounds, for instance, have demonstrated the ability to suppress seizure activity in zebrafish and mouse models, suggesting a direct impact on neuronal excitability [12]. These observations imply that vitamin K may not only enhance its supportive role in mitigating inflammation and oxidative stress but also possesses intrinsic anticonvulsant characteristics that merit further exploration. Vitamin K1 (phylloquinone) and vitamin K2 (menaquinone) are physiologically active forms of Vitamin K. Vitamin K1 is found mainly in green leafy vegetables and their oils, whereas vitamin K2 is restricted to fermented foods; however, dietary data on vitamin K2 intake is lacking in European and American food databases, including the National Health and Nutrition Examination Survey (NHANES) database. Therefore, an accurate estimation of the dietary intake of vitamin K2 is not yet possible. In addition, no large-sample observational studies or randomized clinical trials have been conducted to further demonstrate the relationship between dietary vitamin K1 intake and epileptic disorders in the general population. We performed a cross-sectional study to determine the association between dietary vitamin K1 intake and epilepsy in US adults using data from the NHANES database.

Materials and methods

Study population

To assess the association between dietary vitamin K1 intake and epilepsy in adults from the US, we obtained and analyzed the recorded data from the NHANES database (from 2013 to 2018) maintained by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) in the USA. To ensure a better sample representation of the USA populations, a stratified multistage probability sampling procedure was utilized. In total, 29 400 cases were included in our study. Among them, 11 439 cases aged < 18 years and 7 473 cases with missing data (poverty to income ratio [PIR], marital status, educational level, general health condition, diabetes, hypertension, stroke, patient health questionnaire [PHQ-9], physical activity, and sleep disorder) were excluded from the analysis. Of note, the PHQ-9 questionnaire is a validated and reliable nine-item assessment tool for identifying a major depressive episode according to the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association. Participants were asked by trained interviewers to reply to the nine-item questions of the PHQ-9 at the Mobile Examination Center (MEC), using the Computer-Assisted Personal Interview system.

Before the start of the statistical analysis, dietary vitamin K1 intake was screened for outliers. Extreme cases of dietary vitamin K1 intake, defined as values exceeding two standard deviations from the mean (n=351), were excluded from the analysis, resulting in an approximate normal distribution of the data on dietary vitamin K1 intake. All datasets used in this study were obtained from publicly available databases (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). The CDC provides free access to NHANES data via their official website. The National Center for Health Statistics and Research Ethics Review Committee approved the use of human participants for the NHANES study and written informed consent was provided by each participant.

Assessment of dietary vitamin K intake

Using a validated 24-h recall method, the types and amounts of foods and beverages consumed during the 24-h period prior to the interview were recorded to estimate the total intake of vitamin K1. The first dietary recall was conducted at the MEC, whereas the second dietary recall was performed through a telephone interview 3–10 d later. Total vitamin K1 intake was defined as the calculated intake derived from one 24-h dietary recall or the mean of the calculated intake derived from two 24-h dietary recalls. This approach aimed to partially represent participants' long-term dietary patterns and reduce the potential bias associated with a single-day assessment. The content of vitamin K1 in various consumed foods and beverages was calculated based on data from the food composition table of USDA's Food and Nutrient Database for Dietary Studies (FNDDS). Each food or beverage item consumed is assigned an 8-digit FNDDS

code in NHANES. In addition, FNDDS also included comprehensive information for coding food and beverage portion sizes and nutrient values across the US, enabling the conversion of food and beverage intake information in NHANES into estimated vitamin K1 intake values. The reference vitamin K values in the FNDDS were provided from the USDA National Nutrient Database for Standard Reference.

Epilepsy

Epileptic seizure events were not directly assessed in the NHANES questionnaire data. Instead, information on epilepsy was gathered through face-to-face interviews between investigators and participants. We referenced the same method used to define epilepsy in previous studies [13–17]. Participants were categorized based on whether they reported taking at least one medication specifically for "epilepsy and recurrent seizures" (International Classification of Diseases [ICD] code G40) [15, 16]. All participants provided the names of medications prescribed by a health professional that they had taken within the past 30 days, along with the primary reasons for using each antiseizure medication. Individuals were defined as having epileptic seizure events if they consumed at least one antiseizure medication or reported recurrent seizures. While this identification method has its limitations, it remains the most effective approach for classifying participants in this study as either having epilepsy or not.

