Stroke

ORIGINAL CONTRIBUTION

Association Between Dietary Fiber Intake and Stroke Among US Adults: From NHANES and Mendelian Randomization Analysis

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BACKGROUND: There is debate on the link between dietary fiber intake and stroke risk. The purpose of this study was to look at how it impacts dietary fiber intake and stroke risk, as well as mortality among stroke survivors. Two-sample Mendelian randomization was also used to investigate the causal relationship.

METHODS: This research examined information from 1453 patients with stroke participating in the National Health and Nutrition Examination Survey from 1999 to 2018. To assess the incidence of stroke, we conducted a survey-weighted multivariate logistic regression analysis and subgroup analysis. To evaluate the mortality associated with stroke, we used Kaplan-Meier survival analysis combined with survey-weighted Cox regression models. Using 2-sample Mendelian randomization and inverse-variance weighted method, we established a causal relationship between dietary fiber intake and stroke. The article was organized according to Strengthening the Reporting of Observational Studies in Epidemiology and Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization guidelines.

RESULTS: In the fully adjusted model, dietary fiber intake was negatively associated with stroke (odds ratio, 0.98 [95% CI, 0.97–0.99]; $P<0.0001$; T3 versus T1; odds ratio, 0.71 [95% CI, 0.57–0.88]; $P=0.002$). A stable linear negative relevance was confirmed between dietary fiber intake and stroke risk (nonlinear $P=0.566$) by the multivariate adjusted spline regression model. According to the survey-weighted multivariate Cox regression model, dietary fiber intake significantly reduced all-cause mortality (T3 versus T1; odds ratio, 0.68 [95% CI, 0.47–0.97]; $P=0.04$). Further Kaplan-Meier survival analysis indicated that higher intake of dietary fiber improved the survival of patients with stroke ($P=0.02325$). The 2-sample Mendelian randomization analysis showed that genetic prediction supported a causal relationship between increased dietary fiber intake and reduced risk of small vessel stroke (odds ratio, 0.8326 [95% CI, 0.7051–0.9833]; $P=0.0309$).

CONCLUSIONS: There is a stable negative correlation between dietary fiber intake and stroke risk. High fiber intake is associated with reduced all-cause mortality among stroke survivors. Additionally, genetic prediction further demonstrates a causal relationship between dietary fiber and reduced risk of small vessel stroke.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: dietary fiber ■ odds ratio ■ stroke ■ survival analysis ■ survivors

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ORIGINAL CONTRIBUTION

Nonstandard Abbreviations and Acronyms

BMI	body mass index
MR	Mendelian randomization
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PIR	poverty income ratio
SNP	single-nucleotide polymorphism

Stroke poses a significant global health challenge.[1] Statistics from 2019 reveal that it stands as the second largest contributor to mortality and the third most common cause of combined disability and mortality around the world.[2] Alarmingly, the most recent findings of the American Heart Association indicate that a stroke claims an American life every 3 minutes and 30 seconds, on average. If swift and decisive measures are not taken, projections suggest a potential 50% increase in stroke-related deaths globally by 2050, with economic implications amounting to a staggering $2.3 trillion.[3] Consequently, it is imperative to prioritize the implementation of efficient primary stroke prevention strategies to contain the prevalence of stroke and alleviate its financial burden.

Diet is a crucial modifiable factor in stroke occurrence, assuming a pivotal role in stroke prevention and management.[4] Increasing evidence supports the view that higher dietary fiber intake can reduce the risk of stroke.[5] However, no studies have yet established a causal relationship between dietary fiber and different subtypes of stroke. A US cohort study revealed a pessimistic relevance of overall fiber intake and various inflammatory markers, demonstrating that a grain-fiber-rich diet reduced inflammatory markers like circulating interleukin-18 and C-reactive protein, thereby contributing to the prevention of atherosclerosis.[6] Additionally, elevated dietary fiber intake effectively improves insulin resistance, thus averting the development of hypertension triggered by compensatory hyperinsulinemia.[7] However, in the United Kingdom, a contrasting finding from a prospective cohort study suggests a higher stroke risk among vegetarians, hence the protective effect of dietary fiber intake on stroke remains uncertain.[8] Moreover, previous studies were constrained by sample size, often focusing narrowly on specific age groups, sex, or clinical settings.[9]

Previous epidemiological or observational studies have been limited due to the lack of randomization and the potential for reverse causation and confounding factors. Mendelian randomization (MR) analysis is a novel statistical method that utilizes genetic variants in observational epidemiology, assuming that genetic variants are randomly distributed during gametogenesis and conception.[10] This approach helps to reduce sensitivity to bias or reverse causation, providing a more objective alternative for inferring causality in traditional observational studies.[11] Additionally, the genome-wide association study by Cole et al[12] demonstrated that dietary habits are heritable traits. Therefore, by leveraging data from the National Health and Nutrition Examination Survey (NHANES) and using a 2-sample MR method, we rigorously evaluated the potential associations and causal relationships between dietary fiber intake and stroke. We hypothesized that dietary fiber intake is inversely correlated with the incidence of stroke events and mortality outcomes in stroke survivors and that there are causal relationships between dietary fiber and various stroke subtypes. Our study aims to contribute to the existing body of knowledge by emphasizing the role of dietary factors in stroke prevention and prognosis.

METHODS

Ethical Approval and Consent to Participate

Ethical approval was obtained from the National Center for Health Statistics Ethics Review Board, and all participants signed the informed consent.

Overview of NHANES

The data that support the findings of this study are publicly available at https://www.cdc.gov/nchs/nhanes and https://gwas.mrcieu.ac.uk/. Data and analytic methods are available upon reasonable request from the corresponding author. The data utilized in this study originate from NHANES, a thorough data set on health and nutrition managed by the National Center for Health Statistics. NHANES has been conducting continuous surveys, collecting health and nutritional status data of a representative sample of around 5000 individuals annually across the United States since 1999. The data sets for each cycle contain multiple types of information, such as data from questionnaires on demographic, socioeconomic, diet-, and health-related questions, as well as content from physical examination components such as physiological measurements and laboratory tests. Approval has been obtained from the Research Ethics Review Committee of the National Center for Health Statistics. The NHANES program protocols strictly adhered to the ethical principles set forth in the Declaration of Helsinki. The cross-sectional study conducted in this research strictly adhered to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.[13] The 2-sample MR study conducted in this research strictly adhered to the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization reporting guidelines.[14]

Study Population

The study used data from 10 survey cycles spanning from 1999 to 2018. The exclusion criteria for participants are as follows: (1) participants under the age of 18 years; (2) participants with incomplete or missing stroke questionnaire data; (3) pregnant women; (4) participants without information on dietary fiber intake; and (5) participants lacking covariate data.

