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Association of dietary fiber intake with epileptic seizures in U.S. adults: A Population-base study of 13,277 participants

Yi-Bin Zhang [a,b,c,d,1,†], Ye Xu [a,b,1,†], Shu-Fa Zheng [a,b,c,d,1,†], Yuan-Xiang Lin [a,b,c,d,e], De-Zhi Kang [a,b,c,d,e,*], Pei-Sen Yao [a,b,c,d,*]

[a] Department of Neurosurgery, Neurosurgery Research Institute, the First Affiliated Hospital, Fujian Medical University, NO. 20 Chazhong Road, Taijiang District, Fuzhou 350005, China
[b] Department of Neurosurgery, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou 350212, China
[c] Fujian Provincial Clinical Research Center for Neurological Diseases, the First Affiliated Hospital, Fujian Medical University, Fuzhou 350005, China
[d] Fujian Provincial Institutes of Brain Disorders and Brain Sciences, the First Affiliated Hospital, Fujian Medical University, Fuzhou 350005, China
[e] Clinical research and translation center, the First Affiliated Hospital, Fujian Medical University, Fuzhou 350005, China

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ABSTRACT

Objective: Epilepsy, a neurological disorder, is identified by the presence of recurrent seizures. We aimed to detect dietary fiber intake and its association with epilepsy prevalence in U.S. adults.

Methods: This cross-sectional study obtained data from the 2013–2018 National Health and Nutrition Examination Survey database. Univariate and multivariate logistic regression models were employed to estimate the association between dietary fiber intake and epilepsy prevalence. The restricted cubic spline (RCS) model was also applied to investigate the dose-response relationships between dietary fiber intake and epileptic seizure events(ESEs).

Results: Our final sample included 13,277 NHANES participants, with the average prevalence of ESEs being 1.09 % (145/13277). After adjusting for all confounding factors, the third quartile of dietary fiber intake levels remained significantly associated with a decreased risk of ESEs[odds ratios (OR) 0.54,95 % confidence interval (CI) 0.33–0.88, $P = 0.014$)] compared to the first quartile. Higher fiber intake indicated a stable negative association with ESEs in the multivariate logistic regression analysis, weighted generalized additive model. A nonlinear dose-response relationship was observed between dietary fiber intake levels and decreased ESEs risk (P for overall=0.017, P for nonlinear=0.155). Interaction tests showed no significant effect of demographic and disease status on the association between dietary fiber intake and ESEs.

Conclusion: In this cross-sectional study, people with a high dietary fiber intake were at a reduced risk of ESEs. However, further prospective studies are needed to investigate the effect of dietary fiber intake in epilepsy events and to determine causality.

1. Introduction

Epilepsy is a common chronic disorder of temporary abnormal central nervous system function caused by recurrent episodes of abnormal neuronal discharges[1,2]. The current annual incidence of epilepsy is 20–70 per 100,000 people, and the point prevalence of active epilepsy is 6.38 per 1000 people[2]. Epilepsy, the second most common neurological disorder following stroke, is estimated to affect a minimum of 50

Abbreviations: ASM, antiseizure medication; BBB, blood-brain barrier; BMI, body mass index;CDC, Centers for Disease Control and Prevention; CI, confidence interval;ESEs, epileptic seizure events; MEC, mobile examination center;NHANES, National Health and Nutrition Examination Survey database; ICD, International Classification of Diseases; IPR, income to poverty ratio; IQR, interquartile range; RCS, restricted cubic spline; OR, odds ratios; SCFAs, short-chain fatty acids; USDA, United States Department of Agriculture;VIFs, variance inflation factors.

* Corresponding authors.
E-mail addresses: kdz99988@vip.sina.com (D.-Z. Kang), peisen.yao@163.com (P.-S. Yao).
[1] These authors contributed equally to the article as co-first authors.
[†] These authors have contributed equally to this work.

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million people worldwide[2]. The World Health Organization classifies epilepsy as one of the major neuropsychiatric disorders requiring prevention and treatment[2,3].

Previous literature has proposed nutrients to be associated with the pathogenesis of epilepsy[4]. Nutritional factors have been reported to be involved in regulating electrical brain activity[4]. Dietary fiber is a carbohydrate that endogenous digestive enzymes in the body cannot digest. Increased dietary fiber intake has been suggested to provide beneficial health effects in humans[5]. Observational studies and randomized controlled trials have found that increased dietary fiber intake helps reduce total blood cholesterol, lipids, metabolic syndrome, glucose, and hypertension, known risk factors for epilepsy[6,7].

However, there is limited research establishing the correlation between dietary fiber intake and epilepsy, especially in both basic and clinical studies. A cross-section study initiated by Rania Shehata revealed that vegetables, one of the dietary fibers, are associated with seizures[4]. Over the past few decades, large sample studies on dietary fiber from the United States have been limited. They have not adequately investigated potential demographic and socioeconomic differences in different ethnic groups and their impact on the correlation between dietary fiber intake and epilepsy[3]. In addition, the nutritional habits have changed considerably, with more and more ultra-processed foods lacking dietary fiber consumed over the past few decades. Therefore, the beneficial effects of dietary fiber in epileptic seizure events (ESEs) need to be assessed.

Thus, we conducted a secondary exploratory analysis of a large cross-sectional study based on surveillance data from the 2013–2018 National Health and Nutrition Examination Survey (NHANES) to examine the potential association between dietary fiber intake and ESEs.

2. Methods and materials

2.1. Data source

This study conducted a retrospective cross-sectional analysis using NHANES 2013–2018 data. NHANES is a complex, multistage, large-scale civilian survey jointly conducted by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics. The survey content includes health status, population nutrition, lifestyle factors, physical examination, etc. Detailed descriptions of the NHANES protocol have been published elsewhere [1,3]. In short, NHANES is a survey that uses a stratified, multistage probability sampling design to draw representative samples from American civilians to assess American children and adults' nutritional status and physical conditions. During the interview, participants are asked for the indications of each prescription medication. The design and operation of NHANES are available online (https://wwwn.cdc.gov/nchs/nhanes/default.aspx).

Our analysis incorporated data from three NHANES cycles (2013–2014, 2015–2016, and 2017–2018). The participants had at least one of the following conditions excluded: 1) individuals aged <20 years; 2) those with missing crucial covariates, such as education, income to poverty ratio (IPR), body mass index (BMI), smoking status, chronic conditions, and dietary data. Fig. 1 displays a flow chart of the study's selection process and exclusion criteria.