Covariates

Covariates with potential associations between dietary vitamin K1 intake and epilepsy were identified in this study based on existing literature information and our clinical experience. Covariates included age, sex, alcohol use, general health condition, depression status, physical activity, diabetes, hypertension, stroke, and sleep disorder. Diabetes status was classified as yes, no, or borderline based on the reply to the question: "Have you ever been told you have diabetes or sugar disease by a doctor or health professional?" Stroke status was classified as yes or no based on the response to the question: "Have you ever been told you have had a stroke by a doctor or health professional?" Heavy alcohol use was classified as yes or no based on self-assessment by replying to the question: "Have you ever had 4/5 or more drinks daily? Hypertension was classified as yes or no based on the response to the question: "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" Trouble sleeping status was classified as yes or no based on the reply to the question: "Have you ever been told by a doctor or other health professional that you have trouble sleeping?" The PHQ-9 was also used to calculate depression score, which ranged from 0 to 27. Depression was rated as "none or minimal" (0–4), "mild" (5–9), "moderate" (10–14), "moderately severe" (15–19), or "severe" (20–27). The importance of drug interactions should be highlight, especially in the case of Vitamin K1 and warfarin. Upon careful examination of our data, we have discovered that none of the participants with epilepsy in our study population take warfarin.

Statistical analysis

All statistical analyses abided by the guidelines set forth by the CDC. An appropriate NHANES sample weight was applied when the NHANES multistage cluster surgery design was considered. Continuous data are shown as the mean ± standard error (SE), whereas categorical variables are represented as percentages. We analyzed comparisons of variables between epilepsy and control cases using a weighted linear regression model for continuous variables and a weighted chi-square test for categorical variables. We investigated the association between dietary vitamin K1 intake and epilepsy using both univariate and multivariate logistic regression analyses. Model 1 was adjusted for no factors; model 2 was adjusted for age, sex, and race; whereas model 3 was adjusted for all covariates in the multivariate logistic regression. A weighted generalized additive model (GAM) and smooth curve fitting were used to further explore the association between dietary vitamin K1 intake and epilepsy. GAM is a type of statistical model that extends the linear regression model to accommodate nonlinear relationships between dependent and independent variables. Smooth curve fitting is the process of fitting a smooth function to a set of data points without imposing a rigid parametric form on the relationship between the variables. Hence, smooth curve fitting techniques are used to create a smooth curve that passes through the data points, capturing the underlying trend while minimizing noise. Using the log-likelihood ratio test model, an interaction term was used to investigate the heterogeneity of associations between different stratified subgroups (age, sex, alcohol use, general health condition, depression status, physical activity, diabetes, hypertension, stroke, and sleep disorder). The Empower (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and R version 3.4.3 (http://www.Rproject.org, The R Foundation) software were used for all of our analyses.

Results

Baseline participant characteristics

A total of 10 137 patients with a mean age of 48 years were enrolled in this study. Among these, 84 participants were identified as having epilepsy, with an average dietary vitamin K1 intake of 67.2 ± 6.9 μg/d, whereas 10 053 were in the non-epilepsy group, with an average dietary

vitamin K1 intake of 105.5 ± 1.5 μg/d. The weighted population baseline characteristics are presented in Table 1.