All participants had given written informed consent before participating in the study. The NHANES data set used in this study is available to the public, so no additional ethical or administrative approval is required.

Overview of Study Design

This study is primarily divided into 2 phases. In the initial phase, we conducted a comprehensive analysis of the relationship between dietary fiber intake and incident stroke, taking into account various potential confounding factors. Subsequently, we further analyzed the association between dietary fiber intake and all-cause mortality among stroke survivors. This analysis utilized data from NHANES. In the subsequent stage, we extracted summary statistics for dietary fiber and stroke from genome-wide association study to perform a 2-sample MR analysis. Through this innovative approach, we were able to provide a genetic underpinning to the observed associations, thereby establishing a causal link. The Mendelian randomized model is shown in Figure 1C.

Assessment of Stroke

Stroke determination is based on an individual's self-report before diagnosis by a physician in a face-to-face interview. Participants were queried with the following question: "Has a doctor or another health care provider informed you that you have experienced a stroke[15]?" In our study, we included and assessed various types of stroke, namely any stroke, any ischemic stroke, large artery stroke, cardioembolic stroke, and small vessel stroke. Participants who responded affirmatively were categorized into the stroke group. Conversely, those who reported not being informed of a stroke diagnosis were assigned to the nonstroke group. The interviews also used computer-assisted personal interview technology, in which a trained interviewer collects a patient's stroke history. The questionnaire for the survey is available on the NHANES website. To minimize data entry errors, the computer-assisted personal interview system includes validation checks.

Assessment of Dietary Fiber Intake

The primary variable of interest is dietary fiber intake. Dietary intake information was utilized to calculate the type and amount of food and drink ingested in the 24 hours before the interview (from midnight to midnight) and to approximate calorie intake, nutrients, and other components from these sources.[16] Each NHANES participant underwent 2 interviews recalling dietary intake over a 24-hour period. The primary interview was conducted face to face at a mobile examination center, and the next interview was set 3 to 10 days later, collected over phone. The dietary fiber intake was ascertained from the NHANES, which used a rigorous protocol for data collection. This includes the use of the Food Composition Table to quantify nutrient intake. The complete methodology is detailed in the NHANES Dietary Interview Procedure Manual

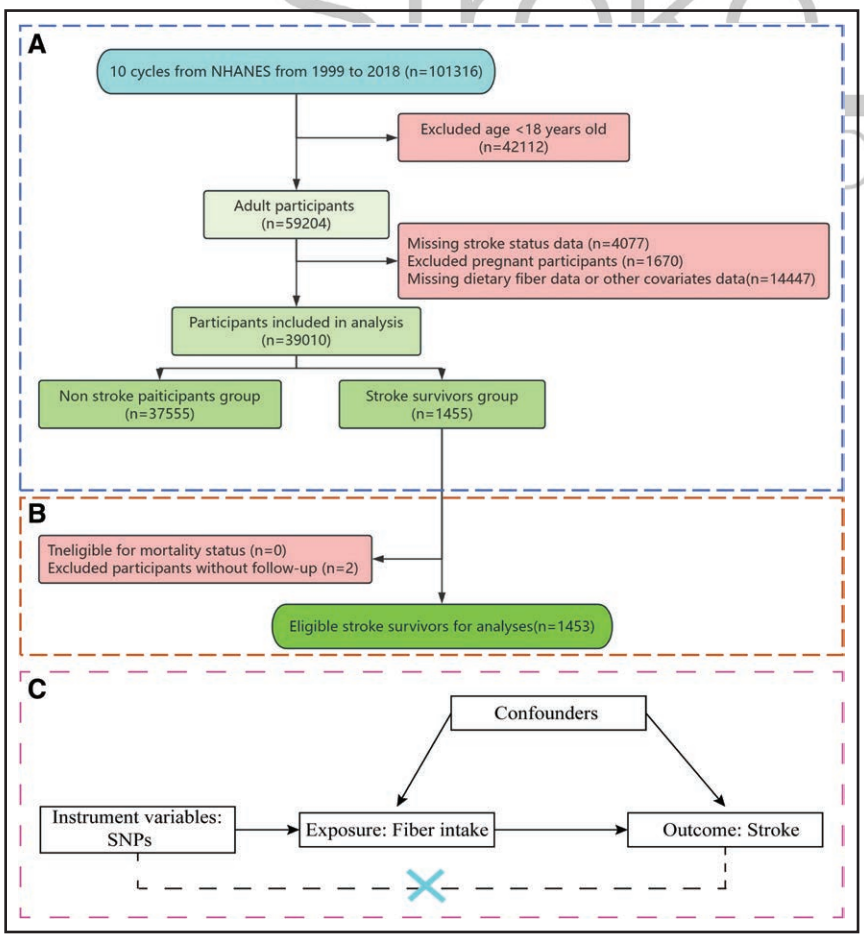

Figure 1. Participant selection flowchart.
A, Relationship between fiber intake and stroke. **B**, Relationship of fiber intake with all-cause mortality in patients with stroke. **C**, Mendelian randomization model of fiber intake and stroke. NHANES indicates National Health and Nutrition Examination Survey; and SNP, single-nucleotide polymorphism.

(https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/questionnaires.aspx?Cycle=2019-2020). We categorize the dietary fiber intake percentages into tertiles. Similar to previous studies, this study selected dietary fiber (g) on total nutrient intake on day 1, a 24-hour first meal recall interview personally collected by a mobile examination center and adjusted for individual weight factors. Sources of dietary fiber, including grains, vegetables, and fruits, are determined by sorting through relevant food categories.

Mortality Outcome

The primary outcome assessed in this study was all-cause mortality. NHANES provides mortality data related to the National Death Index as of December 31, 2019. We investigated mortality from all causes and specific causes, such as cardiovascular ailment (*International Classification of Diseases, Tenth Revision*, codes I00–I09, I11, I13, I20–I51) and neoplasm (*International Classification of Diseases, Tenth Revision*, codes C00–C97). The NHANES data collection baseline marks the beginning of survival time calculation. The follow-up period started from the interview date and continued until the date of death. For participants who did not experience an event, the period was uniformly set to December 31, 2019.