NHANES 2013–2018, National Health and Nutrition Examination Survey 2013–2018.

2.2. Sample size estimation

The sample size for this study was determined based on calculations for cross-sectional studies/surveys[8]. Studies that have been previously published have proposed that the prevalence of epilepsy in the USA might be around 0.5 % to 1 %[9-11]. We aimed to determine the sample size with a precision/absolute error of 5 % and a type 1 error of 5 %.

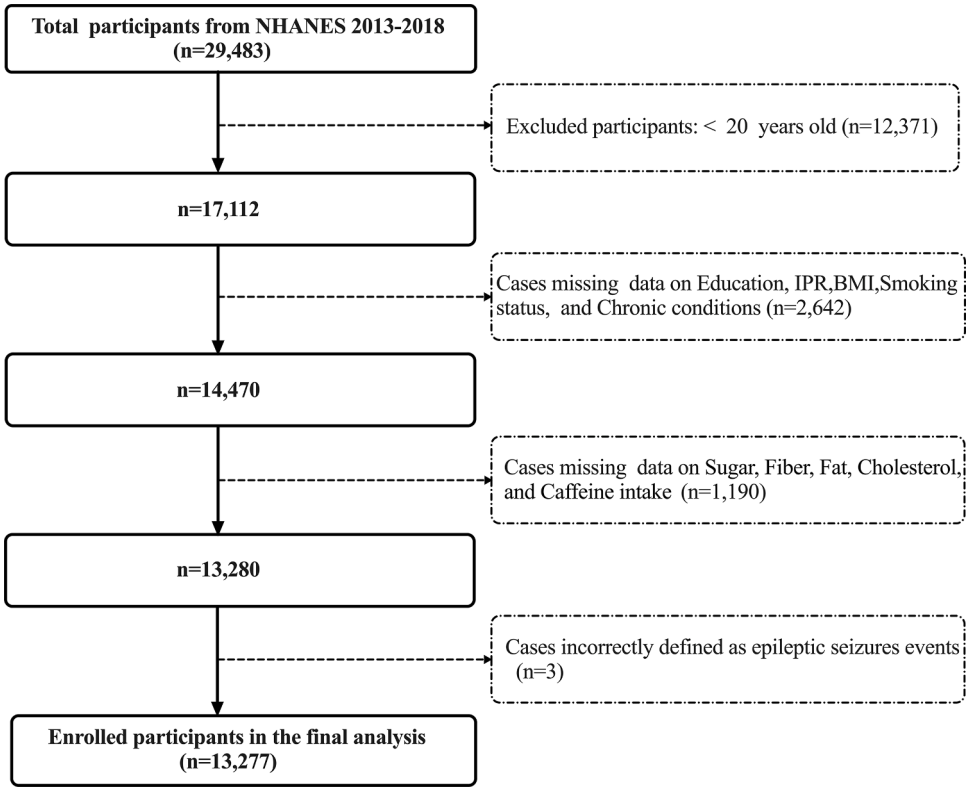

Fig. 1. Selection of study participants in the NHANES 2013–2018.

Therefore, the sample size in the current study varied from 8 to 15. The sample size included in this study far exceeded the estimated sample size, as depicted in Fig. 1.

2.3. Definition of ESEs

ESEs were not directly measured in the NHANES questionnaire data. Information on epilepsy was collected through a face-to-face interaction between the investigator and the participant. We categorized participants according to whether they responded that they were taking at least one medication for "epilepsy and recurrent seizures" (International Classification of Diseases [ICD] G40)[3,11]. All participants provided the names of the medications prescribed by a health professional that they had taken in the last 30 days, along with three main reasons for using each antiseizure medication (ASM). We defined people who consumed at least one ASM or had recurrent seizures as having ESEs [3, 11,12]. This identification method has limitations, but it is the optimal way to classify participants in the study as having epilepsy or not. Thepopulation with seizures or epilepsy had ASMs prescribed, which are detailed in Supplemental Table 1. Upon manual review, if a medication was coded as G40 but not an ASM, we changed the ICD indication to blank and excluded such medications from our definition of treatment for epilepsy.

2.4. Dietary assessment

Through two 24-hour dietary recalls, two trained dietitians collected dietary intake data from the participants using the automated multiple-pass method. The first nutritional recall interview was conducted in the mobile examination center (MEC)visit. The second dietary recall information was collected by telephone interview 3–10 days later[13,14]. The nutritional data collected from the two 24-hour dietary reviews were combined with the United States Department of Agriculture (USDA) Food and Nutrition Database to calculate the participants' daily food intake and various nutrients from all foods. The NHANES Dietary Interviewers Procedure Manuals comprehensively explain the dietary survey methodologies. Even though 24-hour dietary recall may have limitations in reliability and effectiveness, it still offers a more detailed insight into the types and amounts of food consumed compared to food frequency questionnaires. Before the interview at the MEC to obtain the participants' 24-hour nutritional details, a dietary recall interview was conducted to gather information on their fiber, sugar, fat, cholesterol, and caffeine intake.

This study determined daily dietary nutrient intake by averaging two 24-hour dietary recalls and dividing participants into four groups according to quartiles. Dietary fiber, sugar, and fat intake were described as g/d, while cholesterol and caffeine intake were described as mg/d.

2.5. Assessment of covariates

Based on previous studies, we obtained some covariates in association analysis, including gender, age, race, education levels, IPR, BMI, physical activity, hypertension, diabetes, and smoking status through standardized interview questionnaires. Age, IPR, BMI, and dietary nutrient intakes (fiber, sugar, fat, cholesterol, and caffeine) were continuous variables. The remaining variables were categorical. The race was classified as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and others. Education level was classified as <9th Grade, 9th-11th Grade, high school or equivalent, college or above. Physical activity was defined as at least ten continuous minutes in activities of moderate or vigorous intensity outside of work or transportation[15].