Higher dietary vitamin K intake associated with lower incidence of epilepsy

We performed a univariate logistic regression analysis that revealed an inverse association between dietary vitamin K1 intake (10 μg/d) and incidence of epilepsy (odds ratio [OR] = 0.91, 95% confidence interval [CI]: 0.85–0.96, $p = 0.002$). Furthermore, we converted dietary vitamin K1 intake into a categorical variable (Quartile 1–4). Compared with very low dietary vitamin K1 intake (Quartile 1), we observed that the incidence of epilepsy was lower in the higher dietary vitamin K1 intake group, as shown in Table 2. In the multivariate logistic regression analysis, we also found that higher dietary vitamin K1 intake was associated with a lower incidence of epilepsy, when dietary vitamin K1 intake was presented as a continuous variable (10 μg/d) or a categorical variable (Quartile 1–4). The results of Model 1 (adjusted for no covariates), Model 2 (adjusted for age, sex, and race), and Model 3 (adjusted for all covariates) were presented in Table 3. We also used a generalized additive model and smooth curve fitting to further explore the relationship between dietary vitamin K1 intake and epilepsy (Fig. 1). This analysis suggested an inverse relationship between dietary vitamin K1 intake and epilepsy.

Subgroup analysis

We also conducted a subgroup analysis to assess the robustness of the association between dietary vitamin K1 intake and epilepsy. We detected interactions with age, sex, alcohol use, general health condition, depression status, physical activity, diabetes, hypertension, stroke, and sleep disorder. In particular, we found that the adjusted ORs tended to change slightly across the stratified groups, with increased dietary vitamin K1 intake showing an overall protective efficiency against epilepsy. We did not identify any significant interaction terms for the covariates mentioned above (all p values > 0.05), suggesting that the inverse association between dietary vitamin K1 intake and epilepsy was stable and consistent across populations with different demographic characteristics, medical history, and lifestyle habits, as shown in Table 4.

Discussion

The results of this study improve our understanding of the relationship between dietary vitamin K1 intake and epilepsy. In particular, after adjusting for covariates, we detected an inverse relationship between dietary vitamin K1 intake and epilepsy, which was consistent and robust among subgroups with different demographic characteristics, medical history, and lifestyle habits.

Several possible explanations underpin this inverse association between dietary vitamin K intake and epilepsy. Abnormal mitochondrial energy metabolism plays an important role in epilepsy pathogenesis. For instance, brain areas ipsilateral to epileptic lesions are known to be commonly hypometabolic [18–20]. The vitamin K family contains naphthoquinone, which plays a role in the function of the nervous system [5, 21]. Vitamin K affects mitochondrial function via mitochondrial respiration and ATP production. In HT-22 cells and the pentylenetetrazol-induced zebrafish seizure model, vitamin K was reported to increase the ATP level by 11.0–25.2% and 19.0–21.4%, respectively [12, 22]. Another significant mechanism by which vitamin K may affect seizure activity is through its modulation of inflammatory responses. Studies have demonstrated that vitamin K can suppress the expression of inflammatory cytokines, such as interleukin-6, through the inhibition of the nuclear factor kappa B signaling pathway [23, 24]. This is particularly significant in epilepsy, where neuroinflammation is known to increase seizure susceptibility and neuronal injury. By decreasing inflammation, vitamin K may help stabilize neuronal environments and mitigate excitotoxic effects associated with seizures [23, 24]. Moreover, vitamin K has been recognized as a powerful antioxidant, supporting its neuroprotective role. Its antioxidant properties help counteract oxidative stress, a condition often exacerbated during seizures, which can lead to neuronal damage [25–27]. For example, research has shown that vitamin K can inhibit the production of reactive oxygen species, thus protecting neurons from oxidative injury [27]. This antioxidant activity is critical for maintaining neuronal integrity and function, particularly in individuals prone to seizures. Vitamin K regulates the γ-glutamyl carboxylation of vitamin K-dependent proteins, which helps maintain calcium ion homeostasis in cells. Calcium ions play an important role in the onset of seizures, with increased glutamate release into synaptic clefts owing to faulty calcium transport potentially contributing to the occurrence of seizures [24, 28, 29]. Thus, the capacity of vitamin K to alter calcium ion levels in neurons may be crucial for its antiseizure function [22].