Covariate Evaluation

We comprehensively screened 15 confounders that may be associated with stroke and identified age, education level, sex, body mass index (BMI), race, poverty income ratio (PIR), marriage, energy intake, carbohydrate intake, diabetes status, hypertension status, smoking status, alcohol consumption status, hyperlipidemia status, and coronary heart disease status as risk factors.[17] The confounding factors included in our analysis were chosen based on their established association with stroke risk and their common inclusion in dietary and stroke studies conducted by NHANES. This selection ensures that our results are adjusted for variables that could potentially confound the relationship between dietary fiber intake and stroke incidence. Patients ranged in age from 20 to 85 years.[18] The sex represented include male and female.[19] Ethnicities encompass non-Hispanic Whites, non-Hispanic Blacks, Mexican Americans, other Hispanics, and other races.[20] Education levels are categorized as below high school, high school, and college or higher.[21] The mean BMI is 28.80 and is computed by calculating the weight in kilograms divided by the square of height in meters.[22] PIR is classified as ≤1.0, 1.0 to 3.0, and >3.0.[23] According to the latest NHANES criteria, marital status is classified as unmarried, divorced/widowed/separated, and married/living with a partner.[24] Vascular risk factors include hypertension, diabetes (diagnosed by physician, random blood glucose ≥11.1 mmol/L, glycated hemoglobin ≥6.5%, fasting blood glucose ≥7.0 mmol/L, 2-hour glucose ≥11.1 mmol/L, or use of antidiabetic medications),[25] hyperlipidemia (self-reported high cholesterol or total cholesterol levels ≥5.17 mmol/L),[26] and coronary artery disease (self-reported diagnosis).[27] Alcohol consumption, weight, and height were documented at the mobile examination center. Drinkers are defined as those consuming at least 12 drinks annually.[28] Individuals who have never smoked or have smoked <100 cigarettes a whole life are classified as never smokers.[29]

Statistical Analysis

Statistical analyses were all performed using R, version 4.2.0. We utilized complex sample weights as advised by the Centers for Disease Control and Prevention (day 1 sample weights). We aggregated 10 consecutive period sample weights according to NHANES guidelines. In the baseline feature table, continuous variables were reported as survey-weighted means with SE, while categorical variables were presented as sample size (survey-weighted percentage).

In our analysis, we utilized logistic regression, a form of generalized linear model with a logit link function, to determine the association between dietary fiber intake and the incidence of stroke. Dietary fiber intake was modeled as a continuous variable to assess its relationship with the log odds of stroke incidence. The primary model was designed as a univariate analysis without adjustments for any covariates, providing a baseline assessment of the relationship between dietary fiber intake and stroke incidence. Model 1 introduces demographic variables, controlling for race, BMI, sex, and age, to account for fundamental population characteristics. Building upon this, model 2 further adjusts for socioeconomic and lifestyle factors, including PIR, marital status, and education level, which are known to influence health outcomes. Finally, model 3 comprehensively adjusts for all identified confounders, such as energy intake, carbohydrate intake, diabetes status, hypertension status, smoking status, alcohol consumption status, hyperlipidemia status, and coronary heart disease status, to ensure a robust evaluation of the association between dietary fiber intake and stroke incidence. The dose-response relationship between stroke prevalence and dietary fiber intake was surveyed by restricted cubic spline curves. Furthermore, survey-weighted multivariate logistic regression and subgroup analyses were performed, with the outcome variable being categorical (ie, stroke). Dietary fiber intake was treated as a predictor variable and was analyzed both in its continuous form and as a categorical variable (categorized into 3 groups based on intake percentage). This approach enables us to explore both the linear relationship between continuous fiber intake and stroke and the potential nonlinear relationships associated with different levels of intake, thereby assessing the impact of varying levels of dietary fiber intake on stroke. Subgroup analyses were prespecified based on theoretical considerations and previous literature. These analyses were stratified by sex, age, PIR, race, marital status, BMI, education level, hypertension status, hyperlipidemia status, diabetes status, coronary heart disease status, smoking status, and alcohol consumption status to evaluate the consistency of the relationship between stroke prevalence and dietary fiber intake across different subgroups.

For analyzing the influence of dietary fiber intake on stroke survival, Kaplan-Meier analysis of survival and survey-weighted Cox regression models were used to assess its association with all-cause mortality. To explore and illustrate the dose-response relationship between fiber intake and mortality risk, restricted cubic spline models were used, conducting restricted cubic spline analysis for all-cause mortality. Subgroup analyses were also utilized to examine the relationship between dietary fiber and all-cause mortality in various subgroups. The analysis included marriage, age, BMI, sex, race, education level, PIR, hypertension status, diabetes status, hyperlipidemia status, coronary heart disease status, smoking status, and alcohol

consumption status. Multiplicative interaction terms between subgroups are incorporated into the model to assess potential interaction effects. When P was ≤0.05, all statistical analyses in this study were statistically significant.

Two-Sample MR Analysis

MR is a powerful epidemiological tool that hinges on 3 fundamental assumptions to evaluate the causal link between exposure and outcome[30]: (1) the single-nucleotide polymorphisms (SNPs) selected as instrumental variables have a strong correlation with dietary fiber (exposure); (2) genetic variations are independent of other confounding factors; and (3) the SNPs' impact on stroke is mediated exclusively through dietary fiber. Our study utilized data from the Finnish cohort (finngen_R9_C_STROKE), which is part of the FinnGen project.[31] This initiative has scrutinized over 500 000 samples from the Finnish Biobank, with the goal of correlating genetic variations with health outcomes to unravel disease mechanisms and predispositions. The validation cohort comprised publicly available data from the MEGASTROKE consortium,[32] a large-scale international collaboration launched by the International Stroke Genetics Consortium. The MEGASTROKE database includes data from 446,696 individuals of European ancestry (406,111 noncases and 40,585 stroke cases). We also incorporated data from patients with ischemic stroke, intracerebral hemorrhage, and strokes of undetermined etiology (67 162 cases) were also included. Stroke (identifier [ID]: ebi-a-GCST90038613), ischemic stroke (small vessel; ID: ebi-a-GCST006909), lacunar stroke (ID: ebi-a-GCST90014123), and ischemic cerebrovascular disease (ID: bbj-a-129) served as outcomes in this study. Although dietary fiber is not classified as a macronutrient, it is acknowledged as 1 of the 7 essential nutrients. Our exposure data, representing dietary fiber intake (with a corresponding ID of ukb-b-19085), originated from the UK Biobank and encompassed 64 979 individuals of European ancestry. Table 1 provides a comprehensive description of the data sources. To mitigate the influence of linkage disequilibrium, SNPs were screened by P value and elimination of linkage disequilibrium ($P<5\times10^{-5}$, a linkage disequilibrium coefficient of $P=0.01$, a region width of 10 000 kb). The F value was calculated using the following formula: $F=[R2(N-2)/1-R2]$, and the selected instrumental variables with $F>10$ are strongly correlated with exposure. Ultimately, 138 SNPs were chosen as instrumental variables for dietary fiber. To ascertain the causal effect of dietary fiber intake on stroke, we initiated our analysis with the random-effects inverse-variance weighted model.[37] In addition to inverse-variance weighted method, we used 3 other MR techniques (MR-Egger,[38] weighted median,[39] and weighted