The IPR was determined by considering family income and the poverty guidelines the US Department of Health and Human Services set for the survey year[16]. BMI was readily accessible through household and mobile examination center interviews, where skilled technicians obtained it. Using a Toledo digital scale, weight was measured in pounds as the participant stood in the center of the scale facing the recorder, hands at their side, looking straight ahead. Height was determined with a fixed stadiometer that featured a vertical backboard and a movable headboard. All participants were instructed to ensure that the heels of both feet were together, with toes pointed slightly outward at around a 60° angle [15]. A history of hypertension was based on a self-reported physician diagnosis, while a history of diabetes was defined as a self-reported physician diagnosis. Smoking status was grouped into no smoking (<100 cigarettes in a lifetime) and smoking (>100 cigarettes in a lifetime). Further details regarding the covariates mentioned above were available on the NHANES website. We hypothesized that increased dietary fiber intake would be associated with a reduced incidence of epileptic events.

Given the details mentioned, we proposed that an elevated dietary fiber intake might be linked to a reduced likelihood of experiencing epilepsy events.

2.6. Ethics statement

The National Center for Health Statistics Research Ethics Review Board approved the NHANES study, and all who participated in the survey signed an informed consent form. The NHANES database was open to the public and did not require ethical or administrative permission. More details are available on the web (www.cdc.gov/nchs/nhanes/). As a deidentified secondary data analysis using an open-access database, the Ethics Committee of the First Affiliated Hospital of Fujian Medical University waived informed consent.

2.7. Statistical analysis

Continuous variables are expressed as median (interquartile range, IQR), while categorical variables are presented as percentages. The Shapiro-Wilk normality test was used to assess the normality of the distribution of continuous variables. The Chi-square test assessed differences in population characteristics within the survey cycle for categorical variables, and the Mann-Whitney U test or Wilcoxon rank-sum test was applied for continuous variables.

Weighted binary logistic regression models with covariates were employed to estimate the odds ratio (OR) 95 % confidence intervals (CIs) for the associations of dietary fiber with ESEs. Univariate logistic analysis and a multivariate logistic regression model were performed to investigate the independent association between dietary fiber and ESEs. Drawing from previous research [12,17,18], four weighted logistic regression models were created with varying adjustments to account for the different effects of covariates on the outcome variable of ESEs, facilitating statistical inference. Model 1 was unadjusted. Model 2 was adjusted for age, gender, and race. Model 3 was further adjusted for age, gender, race, diabetes and hypertension.. Model 4 was adjusted for age, gender, race, education level, IPR, BMI, sugar, total fat, cholesterol, caffeine, physical activity, diabetes, hypertension, and smoking status. The restricted cubic spline (RCS) models were utilized to assess linear and nonlinear associations[19]. The RCS model is a statistical analysis method used to create a smooth visual curve describing the linear/nonlinear relationship between dietary fiber and ESEs. This study applied the RCS model with the dietary fiber's 5th, 27.5th, 50th, 72.5th, and 95th as the five knots for observing the presence of nonlinear trends.

In addition, we performed sensitivity analyses. First, we performed subgroup analyses for the incidence of ESEs, grouped by sex, age (< 60 yrs or≥60 yrs.), race, BMI (<30 or ≥30), IPR(<1.3, 1.3–3.49, ≥3.5), physical activity, diabetes, hypertension, and smoking status[20-22], and tested for interactions between grouping variables and dietary using likelihood ratio tests. The stratification was conducted to explore potential threshold effects and ensure that outliers or extreme values did not drive the association observed. Then, we also analyzed a set of 3 knots (5th, 50th, and 95th) and 4 knots (5th, 35th, 65th, and 95th) to

test the stability of the nonlinear correlations obtained by RCS[17].

All statistical analyses were performed with R software, version 4.2.1. Statistical significance was determined when $P < 0.05$.

3. Results

3.1. General characteristics of study participants

Fig. 1 presents the study design, sampling, and exclusion. Our final sample included 13,277 NHANES participants, of which 145(1.09 %) were diagnosed with ESEs. Table 1 presents the baseline characteristics of 13,277 participants categorized into quartiles according to their dietary fiber intake quartile. Compared to the lower levels of fiber, we found that participants with higher fiber intakes tended to be male, had higher education levels, lower BMI, more sugar, fat, and cholesterol intakes, fewer participants with hypertension, and fewer smokers. Furthermore, as dietary fiber quartiles increased, the prevalence of epilepsy declined gradually from 1.59 % in Q1 to 0.81 % in Q3. Still, it is interesting that it rose to 0.99 % in Q4.

3.2. Univariate logistics analysis of ESEs-related variable

Given that all continuous variables were not normally distributed, we used Mann-Whitney U testing for group comparisons between individuals with ESEsand those without (Table S2). Age, race, IPR, fiber intake, history of hypertension, and smoking status were all found to be associated with ESEs (Table S2). Also, weighted univariate logistic regression analysis was conducted to observe the associations between age, gender, race, education level, IPR, BMI, physical activity, diabetes, hypertension, smoking status, dietary fiber, sugar, fat, cholesterol intakes, and ESEs in the US population. Age was positively associated with ESEs, with an OR of 1.014 (95 % confidence interval [CI]: 1.004–1.023, Table 2). Participants with a history of hypertension, borderline diabetes, and smoking were more likely to develop ESEs, with ORs of 2.43 (95 % CI: 1.743–3.388), 2.147(95 %CI: 1.040–4.433), and 1.527 (95 % CI: 1.100–2.121), respectively (Table 2). Sugar and caffeine intake were positively associated with the prevalence of ESEs. In addition, IPR and dietary fiber were found to be negatively associated with ESEs, with an OR of 0.735(95 %CI: 0.653–0.827, $P < 0.001$) and 0.975 (95 % CI: 0.958–0.993, $P = 0.007$), respectively. Participants in the Q2-Q4 quartiles of dietary fiber intake were less likely to develop ESEs than those in Q1, with ORs of 0.622 (95 % CI: 0.401–0.965), 0.504(95 %CI: 0.316–0.804), and 0.616 (95 % CI: 0.397–0.956), respectively. However, gender, BMI, physical activity, fat, and cholesterol intake were not found to be associated with ESEs occurrence in this study ($P > 0.05$) (Table 2).

3.3. Multivariable logistics regression analysis of the association between dietary fiber and ESEs

To deal with the issue of multicollinearity caused by multiple covariates, we performed the multilinearity diagnosis that involved all

Table 1
Baseline characteristics of participants according to quartiles of dietary fiber in the NHANES 2013–2018.