It is also crucial to analyze the reasons why Vitamin K1 intake is low in individuals with epilepsy. The dietary habits of individuals with epilepsy may contribute to lower vitamin K intake. Individuals with epilepsy may avoid green leafy vegetables and certain oils that are high in vitamin K1 due to concerns about interactions with their medications. Additionally, the overall dietary patterns of individuals with chronic conditions often lack diversity, which can lead to inadequate intake of essential nutrients, including vitamin K1. This is also compounded by the potential for antiepileptic drugs to cause gastrointestinal side effects. Future research should focus on

Table 1 Baseline characteristics of participants, weighted

	Nonepileptic (*n* = 10 053)	Epileptic (*n* = 84)	*P*-value
Vitamin K1 (μg/d)	105.5 ± 1.5	67.2 ± 6.9	< 0.001
Age (years)	48.0 ± 0.4	53.7 ± 2.5	0.031
Sex, n (%)			0.191
Men	48.6 (47.4, 49.9)	38.4 (24.3, 54.8)	
Women	51.4 (50.1, 52.6)	61.6 (45.2, 75.7)	
Race, n (%)			0.349
Mexican American	8.7 (6.7, 11.3)	11.4 (5.6, 21.7)	
Non-Hispanic White	66.0 (61.9, 69.8)	64.9 (49.9, 77.4)	
Non-Hispanic Black	10.4 (8.5, 12.6)	14.6 (7.0, 27.9)	
Other races	14.9 (13.1, 16.9)	9.2 (4.8, 16.9)	
PIR, n (%)			< 0.001
< 1.2	34.6 (32.0, 37.2)	61.9 (48.8, 73.4)	
≥ 1.2	65.4 (62.8, 68.0)	38.1 (26.6, 51.2)	
Marital status, n (%)			0.020
Married/Living with partner	63.1 (60.9, 65.2)	41.8 (25.1, 60.6)	
Widowed/ Divorced/ Separated	18.6 (17.1, 20.2)	30.4 (19.0, 44.9)	
Never married	18.3 (16.8, 20.0)	27.8 (15.1, 45.6)	
Educational level, n (%)			0.027
< High school	11.8 (10.3, 13.5)	23.3 (14.3, 35.4)	
High school	24.3 (22.6, 26.1)	24.1 (13.6, 39.1)	
> High school	63.8 (61.2, 66.4)	52.6 (37.6, 67.2)	
Heavy alcohol use, n (%)			0.795
Yes	15.0 (13.8, 16.4)	17.6 (9.8, 29.5)	
No	75.1 (73.2, 76.9)	70.7 (52.6, 83.9)	
Unknown	9.9 (8.4, 11.5)	11.8 (4.4, 27.9)	
General health condition, n (%)			< 0.001
Excellent and very good	41.6 (39.4, 43.8)	20.1 (10.1, 35.8)	
Good	40.2 (38.7, 41.8)	32.1 (18.9, 48.8)	
Fair or poor	18.2 (16.7, 19.8)	47.9 (34.4, 61.6)	
Diabetes, n (%)			0.160
Yes	11.3 (10.3, 12.3)	19.8 (9.2, 37.6)	
No	86.5 (85.4, 87.6)	76.4 (59.1, 87.9)	
Borderline	2.2 (1.9, 2.7)	3.8 (0.9, 14.4)	
Hypertension, n (%)			0.002
Yes	33.2 (31.4, 35.0)	58.3 (43.1, 72.0)	
No	66.8 (65.0, 68.6)	41.7 (28.0, 56.9)	
Stroke, n (%)			< 0.001
Yes	3.0 (2.5, 3.4)	25.8 (14.2, 42.3)	
No	97.0 (96.6, 97.5)	74.2 (57.7, 85.8)	
PHQ-9 score, n (%)			< 0.001
0–4	75.7 (74.3, 77.0)	55.0 (41.1, 68.1)	
5–9	16.1 (15.1, 17.1)	22.4 (13.0, 35.9)	
10–14	5.4 (4.7, 6.1)	7.7 (3.3, 17.1)	
15–19	2.0 (1.6, 2.5)	13.2 (5.5, 28.2)	
20–27	0.9 (0.7, 1.1)	1.8 (0.4, 7.9)	
Vigorous activity, n (%)			0.657
Yes	25.4 (23.6, 27.2)	22.9 (13.4, 36.3)	
No	74.6 (72.8, 76.4)	77.1 (63.7, 86.6)	
Sleep disorder, n (%)			0.002
Yes	31.0 (29.2, 32.9)	51.7 (36.7, 66.3)	
No	69.0 (67.1, 70.8)	48.3 (33.7, 63.3)	
Vitamin K1 quartile, n (%)			< 0.001
Q1 (30.9 ± 0.4 μg/d)	23.8 (22.4, 25.2)	49.0 (37.4, 60.8)	