Table 1. Details Regarding the Data Sources for Exposure and Outcomes Included in This Mendelian Randomization Investigation

Exposures or outcome	Publication date, y	Cases	Controls	Population	Integrative epidemiology unit ID or URL
Lacunar stroke[33]	2021	232 596	6 898 454	European	ebi-a-GCST90014123
Lacunar stroke[33]	2021	225 419	6 909 434	European	ebi-a-GCST90014122
Ischemic stroke[34]	2021	174 686	12 454 188	European	ebi-a-GCST90018644
Ischemic stroke[34]	2021	484 121	24 174 314	European	ebi-a-GCST90018864
Stroke[35]	2021	484 598	9 587 836	European	ebi-a-GCST90038613
Ischemic stroke[34]	2019	210 054	8 885 705	European	bbj-a-129
Ischemic stroke (large artery atherosclerosis)[32]	2018	150 765	8 418 349	European	ebi-a-GCST006907
Ischemic stroke[32]	2018	440 328	7 537 579	European	ebi-a-GCST005843
Ischemic stroke (cardioembolic)[32]	2018	211 763	7 954 834	European	ebi-a-GCST005842
Stroke[32]	2018	446 696	7 633 440	European	ebi-a-GCST005838
Ischemic stroke (large artery atherosclerosis)[32]	2018	150 765	7 992 739	European	ebi-a-GCST005840
Stroke[36]	2018	361 194	12 404 026	European	ukb-d-C_STROKE
Stroke, excluding SAH[36]	2018	361 194	11 574 899	European	ukb-d-I9_STR
Stroke, including subarachnoid hemorrhage[36]	2018	361 194	11 849 007	European	ukb-d-I9_STR_SAH
Ischemic stroke, excluding all haemorrhages[36]	2018	361 194	11 321 390	European	ukb-d-I9_STR_EXH
Ischemic stroke[32]	2018	440 328	8 296 492	European	ebi-a-GCST006908
Ischemic stroke (small vessel)[32]	2018	198 048	8 280 845	European	ebi-a-GCST006909
Stroke[32]	2018	446 696	8 211 693	European	ebi-a-GCST006906
Stroke[31]	2022	39 818	271 817	European	https://www.finngen.fi/fi
Stroke[32]	2018	40 585	406 111	European	https://www.megastroke.org/
Ischemic stroke[32]	2018	34 217	406 111	European	https://www.megastroke.org/
Large artery stroke[32]	2018	4373	146 392	European	https://www.megastroke.org/
Small vessel stroke[32]	2018	5386	192 662	European	https://www.megastroke.org/
Cardioembolic stroke[32]	2018	7193	204 570	European	https://www.megastroke.org/
Englyst dietary fiber[36]	2018	64 979	9 851 867	European	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=100 009

mode methods), which helped to more comprehensively evaluate the causal relationship between exposure and outcome. Results were expressed as odds ratios (ORs) with 95% CIs. Heterogeneity and pleiotropy were assessed using Cochran Q test and the MR-Egger test, respectively. The stability of MR results was tested using the leave-one-out method. The MR analysis was conducted using R software (version 4.3.2) in conjunction with the TwoSampleMR package, with statistical significance defined as $P \leq 0.05$.

RESULTS

Participant Traits

The study included a total of 101 316 participants from the NHANES database for 10 cycles (1999–2018), and 39 010 subjects were finally included in the data analysis after screening. Part I: we evaluated 101 316 participants from NHANES over 10 consecutive cycles. First exclude data due to age <18 years (n=42 112) and pregnant status participants (n=1670), then exclude participants for whom the stroke questionnaire data were incomplete or missing (n=4077), and finally exclude missing values of dietary fiber and covariates. They included age, sex, race, education level, BMI, PIR, marriage, energy intake, carbohydrate intake, diabetes, hypertension status, smoking status, alcohol status, hyperlipidemia status, and coronary heart disease status (n=14 447). In total, 39 010 participants were included to investigate cross-sectional links between dietary fiber intake and stroke, with 1455 individuals reporting a diagnosis of stroke confirmed by a physician (Figure 1A). Part II: to further explore the longitudinal relationship between dietary fiber intake and stroke mortality, a total of 1453 adult participants meeting selection criteria were included in our survival analysis assessment (Figure 1B). In our analysis, we excluded 2 participants for whom follow-up data on survival status were lacking. The median follow-up duration for the remaining participants was 6.9 years, providing a substantial period for the assessment of outcomes. The systematic flow of subject screening is shown in Figure 1. A weighted baseline table (Table 2) was created using tertile classification based on daily dietary fiber intake. The mean age (SE) of the participants included was 47.10 (0.21) years. Among them, 50.24% were male, 46.87% were non-Hispanic White, and 60.53% had more than high educational backgrounds; 38.38% had a PIR level >3.0; 60.43% were married or cohabiting; 46.64% were smokers, and 68.71% were drinkers; and 17.11% had diabetes, 42.62% had hypertension, 70.14% had hyperlipidemia, and 4.25% had coronary heart disease. Simultaneously, we categorized the participants into a nonstroke group (n=37 555) and a stroke group (n=1455) based on their history of stroke. We found that the mean dietary fiber intake (SE) of the participants was 16.64 (0.12) g/d. The baseline characteristics according to stroke classification are detailed in Table S1. We also summarized the basic characteristics of the stroke population. The stroke population was mostly female, older, higher education level, middle income, smoking and drinking status, and mostly experiencing hypertension and hyperlipidemia. The mean age (SE) of the stroke group was 63.52 (0.62) years, and the mean dietary fiber intake (SE) was 14.33 (0.31) g/d, which was less than the average dietary fiber intake observed in the nonstroke group (Table S2). The weighted incidence rate of stroke in this study was 3.73%, with a lower prevalence of stroke observed in the high dietary fiber intake group compared with the low dietary fiber intake group (T1, 4.74%; T2, 3.55%; T3, 2.87%), and their basic characteristics are presented in Table 2.