Variables	Dietary fiber intake				*P*-value
	Q1<9.40	Q2 9.40–14.50	Q3 14.60–21.80	Q4≥21.90	
N	3271	3316	3343	3347	
Gender (n, %)					<0.001
Male	1347 (41.18 %)	1447 (43.64 %)	1632 (48.82 %)	1970 (58.86 %)	
Female	1924 (58.82 %)	1869 (56.36 %)	1711 (51.18 %)	1377 (41.14 %)	
Age (yrs)	49.00 (34.00–64.00)	49.00 (34.00–64.00)	50.00 (35.00–64.00)	50.00 (35.00–63.00)	0.695
Race (n, %)					<0.001
Mexican American	288 (8.80 %)	345 (10.40 %)	502 (15.02 %)	734 (21.93 %)	
Other Hispanic	308 (9.42 %)	329 (9.92 %)	343 (10.26 %)	367 (10.97 %)	
Non-Hispanic White	1351 (41.30 %)	1383 (41.71 %)	1398 (41.82 %)	1129 (33.73 %)	
Non-Hispanic Black	936 (28.62 %)	765 (23.07 %)	609 (18.22 %)	483 (14.43 %)	
Other	388 (11.86 %)	494 (14.90 %)	491 (14.69 %)	634 (18.94 %)	
Education (n, %)					<0.001
Less than 9th Grade	255 (7.80 %)	202 (6.09 %)	246 (7.36 %)	358 (10.70 %)	
9–11th Grade	498 (15.22 %)	388 (11.70 %)	331 (9.90 %)	346 (10.34 %)	
High school Grad/GED	901 (27.55 %)	829 (25.00 %)	757 (22.64 %)	568 (16.97 %)	
Some college or AA degree	1129 (34.52 %)	1097 (33.08 %)	1080 (32.31 %)	911 (27.22 %)	
College graduate or above	488 (14.92 %)	800 (24.13 %)	929 (27.79 %)	1164 (34.78 %)	
Income-poverty ratio	1.70 (0.93–3.30)	2.14 (1.15–3.90)	2.26 (1.24–4.27)	2.51 (1.22–4.74)	<0.001
Body mass index(kg/m^2)	28.90 (24.60–34.00)	28.60 (24.70–33.50)	28.40 (24.50–33.30)	27.80 (24.25–32.05)	<0.001
Physical activity (n, %)					0.102
No	1825 (55.79 %)	1929 (58.17 %)	1855 (55.49 %)	1870 (55.87 %)	
Yes	1446 (44.21 %)	1387 (41.83 %)	1488 (44.51 %)	1477 (44.13 %)	
Sugar (g/d)	65.09 (36.27–109.27)	85.19 (54.08–130.19)	97.87 (65.62–141.31)	116.14 (77.25–167.85)	<0.001
Total fat(g/d)	51.15 (33.84–72.82)	70.87 (50.87–95.35)	83.57 (60.05–112.98)	99.16 (68.42–137.72)	<0.001
Cholesterol(mg/d)	181.00 (100.00–334.00)	230.00 (135.00–406.00)	264.00 (153.00–451.00)	270.00 (145.00–467.00)	<0.001
Caffeine(mg/d)	90.00 (7.00–196.50)	98.00 (11.00–204.00)	101.00 (13.00–208.50)	96.00 (14.00–204.00)	0.843
Diabetes (n, %)					0.117
No	2717 (83.06 %)	2748 (82.87 %)	2765 (82.71 %)	2783 (83.15 %)	
Yes	485 (14.83 %)	468 (14.11 %)	481 (14.39 %)	456 (13.62 %)	
Borderline	69 (2.11 %)	100 (3.02 %)	97 (2.90 %)	108 (3.23 %)	
Hypertension (n, %)					<0.001
No	1958 (59.86 %)	2056 (62.00 %)	2099 (62.79 %)	2243 (67.02 %)	
Yes	1313 (40.14 %)	1260 (38.00 %)	1244 (37.21 %)	1104 (32.98 %)	
Smoking status (n, %)					<0.001
No	1625 (49.68 %)	1868 (56.33 %)	1982 (59.29 %)	2044 (61.07 %)	
Yes	1646 (50.32 %)	1448 (43.67 %)	1361 (40.71 %)	1303 (38.93 %)	
Epileptic seizure events (n, %)					0.014
No	3219 (98.41 %)	3283 (99.00 %)	3316 (99.19 %)	3314 (99.01 %)	
Yes	52 (1.59 %)	33 (1.00 %)	27 (0.81 %)	33 (0.99 %)	

Median interquartile range (IQR) for continuous variables, count (percentage) for categorical variables.

Table 2
Weighted univariate logistics analysis of ESEs-related variable.

Variables	OR (95 %CI)	*P* value
Gender		
Male	Reference	Reference
Female	0.891 (0.642–1.236)	0.48838
Age	1.014 (1.004, 1.023)	0.00448
Race		
Mexican American	Reference	Reference
Other Hispanic	1.252 (0.660–2.376)	0.49152
Non-Hispanic White	1.247 (0.756–2.055)	0.38722
Non-Hispanic Black	0.902 (0.505–1.614)	0.72922
Other	0.463 (0.216–0.992)	0.04752
Education		
Less than 9th Grade	Reference	Reference
9–11th Grade	1.426 (0.692–2.937)	0.33625
High school Grad/GED	1.234 (0.630–2.419)	0.53968
Some college or AA degree	1.053 (0.543–2.039)	0.87896
College graduate or above	0.740 (0.364–1.502)	0.40421
Income-poverty ratio	0.735 (0.653–0.827)	<0.00001
Body mass index	1.009 (0.988–1.031)	0.40961
Physical activity		
No	Reference	Reference
Yes	0.834 (0.596–1.166)	0.28789
Sugar	1.002 (1.000–1.004)	0.02562
Fiber	0.975 (0.958–0.993)	0.00732
Total fat	0.999 (0.995–1.002)	0.5476
Cholesterol	1.000 (0.999–1.001)	0.7649
Caffeine	1.001 (1.000–1.001)	0.03598
Dietary fiber intake		
Q1	Reference	Reference
Q2	0.622 (0.401–0.965)	0.03413
Q3	0.504 (0.316–0.804)	0.00407
Q4	0.616 (0.397–0.956)	0.03073
Diabetes		
No	Reference	Reference
Yes	1.370 (0.891–2.106)	0.15119
Borderline	2.147 (1.040–4.433)	0.03889
Hypertension		
No	Reference	Reference
Yes	2.430 (1.743–3.388)	<0.00001
Smoking status		
No	Reference	Reference
Yes	1.527 (1.100–2.121)	0.01145