Table 1 (continued)

	Nonepileptic (*n* = 10 053)	Epileptic (*n* = 84)	*P*-value
Q2 (62.4 ± 0.2 μg/d)	24.8 (23.3, 26.4)	22.1 (12.7, 35.5)	
Q3 (104.7 ± 0.5 μg/d)	26.2 (25.1, 27.4)	17.3 (9.7, 29.0)	
Q4 (219.3 ± 2.2 μg/d)	25.2 (23.5, 26.9)	11.6 (4.9, 24.8)	

identifying the underlying causes and developing targeted interventions to improve dietary vitamin K1 intake among epilepsy individuals.

The incidence of epilepsy varies according to demographic characteristics, medical history, and lifestyle habits. Epilepsy is substantially more likely to occur in individuals who have a regular, abusive alcohol consumption pattern [30–32]. Epileptic individuals should consult with their healthcare providers regarding alcohol consumption, as some individuals may need to avoid alcohol altogether due to their specific condition or treatment regimen. Studies also found that epilepsy is associated with a higher risk of diabetes and poor outcomes following diabetes, including pneumonia, urinary tract infection, and septicemia [33, 34]. Several population-based studies and clinical data have revealed a strict relationship between depression and epilepsy. The incidence of epilepsy in patients with depressive symptoms was significantly higher than that in patients without depressive symptoms. Studies have suggested that epilepsy and depression may share regulatory substrates involving the hyperactivity of the hypothalamus-pituitary-adrenal axis [35–38]. While recent advances in the treatment of acute stroke have increased life expectancy, the prevalence of stroke-related epilepsy has also increased. Stroke causes approximately 10% of epilepsy and 55% of newly diagnosed seizures in older adults [39, 40]. Sleep affects the distribution and frequency of epileptiform discharges in humans, with sleep disorders being closely associated with epileptogenesis [41–43]. According to the subgroup analysis in our study, the inverse association between dietary vitamin K1 intake and epilepsy was stable in the subgroups stratified by age, sex, alcohol use, general health condition, depression status, physical activity, diabetes, hypertension, stroke, and sleep disorders, thereby indicating that increased dietary vitamin K1 intake may benefit people with epilepsy across various population settings.

Despite the stratification of the inverse association between vitamin K intake and epilepsy across different demographic characteristics, medical history, and lifestyle habits, many key covariates were not analyzed due to lack of data. Genetic predisposition to epilepsy has been well-documented, with certain genetic mutations or variations increasing an individual's susceptibility to developing epilepsy. Individuals with a family history of epilepsy or known genetic risk factors may have a heightened susceptibility for the condition, potentially influencing their response to dietary factors such as vitamin K1 intake. Moreover, environmental factors play a crucial role in the development and progression of epilepsy. Factors such as prenatal exposure to toxins, early-life stressors, and infections can all contribute to the risk of epilepsy. Acknowledging the complexity of gene-environment interactions is essential when interpreting the association between vitamin K1 intake and epilepsy. Future research should incorporate comprehensive genetic and environmental data to elucidate the underlying mechanisms and identify potential modifiers of this relationship. Of further note, no usage of warfarin was among the participants with epilepsy in our study, thereby mitigating the potential interactions with vitamin K1. While this finding allows us to draw conclusions free from the confounding effects of warfarin, it is important to note that individuals taking warfarin should pay special attention to their vitamin K1 intake due to the notable drug interactions.