Association Between Dietary Fiber Intake and Stroke

The survey-weighted generalized linear models were used to evaluate the association between dietary fiber intake and the risk of incident stroke. We found that dietary fiber is inversely linked to stroke and may reduce stroke risk (Table 3). As a continuous variable, in the fully adjusted model, dietary fiber intake was negatively related with stroke (OR, 0.98 [95% CI, 0.97–0.99]; $P<0.0001$). As a categorical variable, all 4 models demonstrated a protective effect of dietary fiber intake against stroke. In the fully adjusted model, participants in T2 (OR, 0.81 [95% CI, 0.68–0.96]; $P=0.02$) and T3 (OR, 0.71 [95% CI, 0.71–0.88]; $P=0.002$) experienced a 19% and 29% reduction in incident stroke, respectively, compared with participants in T1. The same conclusion can be found in the original model, model 1, and model 2. The P for trend for all of the above models was <0.001, indicating that as dietary fiber intake increased, there was a tendency for stroke prevalence to decrease, suggesting a protective effect. Among all models, the strongest protective effect was found in T3, when dietary fiber intake exceeded 18.3 g/d and stroke risk was lowest. Multivariate adjusted spline regression model further confirmed that dietary fiber intake had a stable linear negative correlation with the risk of stroke (nonlinear $P=0.566$), and the OR curve of stroke showed a steady decline with the increase of dietary fiber intake (Figure 2). We also conducted restricted cubic spline curve analysis for groups of drinking status and found that the OR curve of the nondrinking group showed a more obvious trend of decline than that of the drinking group with the increase of dietary fiber intake. The above analysis was performed under the fully adjusted model.

Association Between Dietary Fiber Intake and Mortality Outcomes

After adjusting for other potentially influential factors, dietary fiber intake demonstrated an inverse association with mortality outcomes among individuals who

Table 2. Traits of the Study Population Sorted by Dietary Fiber Intake

Characteristic	Dietary fiber intake				
	Overall	T1	T2	T3	
n	38 999	13 144	12 942	12 913	*P* value
Age, y	47.10 (0.21)	46.15 (0.23)	47.74 (0.30)	47.35 (0.30)	<0.0001
BMI, kg/m^2	28.80 (0.07)	29.21 (0.09)	28.92 (0.11)	28.28 (0.10)	<0.0001
Sex, n (%)					<0.0001
Female	19 404 (49.76)	7602 (57.84)	6728 (51.99)	5074 (39.29)	
Male	19 595 (50.24)	5542 (42.16)	6214 (48.01)	7839 (60.71)	
Race, n (%)					<0.0001
Non-Hispanic White	18 280 (46.87)	5961 (45.35)	6408 (49.51)	5911 (45.78)	
Non-Hispanic Black	7999 (20.51)	3645 (27.73)	2510 (19.39)	1844 (14.28)	
Mexican American	6535 (16.76)	1612 (12.26)	2017 (15.58)	2906 (22.50)	
Other race	6185 (15.86)	1926 (14.65)	2007 (15.51)	2252 (17.44)	
Education level, n (%)					<0.0001
Less than high school	4187 (10.74)	1432 (10.89)	1249 (9.65)	1506 (11.66)	
High school	11 204 (28.73)	4511 (34.32)	3648 (28.19)	3045 (23.58)	
More than high school	23 608 (60.53)	7201 (54.79)	8045 (62.16)	8362 (64.76)	
PIR, n (%)					<0.0001
≤1.0	7697 (19.74)	3164 (24.07)	2293 (17.72)	2240 (17.35)	
1.0–3.0	16 336 (41.89)	5813 (44.23)	5421 (41.89)	5102 (39.51)	
>3.0	14 966 (38.38)	4167 (31.70)	5228 (40.40)	5571 (43.14)	
Marriage, n (%)					<0.0001
Divorced/separated/widowed	8655 (22.19)	3372 (25.65)	2941 (22.72)	2342 (18.14)	
Married/living with partner	23 566 (60.43)	7154 (54.43)	7879 (60.88)	8533 (66.08)	
Never married	6778 (17.38)	2618 (19.92)	2122 (16.40)	2038 (15.78)	
Drinking status, n (%)					<0.001
No	12 204 (31.29)	4340 (33.05)	4056 (31.34)	3808 (29.49)	
Yes	26 795 (68.71)	8804 (66.98)	8886 (68.66)	9105 (70.51)	
Smoking status, n (%)					<0.0001
No	20 810 (53.36)	6447 (49.05)	7111 (54.95)	7252 (56.16)	
Yes	18 189 (46.64)	6697 (50.95)	5831 (45.05)	5661 (43.84)	
Diabetes, n (%)					0.02
No	32 327 (82.89)	10 839 (82.46)	10 688 (82.58)	10 800 (83.64)	
Yes	6672 (17.11)	2305 (17.54)	2254 (17.42)	2113 (16.36)	
Hypertension, n (%)					0.002
No	22 376 (57.38)	7210 (54.85)	7403 (57.20)	7763 (60.12)	
Yes	16 623 (42.62)	5934 (45.15)	5539 (42.80)	5150 (39.88)	
Coronary heart disease, n (%)					0.52
No	37 341 (95.75)	12 557 (95.53)	12 403 (95.84)	12 381 (95.88)	
Yes	1658 (4.25)	587 (4.47)	539 (4.16)	532 (4.12)	
Hyperlipidemia, n (%)					<0.001
No	11 645 (29.86)	3835 (29.18)	3808 (29.42)	4002 (30.99)	
Yes	27 354 (70.14)	9309 (70.82)	9134 (70.58)	8911 (69.01)	
Stroke, n (%)					<0.0001
No	37 546 (96.27)	12 521 (95.26)	12 482 (96.45)	12 543 (97.13)	
Yes	1453 (3.73)	623 (4.74)	460 (3.55)	370 (2.87)	
Energy intake, kcals/d	2174.86 (7.46)	1612.25 (9.25)	2138.01 (11.84)	2740.45 (13.03)	<0.0001
Carbohydrate intake, g/d	260.06 (0.98)	185.81 (1.30)	252.09 (1.63)	337.79 (1.72)	<0.0001

Continuous variables are shown as weighted means with SE. Categorical variables are presented as unweighted counts along with weighted percentages. Dietary fiber intake: T1, ≤10.9 g/d; T2, 10.9–18.3 g/d; T3, ≥18.3 g/d. BMI indicates body mass index; and PIR, poverty income ratio.