ESEs, epileptic seizure events; OR odds ratio (OR); CI, confidence interval.

variables. We assessed tolerance and variance inflation factors (VIFs) as diagnostic tools to identify multicollinearity. If a VIF is greater than five or the tolerance is <0.2, it suggests the presence of multiple collinearities. In the multilinearity diagnosis, the highest VIF (2.222) and lowest tolerance (0.45) occurred in the total fat. Multilinearity was not observed in the variables (Table S3). Four weighted logistic regression models were used to analyze the relationship between dietary fiber intake and ESEs in American adults, as presented in Table 3. All four logistic regression models showed a significant negative association between dietary fiber intake and ESEs. Models 1 and 2 showed that participants in quartiles Q2-Q4 had a lower risk of epilepsy compared to those in Q1(Table 3). In model 3, quartile Q2 and Q3 were significantly associated with a lower risk of ESEs, with ORs and CIs of 0.62 (95 % CI:0.40–0.97, $P = 0.034$) and 0.49 (95 %CI: 0.31–0.97, $P = 0.003$), respectively. In model 4, it was found that only quartile Q3 had a significant impact on lowering the risk of ESEs. The odds ratio and confidence interval were 0.54 (95 %CI: 0.33–0.88, $P = 0.014$), indicating that individuals in quartile Q3 had a 54 % decreased risk of ESEs compared to those in the lowest quartile (Q1).

Models 1–2 showed higher dietary fiber intake significantly reduced the risk of ESEs , with the P for trend ranging from 0.0407 to 0.0398 (Table 3).. Still, it is interesting that only quartile Q3 was significantly associated with a lower risk of ESEs in model 4. The P for trend was not significant in models 3–4. Therefore, the results of the regression models support the conclusion that an appropriate range of dietary fiber intake (quartile Q3) is associated with a lower likelihood of ESEs.

3.4. Nonlinear associations between dietary fiber intake and the risk of ESEs

RCS enables the flexible modeling of the relationship between fiber intake and epileptic seizure-related conditions without imposing a strictly linear or ordered structure. Consequently, we explored the relationship between fiber intake and ESEs by applying RCS. The association observed was not driven by outliers or extreme values. We have included four RCS plots to illustrate the visual relationship. Additionally, four models were developed to adjust for different confounding factors. All four nonlinear RCS models demonstrated a significant association between higher dietary fiber intake and lower ESEs risk (Fig. 2A-D, *P* for nonlinear >0.05). Stated differently, the prevalence of ESEs showed an inverse relationship with fiber intake, even after adjusting for all potential confounders (Overall $P = 0.0017$, Nonlinear $P = 0.155$).

3.5. Subgroup analysis of the association between dietary fiber intake and ESEs

Prior literature has identified subgroup analyses to validate the reliability and robustness of associations between independent and outcome variables across demographics, ethnicity, lifestyle, and disease state populations[23,24]. Therefore, we performed subgroup analyses of sex, age, race, IPR, BMI, physical activity, hypertension, diabetes, and smoking. As shown in Fig. 3, our findings indicated no significant associations were observed between fiber intake and epilepsy when stratifying by gender($P = 0.83$), age ($P = 0.15$), race ($P = 0.10$), IPR($P = 0.40$), BMI($P = 0.81$), physical activity($P = 0.43$), hypertension($P = 0.45$), diabetes($P = 0.22$), and smoking status($P = 0.45$). The results suggested that the negative association between dietary fiber intake and

Table 3
ORs (95 % CIs) of the association between dietary fiber intake and epileptic seizure events in four models.

	Model 1		Model 2		Model 3		Model 4	
	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value	OR (95 %CI)	*P* value
Epilepsy								
Q1	Reference		Reference		Reference		Reference	
Q2	0.62 (0.40–0.97)	0.0341	0.62 (0.40–0.96)	0.0321	0.62 (0.40–0.97)	0.0344	0.65 (0.41–1.02)	0.062
Q3	0.50 (0.32–0.80)	0.0041	0.49 (0.31–0.78)	0.0029	0.49 (0.31–0.79)	0.0034	0.54 (0.33–0.88)	0.014
Q4	0.62 (0.40–0.96)	0.0307	0.61 (0.39–0.96)	0.0318	0.98 (0.96–1.00)	0.0578	0.68 (0.40–1.16)	0.155
P for trend	0.0407		0.0398		0.0578		0.195	

OR, odd ratio; CI, confidence interval.
Model 1 was unadjusted.
Model 2 was adjusted for age, gender, and race.
Model 3 was further adjusted for age, gender, race,diabetes, and hypertension..
Model 4 was further adjusted for age,gender,race,education level, IPR, BMI, physical activity, sugar, total fat, cholesterol, caffeine, diabetes, hypertension, and smoking status.