Limitations

The limitations of this study must also be considered. First, given the cross-sectional nature of this investigation, we could only infer an association rather than causal interference. Second, assessing vitamin K1 intake by using 24-h recall methods may not be as accurate and could be potentially prone to recall bias. For chronic diseases, epilepsy should not be considered a condition influenced by short-term dietary changes. We recommend that future research employ dietary assessment tools with longer time spans to enhance the understanding of diet's potential impact on epilepsy. This would

Table 2 Results of univariate regression analysis

	Statistics	OR (95% CI) *P*-value
Age (years)	48.0 ± 0.4	1.02 (1.00, 1.04) 0.034
Vitamin K1 intake (10 μg/d)	10.5 ± 0.2	0.91 (0.85, 0.96) 0.002
Sex, n (%)		
Men	48.6	Ref.
Women	51.4	1.52 (0.81, 2.84) 0.201
Race, n (%)		
Mexican American	8.7	Ref.
Non-Hispanic White	10.4	0.75 (0.32, 1.79) 0.527
Non-Hispanic Black	66.0	1.08 (0.43, 2.69) 0.872
Other races	14.8	0.47 (0.19, 1.16) 0.108
PIR, n (%)		
< 1.2	34.8	Ref.
≥ 1.2	65.2	0.33 (0.20, 0.53) 0.001
Marital status, n (%)		
Married/Living with partner	63.0	Ref.
Widowed/Divorced/Separated	18.7	2.47 (1.20, 5.10) 0.019
Never married	18.4	2.29 (0.97, 5.43) 0.066
Educational level, n (%)		
< High school	11.9	Ref.
High school	24.3	0.50 (0.25, 1.03) 0.066
> High school	63.8	0.42 (0.23, 0.76) 0.007
Heavy alcohol use, n (%)		
Yes	15.1	Ref.
No	75.1	0.81 (0.40, 1.64) 0.553
Unknown	9.9	1.02 (0.39, 2.68) 0.969
General health condition, n (%)		
Excellent and very good	41.5	Ref.
Good	40.2	1.65 (0.66, 4.12) 0.285
Fair or poor	18.4	5.45 (2.66, 11.18) < 0.001
Diabetes, n (%)		
Yes	11.3	Ref.
No	86.4	0.50 (0.21, 1.19) 0.123
Borderline	2.2	0.96 (0.20, 4.51) 0.958
Hypertension, n (%)		
Yes	33.3	Ref.
No	66.7	0.36 (0.20, 0.62) 0.001
Stroke, n (%)		
Yes	3.1	Ref.
No	96.9	0.09 (0.04, 0.18) < 0.001
PHQ-9 score, n (%)		
0–4	75.5	Ref.
5–9	16.1	1.92 (1.02, 3.61) 0.049
10–14	5.4	1.98 (0.80, 4.85) 0.145
15–19	2.1	8.96 (3.43, 23.38) 0.001
20–27	0.9	2.66 (0.56, 12.59) 0.226
Vigorous activity, n (%)		
Yes	25.4	Ref.
No	74.6	1.15 (0.63, 2.08) 0.659
Sleep disorder, n (%)		
Yes	31.2	Ref.
No	68.8	0.42 (0.24, 0.74) 0.004
Vitamin K1 quartile, n (%)		
Q1 (30.9 ± 0.4 μg/d)	24.0	Ref.
Q2 (62.4 ± 0.2 μg/d)	24.8	0.43 (0.24, 0.79) 0.009
Q3 (104.7 ± 0.5 μg/d)	26.1	0.32 (0.17, 0.60) 0.001
Q4 (219.3 ± 2.2 μg/d)	25.1	0.22 (0.09, 0.53) 0.002