ORIGINAL CONTRIBUTION

Table 3. Results of a Weighted Multiple Logistic Regression Analysis Investigating the Relationship Between Fiber Intake and Stroke

	Primary model		Model 1		Model 2		Model 3	
Variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Continuous	0.97 (0.97–0.98)	<0.0001	0.97 (0.97–0.98)	<0.0001	0.98 (0.97–0.99)	<0.0001	0.98 (0.97–0.99)	<0.0001
Fiber intake (tertile)								
T1	Reference		Reference		Reference		Reference	
T2	0.77 (0.66–0.91)	0.002	0.73 (0.62–0.87)	<0.001	0.80 (0.68–0.94)	0.01	0.81 (0.68–0.96)	0.02
T3	0.61 (0.52–0.71)	<0.0001	0.62 (0.53–0.73)	<0.0001	0.72 (0.60–0.85)	<0.001	0.71 (0.57–0.88)	0.002
P for trend		<0.0001		<0.0001		<0.001		0.001

Primary model: adjusted for none. Model 1: age, sex, BMI, and race of participants were adjusted. Model 2: age, sex, BMI, education level, race, PIR, and marriage of participants were adjusted. Model 3: age, sex, race, education level, BMI, PIR, marriage, energy intake, carbohydrate intake, diabetes status, hypertension status, smoking status, alcohol consumption status, hyperlipidemia status, and coronary heart disease status of participants were adjusted. T1, ≤10.9 g/d; T2, 10.9–18.3 g/d; T3, ≥18.3 g/d. BMI indicates body mass index; OR, odds ratio; and PIR, poverty income ratio.

had experienced a stroke. According to the multivariable Cox regression analysis, greater dietary fiber intake was significantly linked to lower all-cause mortality in patients with stroke (Table 4). In models utilizing dietary fiber percentage, all except the primary model indicated an observable reduction in all-cause mortality. In the fully adjusted model, participants in T2 (hazard ratio, 0.77 [95% CI, 0.59–0.99]; *P*=0.04) and T3 (hazard ratio, 0.68 [95% CI, 0.47–0.97]; *P*=0.04) exhibited a 23% and 32% reduction in the risk of all-cause mortality, respectively, compared with those in T1. The same conclusion can be found in models 1 and 2. The *P* for trend of the above models is <0.05, which means that with the increase of dietary fiber intake, the all-cause mortality of stroke tends to decrease, which plays a role in improving the survival rate. Additional Kaplan-Meier analysis of survival stratified participants into high and low dietary fiber intake groups. Figure 3 illustrates a statistically significant disparity in all-cause mortality rates between these groups (*P*=0.02325). The results suggest that high intake of dietary fiber tends to improve the survival rate of patients with stroke. Figure S1, presented in the Supplemental Material, delineates the Kaplan-Meier survival analysis for all-cause mortality across the 3 quantiles of dietary fiber intake. Our analysis indicates that the highest tertile (T3) exhibits a higher survival rate compared with T2 and T1, with T2 demonstrating better survival outcomes than T1. This trend suggests that an increase in dietary fiber intake is associated with improved survival rates among stroke survivors, emphasizing the potential impact of dietary fiber on poststroke prognosis. In addition, the dose-response relationship between mortality and dietary fiber intake was examined using a multivariable-adjusted spline regression model. We identified a nonlinear inverse relationship between dietary fiber intake and all-cause mortality (nonlinear *P*=0.00006). As dietary fiber intake increased, the hazard ratio for all-cause mortality decreased sharply. The inflection point of the hazard ratio curve for all-cause

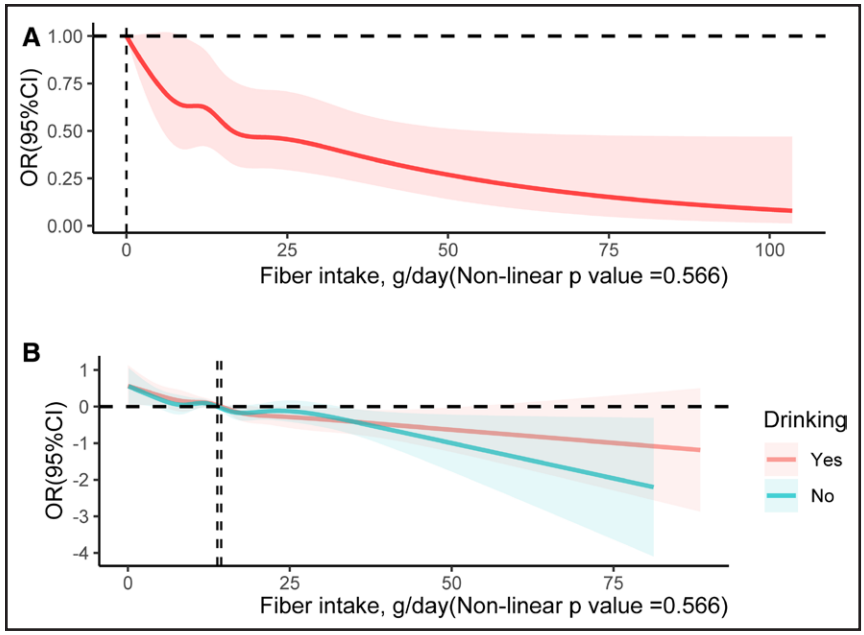

Figure 2. Restricted cubic spline curves illustrating the dose-response relationship between fiber intake and stroke.
Panel **A** shows the overall relationship, while panel **B** stratifies the relationship by drinking status. The analysis adjusted for race, age, body mass index, sex, poverty income ratio, education level, marriage, energy intake, carbohydrate intake, diabetes status, hypertension status, smoking status, alcohol consumption status, hyperlipidemia status, and coronary heart disease status. OR indicates odds ratio.

Table 4. Survey-Weighted Cox Regression Analysis Was Conducted to Assess the Relationship Between Dietary Fiber Intake and All-Cause Mortality Among Patients With Stroke

	Primary model		Model 1		Model 2		Model 3	
Outcome	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause mortality: 650 deaths among 1453 patients								
Fiber intake (tertile)								
T1	Reference		Reference		Reference		Reference	
T2	0.93 (0.70–1.24)	0.63	0.74 (0.58–0.95)	0.02	0.75 (0.58–0.97)	0.03	0.77 (0.59–0.99)	0.04
T3	0.80 (0.60–1.08)	0.14	0.69 (0.52–0.91)	0.01	0.71 (0.54–0.95)	0.02	0.68 (0.47–0.97)	0.04
P for trend		0.14		0.01		0.01		0.03

Primary model: adjusted for none. Model 1: age, sex, BMI, and race of participants were adjusted. Model 2: age, sex, BMI, education level, race, PIR, and marriage of participants were adjusted. Model 3: age, sex, race, education level, BMI, PIR, marriage, energy intake, carbohydrate intake, diabetes status, hypertension status, smoking status, alcohol consumption status, hyperlipidemia status, and coronary heart disease status of participants were adjusted. T1, ≤10.9 g/d; T2, 10.9–18.3 g/d; T3, ≥18.3 g/d. BMI indicates body mass index; HR, hazard ratio; and PIR, poverty income ratio.

mortality (Figure S2) was at the dietary fiber intake of 19.3 g/d.