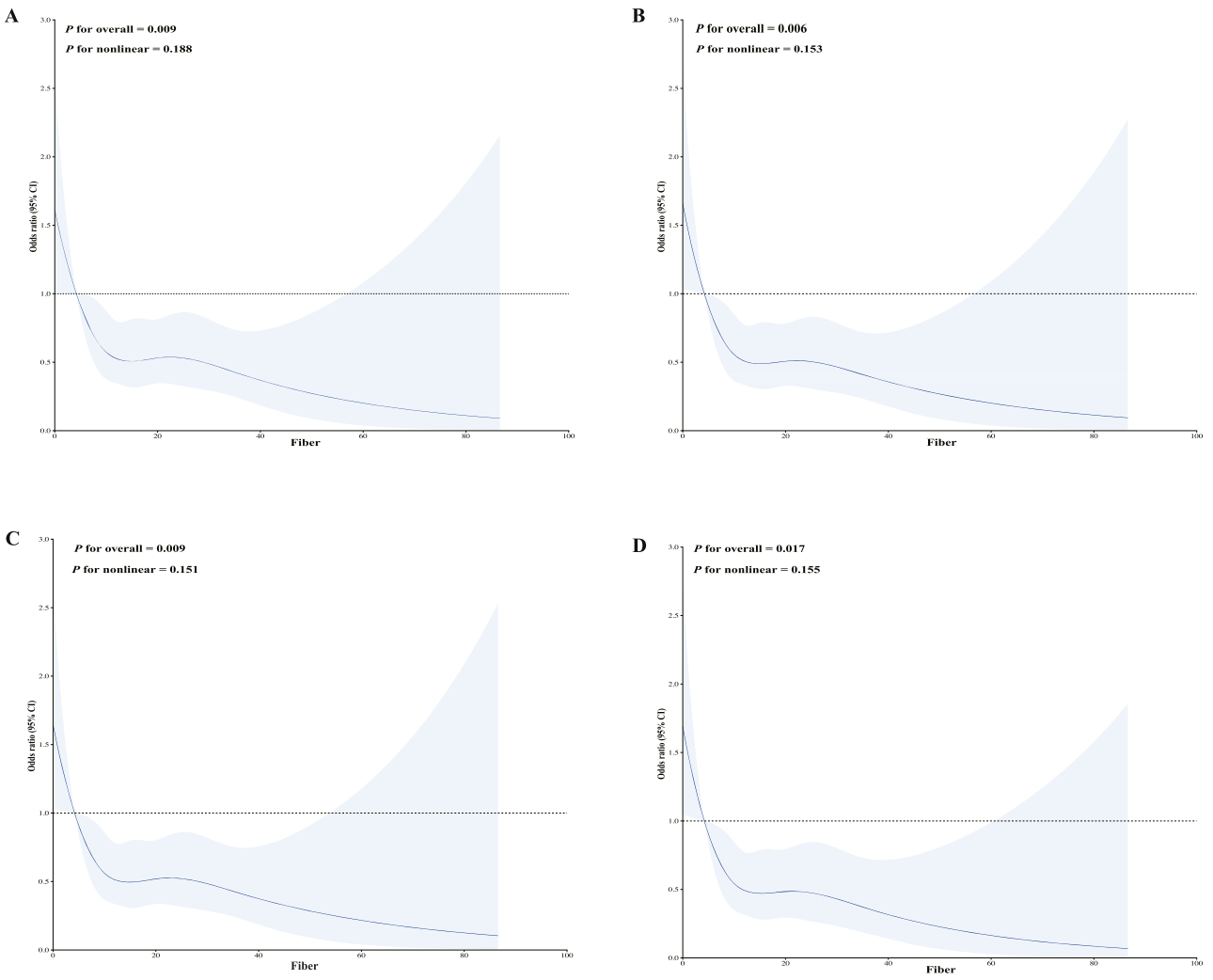

Fig. 2. Association between dietary fiber intake and ESEs evaluated by restricted cubic splines.
The horizontal axis represents the dietary fiber intake (g/d), and the vertical axis represents the relative probability of developing ESEs. Solid gray lines represent odds ratios, with light-red shaded areas indicating the 95 % confidence intervals.
A. Association of dietary fiber intake with ESEs by unadjusted covariates. ($P = 0.009$, P for nonlinear= 0.188).
B. Correlation between dietary fiber intake and ESEs after adjustment for age, gender, and race ($P = 0.006$, P for nonlinear = 0.153).
C. Association of dietary fiber intake with ESEs after adjustment for age, gender, race, hypertension, and diabetes ($P = 0.009$, P for nonlinear = 0.151).
D. Correlation between dietary fiber intake and ESEs after adjustment for full covariates, including age, gender, race, education level, IPR, BMI, physical activity, sugar, total fat, cholesterol, caffeine, hypertension, diabetes, and smoking status($P = 0.017$, P for nonlinear = 0.155).
All P values for nonlinearity were greater than 0.05.

ESEs was robust in populations with different demographics, lifestyles, and disease statuses. It might be appropriate for various people. However, we found a significant positive association with younger participants (< 60 yrs) [0.96(0.093–0.99), $P = 0.02$], while participants with >60 years did not show a significant association with dietary fiber intake. Moreover, participants who had higher dietary fiber intake and a lower risk of ESEs were more likely to be non-Hispanic black [0.92 (0.85–0.98), $P = 0.02$], IPR<1.3[0.96(0.93–1.00), $P = 0.03$], physical inactivity [0.97(0.94–1.00), $P = 0.04$], and without diabetes [0.97 (0.95–1.00), $P = 0.020$]. Constructing RCS models with 3 and 4 knots also indicated a significant nonlinear association between dietary fiber intake and ESEs (Fig. S1–2).

4. Discussion

This study investigated the association between dietary fiber intake and ESEs using data collected from three cycles of the NHANES (2013–2018). Our results demonstrated that dietary fiber intake was associated with a lower risk of ESEs, with the association being particularly remarkable at levels of 14.6 g/d-21.80 g/d. Furthermore, higher fiber intake indicated a stable negative association with ESEs in the multivariate logistic regression analysis, weighted generalized additive model, and RCS models. Interaction tests revealed no statistically significant effects of demographics, lifestyles, and disease status on the association between dietary fiber intake and ESEs.

At present, the etiology, inducement, and treatment of epilepsy have been widely discussed, but few articles report the nutritional status and dietary habits of patients with ESEs or epilepsy[25]. In the last decade, the impact of diet on the progression and prognosis of chronic diseases has been an area of focus, especially the potential role of dietary fiber [5, 26-30]. Recent studies have shown that the intake of fruits was lower in epileptic patients than in controls, but the opposite was true for the information of fats[1,25]. Hence, healthy dietary choices should be part of lifestyle interventions, which may improve outcomes for some people with epilepsy. Dietary modification has long been recognized as a potential treatment for epilepsy[1]. In epilepsy clinics, patients are often