Data are presented as the mean ± standard error (SE) for continuous variables, whereas as percentage (%) for categorical variables. P value was calculated using logistic regression analysis. OR, odds ration; 95% CI, 95% confidence interval; PIR, poverty to income ratio; PHQ-9, patient Health Questionnaire-9

provide a more comprehensive representation of participants' dietary habits and potentially reveal more robust associations between long-term dietary Vitamin K1 patterns and epilepsy. Third, despite the inclusion of various confounding variables in the analysis, the present study lacked information on some potential confounding factors, such as genetic predisposition to epilepsy, environmental factors, or other unmeasured variables, which could either mask or exaggerate the true association between vitamin K1 intake and epilepsy. We defined patients with epilepsy based on prescription medication history, potentially overlooking individuals with epilepsy who were not currently on medication or those with undiagnosed epilepsy or misdiagnosed with epilepsy. Future research should aim to include a broader range of diagnostic criteria (including clinical history, EEG findings, and other relevant diagnostic tools) and important disease-related covariates (inlcuding number of seizures, type of seizure, number of anti-seizure medications, and age of seizure onset) to capture a more comprehensive understanding of the relationship between Vitamin K1 and seizure. This study was also limited by the low rate of participants with epilepsy, which could lead to nonresponder bias and an underrepresentation of the surveyed population. It should be noted that factors such as nonresponse bias or underrepresentation of certain demographic groups could affect the generalizability of our findings. Furthermore, our findings should be interpreted with caution, as we represented an aggregate analysis that did not account for the distinct pathophysiological mechanisms underlying different forms of epilepsy. Future studies should be conducted in a larger cohort of epilepsy patients to gather more detailed information and permit more nuanced subgroup analyses, thereby allowing for a clearer examination of the association between vitamin K1 intake and epilepsy.

Table 3 Results of multivariate regression analysis

Variable	Model 1[1] (OR (95% CI), *P* value)	Model 2[2] (OR (95% CI), *P* value)	Model 3[3] (OR (95% CI), *P* value)
Vitamin K1 intake (10 μg/d)	0.91 (0.85,0.96) 0.002	0.90 (0.85,0.96) 0.003	0.93 (0.88,0.98) 0.011
Vitamin K1 intake (quartile)			
Q1 (30.9 ± 0.4 μg/d)	Ref	Ref	Ref
Q2 (62.4 ± 0.2 μg/d)	0.43 (0.24,0.79) 0.009	0.42 (0.23,0.76) 0.007	0.43 (0.23,0.80) 0.016
Q3 (104.7 ± 0.5 μg/d)	0.32 (0.17,0.60) 0.001	0.31 (0.16,0.58) 0.001	0.40 (0.21,0.77) 0.014
Q4 (219.3 ± 2.2 μg/d)	0.22 (0.09,0.53) 0.002	0.22 (0.09,0.53) 0.002	0.31 (0.13,0.73) 0.016

In sensitivity analysis, vitamin K intake was converted from a continuous variable to a categorical variable (quartile). OR, odds ration; 95% CI, 95% confidence interval; PHQ-9, patient Health Questionnaire-9

[1]Model 1: not adjusted for covariates

[2]Model 2: adjusted for age, sex, and race

[3]Model 3: adjusted for age, sex, race, marital status, educational level, PIR, heavy alcohol use, general health, stoke, PHQ-9, vigorous activity, diabetes, hypertension, and sleeping disorders

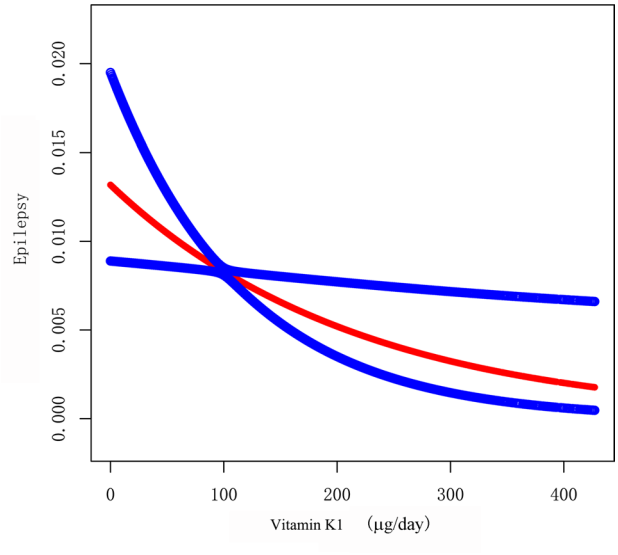

Fig. 1 The relationship between dietary vitamin K1 intake and epilepsy using the generalized additive model and smooth curve fitting