Subgroup Analysis

We used stratified weighted multivariate regression analyses to conduct subgroup analyses, divided by education level, PIR, age, sex, marriage, BMI, race, drinking status, smoking status, hypertension, diabetes, coronary heart disease, and hyperlipidemia to further investigate the relationships of fiber intake with stroke in various populations. Figure S3A presents subgroup analyses investigating the relationship between fiber intake and stroke, examining interactions between fiber intake and categorical variables. The findings revealed a consistent inverse relationship between fiber intake and stroke incidence across various demographic characteristics, lifestyle habits, and disease conditions (P>0.05 for most interactions). Notably, significant interactions were observed between fiber intake and both smoking status and education level, with an interaction P value of 0.04. Figure S3B illustrates subgroup analyses exploring the relationship between fiber intake and all-cause mortality. The findings consistently showed a pessimistic correlation between fiber intake and all-cause mortality across various demographic traits, living habits, and disease conditions (P>0.05 for all interactions).

Two-Sample Mendelian Analysis of Fiber Intake and Stroke, With Validation

To provide further validation for our observational findings across the NHANES cohorts, we conducted a 1-way 2-sample MR analysis to assess the causal relationship between fiber intake and stroke risk. Based on the inverse-variance weighted method, overall, no causal relationship was observed between fiber intake and ischemic stroke, large artery stroke, or cardioembolic stroke. However, a causal relationship was found between fiber intake and small vessel stroke. Based on our results, there is a significant association between increased fiber intake and reduced risk of small vessel stroke (OR, 0.8326 [95% CI, 0.7051–0.9833]; P=0.0309; Figure 4). Sensitivity analysis showed that the selected SNPs exhibited no horizontal pleiotropy (intercept, −0.0073; P=0.3515) or heterogeneity (Cochran Q, 126.956; P=0.4844). To further strengthen our conclusions, we validated our findings using genome-wide association study summary data from the MEGASTROKE consortium, which confirmed a similar phenomenon (OR, 0.8367 [95% CI, 0.7099–0.9862]; P=0.0335). Sensitivity analysis showed that the selected SNPs exhibited no horizontal pleiotropy (intercept, −0.0051; P=0.5280) or heterogeneity (Cochran Q=121.8198; P=0.5385). Scatter plots and funnel plots are used to demonstrate the

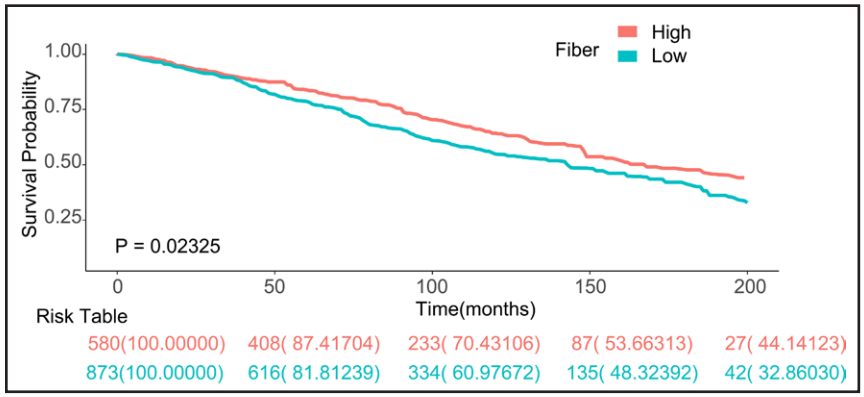

Figure 3. Mortality outcomes depicted by Kaplan-Meier curves of survival: all-cause mortality among patients with stroke categorized by fiber intake.

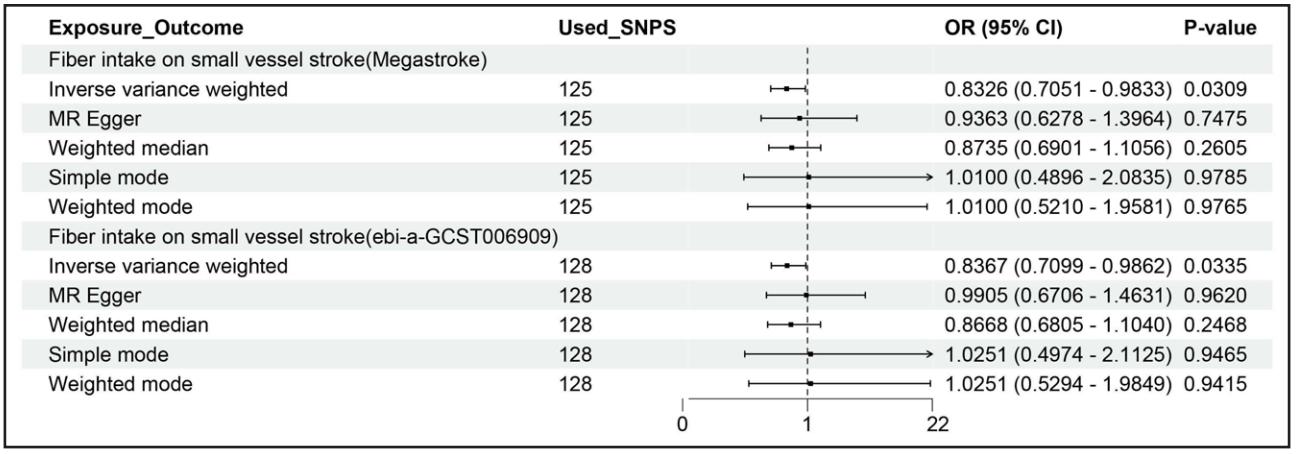

Figure 4. Validation of the results of the primary Mendelian randomization (MR) analyses against the MEGASTROKE data. Estimation of the causal effect of dietary fiber intake on small vessel stroke using different MR analysis methods. OR indicates odds ratio; and SNP, single-nucleotide polymorphism.

stability of the results (Figures S4 through S11). For a comprehensive view of the results, including those not discussed in the main text due to lack of statistical significance, refer to Table S3.