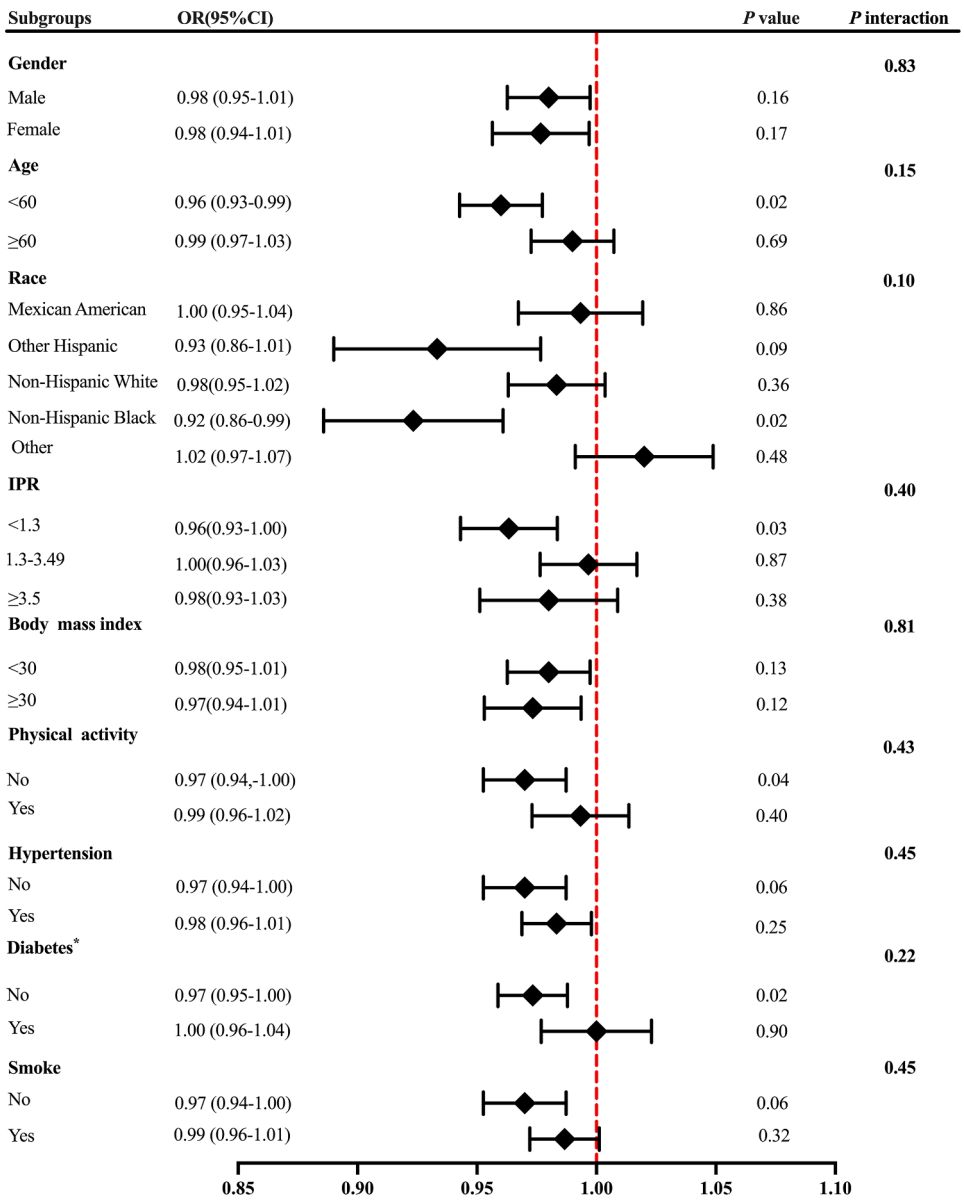

Fig. 3. Association of dietary fiber intake with ESEs across subgroups.
The subgroup analysis was performed using model 4, adjusted for age, gender, race, education level, IPR, BMI, physical activity, sugar, total fat, cholesterol, caffeine, hypertension, diabetes, and smoking status.

asked what foods they eat to explore the relationship between food and seizures. Foods are often considered to be seizure triggers and appropriate nutritional intake can be regarded as therapeutic. A cross-sectional study of 12,788 participants conducted by Ran Ding revealed that people with epilepsy consumed more pro-inflammatory foods and nutrients than non-epileptic patients, which included a substantial portion of dietary fiber, indicating a possible association between fiber diet and epilepsy [1].

Dietary fibers include soluble and insoluble fibers, indigestible carbohydrates, and plant lignin. Soluble fibers include viscous fibers such as gums, non-viscous fibers, pectin, and β-glucan, and insoluble fibers include cellulose, lignin, and hemicellulose. Dietary fiber prolongs food's transport time, delays nutrient absorption, and increases feces' volume, which helps slow the absorption of glucose, cholesterol, and lipids. In addition, dietary fiber produces short-chain fatty acids through fermentation by intestinal bacteria, which can reduce cholesterol synthesis in the liver and blood. Increasing dietary fiber intake may reduce the incidence of epilepsy by improving risk factors such as diabetes and dyslipidemia. A cohort study showed that patients with less vegetable intake were more likely to have poor seizure control, similar to our findings[25].

Variations in ethnicity and economic status can result in different dietary fiber intakes due to different nutritional habits[27]. Prior investigations have revealed that Hispanic blacks and individuals from lower-income families have less information on dietary fiber than other adults[27]. Our subgroup analysis study has verified that a decrease in dietary fiber intake (Hispanic blacks and individuals from lower-income families<1.3) is correlated with an increased incidence of epilepsy. Our study suggests that participants of different races and economic statuses could benefit from epilepsy by increasing their dietary fiber levels. Physical inactivity may be correlated with a decrease in dietary fiber absorption in the intestines, which could potentially raise the risk of epilepsy. Previous observational and randomized controlled studies have shown that diabetes mellitus, hypertension, and hypercholesterolemia are risk factors for epilepsy[4]. According to the subgroup analyses in this study, the negative association between fiber intake and

epilepsy was stable in the subgroups stratified by hypertension and diabetes. In addition, we did not find any dependence of this association with age, gender, race, smoking status, physical activity, diabetes, or hypertension (all interactions $p > 0.05$), implying that this negative association may apply to various population settings.

The mechanisms by which dietary fiber acts on epilepsy or ESEs are largely unknown, and there has been little research on their relationship. Recently, the concept of the gut-brain axis has attracted attention in the epilepsy fields[31]. The potential mechanisms that underpin the protective effects of dietary fiber consumption on epilepsy may be attributed to gut function and, specifically, the gut microbiota maintaining the intestinal and blood-brain barrier (BBB) integrity[27]. Gut microbiota ferments dietary fiber in the colon to promote short-chain fatty acids (SCFAs) as end products. SCFAs provide a major energy source for colonocytes, are essential for maintaining the integrity of the intestinal barrier and have broad implications in immune and inflammatory regulation[32]. Prior studies have demonstrated that dietary fiber can influence intestinal SCFA levels by affecting intestinal flora activity[33]. Inhibition of histone deacetylase by the naturally occurring short-chain fatty acids sodium butyrate and sodium propionate leads to hyperacetylation of several histones (H3 and H4) central to the expression of genes associated with inflammation, as well as translocation of the light-chain enhancers of the well-known inflammation-mediating nuclear factor kappa-activated B cells (NF-κB), which reduces the activation of the oxidative stress and inflammation cascade response, ultimately reducing the occurrence of epilepsy [34-36]. Dietary fiber may reduce inflammation and alleviate epilepsy by modulating the gut microbiota and its metabolite SCFAs. The bidirectional communication between the gut and the central nervous system, facilitated by microbial metabolites, posits a plausible mechanism for the observed attenuation of epileptic hyperexcitability.