Table 4 Subgroup analysis

	OR (95% CI), *P* value	*P* for interaction
Stratified by age		0.185
Age < 60 (*n* = 6680)	0.90 (0.84, 0.97) 0.012	
Age ≥ 60 (*n* = 3457)	0.97 (0.90, 1.03) 0.324	
Stratified by sex		0.438
Men (*n* = 4953)	0.89 (0.78, 1.02) 0.108	
Women (*n* = 5184)	0.95 (0.89, 1.01) 0.126	
Heavy alcohol use		0.925
Yes (*n* = 1491)	0.92 (0.81, 1.03) 0.160	
No (*n* = 7325)	0.93 (0.87, 0.99) 0.031	
Unknown (*n* = 1321)	0.95 (0.82, 1.10) 0.519	
General health condition		0.999
Excellent and very good (*n* = 3420)	0.93 (0.79, 1.09) 0.362	
Good (*n* = 4238)	0.93 (0.84, 1.03) 0.166	
Fair or poor (*n* = 2479)	0.93 (0.87, 0.99) 0.033	
PHQ-9 score		0.527
0–4 (*n* = 7535)	0.90 (0.84, 0.97) 0.018	
5–9 (*n* = 1724)	0.99 (0.90, 1.09) 0.799	
10–14 (*n* = 555)	0.92 (0.80, 1.05) 0.224	
15–19 (*n* = 221)	0.92 (0.83, 1.02) 0.117	
20–27(*n* = 102)	0.86 (0.74, 0.99) 0.054	
Stratified by vigorous activity		0.386
Yes (*n* = 2321)	0.86 (0.70, 1.06) 0.168	
No (*n* = 7816)	0.94 (0.90, 0.99) 0.025	
Stratified by diabetes		0.473
Yes (*n* = 1516)	0.88 (0.78, 0.99) 0.053	
No (*n* = 8355)	0.94 (0.89, 1.00) 0.054	
Borderline (*n* = 266)	0.84 (0.66, 1.08) 0.190	
Stratified by hypertension		0.534
Yes (*n* = 3798)	0.91 (0.85, 0.98) 0.017	
No (*n* = 6339)	0.95 (0.88, 1.02) 0.170	
Stratified by stroke		0.539
Yes (*n* = 406)	0.91 (0.82, 1.00) 0.055	
No (*n* = 9731)	0.94 (0.88, 0.99) 0.037	
Stratified by sleeping disorders		0.123
Yes (*n* = 2898)	0.97 (0.91, 1.03) 0.348	
No (*n* = 7239)	0.86 (0.76, 0.97) 0.028	

The results of subgroup analysis were adjusted for all covariates except effect modifier

OR, odds ration; 95% CI, 95% confidence interval; PHQ-9, patient Health Questionnaire-9

Conclusion

A higher dietary vitamin K1 intake was associated with a decreased likelihood of epilepsy. Our study did not establish a cause-and-effect relationship. Our findings need to be confirmed by further large-scale prospective studies and randomized trials.

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Author contributions
Study conception and design: JL and LJ. Acquisition of data: TC and BW. Analysis and interpretation of data: TC, BW, JL, and LJ. Drafting of the manuscript: LJ and TC. Critical revision of the manuscript for important intellectual content: BW, JL, and LJ. Administrative, technical, and material support: TC, BW, JL, and LJ. TC and BW contributed equally to this work. JL and LJ contributed equally to this work. All authors approved the final version of the manuscript.

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Data availability
All datasets used in this study were obtained from the publicly available NHANES database (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The National Center for Health Statistics and Research Ethics Review Committee approved the use of human participants for the NHANES study. In addition, written informed consent was provided by each participant. Due to the retrospective nature of this study (publicly available NHANES data), the requirement for an institutional review board approval was waived.

Consent for publication
NA.

Competing interests
The authors declare no competing interests.

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