DISCUSSION

This study comprehensively examined the relationship between dietary fiber intake and stroke using multiple analytical methods. We first established a baseline association between fiber intake and stroke incidence in a large population-based sample, suggesting a potential preventive role of dietary fiber. Further analysis revealed that dietary fiber intake was associated with lower mortality among stroke survivors. A 2-stage MR approach provided genetic evidence supporting a causal link between dietary fiber intake and stroke, particularly small vessel stroke. Collectively, our findings demonstrate an inverse association between dietary fiber intake and stroke, highlighting its importance in stroke prevention and management.

Utilizing the NHANES data spanning for US adults from 1999 to 2018, this study revealed a statistically significant pessimistic correlation between dietary fiber intake and the incident stroke. The multivariate adjusted spline regression model confirmed a consistent linear passive relationship between dietary fiber intake and stroke risk (nonlinear P=0.566). Notably, in the fully adjusted model, T3 highlights that the stroke-preventive effect becomes most significant when dietary fiber intake surpasses a threshold of ≈18.3 g/d, marking a point where stroke risk is minimal. However, stark US statistics reveal that 90% of women and 97% of men fail to meet the healthy recommended daily intake of dietary fiber, which is not even >20 g/d.[22,40] A British cohort study on women concurred, finding a reduced overall stroke risk with higher fiber consumption.[41] A systematic review and meta-analysis demonstrated a significant relationship between increased total dietary fiber intake and a decreased danger of experiencing a first stroke.[42] Therefore, it was established that augmenting total dietary fiber intake contributes to reducing stroke risk, thereby emphasizing the crucial role of enhancing fiber intake in stroke prevention.

The reduction in stroke danger related to dietary fiber intake encompasses several potential biological mechanisms, chief among them being the regulation of inflammation in the body.[43] Specifically, dietary fiber inhibits inflammatory marker levels such as interleukin-18 and C-reactive protein, potentially suppressing atherosclerosis and consequently reducing stroke risk.[3] Additionally, dietary fiber, particularly soluble fiber, effectively modulates blood lipids, reducing cholesterol levels and improving atherosclerosis.[44] The positive impact of dietary fiber on intestinal microecology is also noteworthy, as it shapes the composition of intestinal microbiota. Dietary fiber intake reduces the negative impacts of antibiotics on gut flora and generates metabolic products such as short-chain fatty acids that have anti-inflammatory properties, vascular protective qualities, consequently lowering the risk of stroke.[4] Additionally, dietary fiber intake has been associated with enhanced insulin sensitivity, indirectly reducing stroke risk by ameliorating insulin resistance and its associated hypertension.[7]

According to our multivariate Cox regression model, dietary fiber intake significantly reduced all-cause mortality (P<0.05). Furthermore, Kaplan-Meier analysis of survival indicated that high dietary fiber intake improved survival among patients with stroke (P=0.02325). These findings are supported by research from the Japanese National Cancer Research Center, which conducted a long-term study revealing that individuals with higher dietary fiber intake, irrespective of sex, had a lower risk of mortality from cardiovascular diseases (including stroke) and certain cancers.[45]

The impact of genetic factors on dietary fiber intake is complex, involving taste perception, appetite regulation, and gut hormone secretion, which collectively shape individual food preferences and consumption patterns. Variants in the bitter taste receptor gene *TAS2R38* affect bitterness perception, altering preferences for bitter-tasting, fiber-rich foods such as broccoli. The *AVI* genotype, derived from the *TAS2R38* taste gene, is associated with reduced sensitivity to bitter tastes. For instance, individuals with the *AVI/AVI* genotype, particularly women, tend to consume higher amounts of dietary fiber.[46] In addition, individuals carrying fat mass and obesity-associated gene variants exhibit elevated ghrelin levels, even postprandially, leading to a preference for high-fat, high-protein foods while potentially reducing fiber intake.[47] Furthermore, reduced dietary fiber consumption, coupled with *Slc5a8* deficiency, impairs short-chain fatty acid absorption, compromising gut barrier function and promoting inflammation. This disruption may affect individual tolerance and preference for fiber-rich foods.[48] Our analysis further indicates that genetically mediated high dietary fiber intake is particularly effective in reducing small vessel stroke risk. Short-chain fatty acids, as key metabolic products of dietary fiber, activate G-protein-coupled receptors 41 and 43 and inhibit histone deacetylases, thereby suppressing inflammatory cytokine production (eg, interleukin-6 and interleukin-8) and adhesion molecule expression (eg, vascular adhesion molecule-1), ultimately reducing endothelial inflammation and small vessel pathology.[49] The studies demonstrate that genetic factors influence dietary fiber preferences and intake through multiple biological pathways. Metabolites derived from fiber can modulate the inflammatory response, which in turn mediates the potential causal protective effect of dietary fiber against small vessel stroke. These findings provide a genetic basis for personalized nutritional interventions.

Although our study provides valuable insights into the relationship between dietary fiber intake and stroke, several limitations should be acknowledged. First, although our cross-sectional data were derived from diverse US populations, the genome-wide association study data we utilized primarily originated from European populations. This demographic bias may restrict the generalizability of our results to other ethnicities or regions. Second, our study focused solely on total dietary fiber intake without differentiating between various fiber sources. This approach, along with the use of relatively broad thresholds to select fiber phenotypes, may have led to biased results and left the distinct impacts of different fiber types on stroke risk uncertain. Furthermore, the current genetic tools have not yet distinguished gene expression in brain tissue from that in other tissues. The lack of tissue-specific expression data hinders our ability to precisely assess the contribution of brain-specific gene expression to health outcomes, potentially limiting the in-depth understanding of certain disease mechanisms. Last, although we conducted multiple sensitivity analyses to confirm the robustness of our results, these analyses are still based on statistical modeling. The true biological mechanisms underlying these findings require experimental research to verify the existence of these causal relationships.

CONCLUSIONS

In conclusion, our study exhibited a robust negative relationship between dietary fiber intake and the incident stroke together with stroke-related all-cause mortality, particularly when considering overall dietary fiber intake. Given the widespread insufficiency in dietary fiber intake, it is imperative to enhance fiber intake among stroke survivors. To conclusively ascertain whether an increased dietary fiber intake truly diminishes the risk of mortality following a stroke, future randomized controlled trials are indispensable.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S11

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