On the other hand, in addition to microbial metabolites, the gut-brain axis contains hormonal signals that may contribute to the neuroprotective effects of dietary fibers. Enteroendocrine cells respond to fiber-rich foods by releasing hormones such as glucagon-like peptide-1 and peptide YY, which reduce the occurrence of epilepsy or ESEs. Furthermore, mitochondrial dysfunction and altered energy metabolism are implicated in epilepsy. By promoting the production of SCFAs during fermentation, dietary fiber may enhance mitochondrial function and cellular energy homeostasis. This improvement in energy metabolism could provide a neuroprotective environment[37], reducing the likelihood of aberrant neuronal activity associated with epileptic seizures. Finally, dietary fiber attenuates microglia activation and pro-inflammatory cytokine release, disrupting the cascade of responses that lead to neuronal hyperexcitability and epilepsy, thus creating an environment conducive to neuronal health. SCFAs play a crucial role in microglial maturation, the gut-brain nervous system, BBB permeability, and stress responses through direct or indirect pathways, all strongly associated with epilepsy[38].

While our study suggests a link between dietary fiber and ESEs risk, we need further research to understand how dietary fiber affects epilepsy development and progression. A multidisciplinary approach involving laboratory experiments, animal studies, analysis of human tissue, epidemiological investigations, clinical trials, and genetic research is essential for a complete understanding. Our findings will encourage more research in this area, potentially leading to improved strategies for preventing and treating ESEs or epilepsy.

5. Strengths and limitations

Our study has several strengths. First, it is based on NHANES, a cross-sectional survey database containing detailed data on disease status and various lifestyle factors, which provides a high degree of generalizability. Second, in our analysis, multiple confounders were adjusted to accurately estimate the association between dietary fiber intake and epilepsy or ESEs in U.S. adults, providing a more comprehensive guide to dietary formulation for people with epilepsy. However, the present study has several limitations that should be acknowledged. First, due to its inherent limitations, the study's cross-sectional design precludes the drawing of causal conclusions. Therefore, future prospective cohort studies should be conducted to investigate further the impact of dietary fiber intake on patients with epilepsy or ESEs. Additionally, the dietary fiber intake was obtained through a 24-hour dietary recall interview, potentially leading to self-reported bias in the findings. The phenomenon of overreporting and underreporting of food intake could be present. Due to the absence of data on the specific types of dietary fiber in the NHANES database, our analysis explored the association between total dietary fiber intake and ESEs. The various types of dietary fiber, whether soluble or insoluble, could have distinct effects on different diseases and ESEs or epilepsy, making the findings not applicable to just one type of dietary fiber. The NHANES database's lack of a comprehensive food frequency questionnaire hindered the study from adjusting for intrapersonal variability in dietary fiber intake. Since the NHANES database did not consistently track dietary fiber intake, the study could not determine a causal relationship between fluctuations in dietary fiber and ESEs or epilepsy. Third, the criteria for inclusion of ESEs rely on self-reported medication history, with a lack of information on the methods of diagnosing epileptic seizures and the type of epilepsy, as well as a lack of confirmations from doctors or other healthcare professionals. The ESEs identification approaches were not likely validated in the data source. Using "at least one antiseizure medication (ASM) intake" or the ICD code (G40) as a proxy variable for epilepsy identification might lead to inaccuracies and not capture all cases of epilepsy. Therefore, our result demonstrated that the prevalence of people who consumed at least one antiseizure medication or had recurrent seizures was 1 %, which might have a potential risk of bias inherent in self-reported data. Fourth, the present study had the limitations of subgroup analysis. The robustness of the association should be interpreted in the context of the data's validity. Last, although the sample size of this study was sufficiently large, the sample size of 145 participants with ESEs was far smaller than that of the control group, which may have affected the validity of the analyses.

6. Conclusions

In conclusion, our study indicates an association between dietary fiber intake and reduced risk of ESEs. Ascertaining the range of dietary fiber intake may benefit people with epilepsy or ESEs. People with epilepsy or ESEs may benefit from individual nutritional assessment and dietary alteration, which may comprise a novel approach to epilepsy treatment. Further research is needed to investigate the potential use of dietary composition modification as a preventive or therapeutic intervention for epilepsy. Nevertheless, these results provide new insights into the role of the gut-brain axis in the pathogenesis of epilepsy and offer hope for adjunctive epilepsy treatments as well as new therapeutic approaches to improve the prognosis of patients with epilepsy.

Ethics approval and consent to participate

The data used in this study were obtained from the NHANES conducted by the National Center for Health Statistics (NCHS) with appropriate ethical approval. NCHS and the Research Ethics Review Board (ERB) reviewed and approved the studies involving human participants. All informed consent had been obtained from the eligible subjects before data collection, and NHANES health examinations were initiated. As a deidentified secondary data analysis using an open-access database, the Ethics Committee of the First Affiliated Hospital of Fujian Medical University waived informed consent. All authors affirmed that the methods complied with the appropriate NHANES Analytic Guidelines.

Author's contributions

Yi-Bin Zhang, De-Zhi Kang, and Pei-Sen Yao formulated the theoretical framework. Yi-Bin Zhang, Ye Xu, and Shu-Fa Zheng prepared the initial draft of the manuscript. Shu-Fa Zheng and Yuan-Xiang Lin assisted in conducting the analytical calculations. Yuan-Xiang Lin, De-Zhi Kang, and Pei-Sen Yao contributed to the development of the theoretical framework, recorded and analyzed covariates, engaged in critical discussions, and contributed to the final version of the manuscript.

Data availability

Data will be made available on request.

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2024.09.005.

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