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Associations between dietary index for gut microbiota and stroke, and the mediating role of inflammation: a prospective cohort study†

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Background: There has been a growing focus on the link between diet, gut microbiota, and stroke. The dietary index for gut microbiota (DI-GM), a novel indicator reflecting the effect of diet on gut microbiota diversity, has not been extensively studied in relation to stroke. This study aimed to examine the association between DI-GM and stroke, and to explore the potential mediating role of inflammatory biomarkers. *Methods*: We included 124 943 participants from the UK Biobank without stroke at baseline. The DI-GM was calculated using 24-hour dietary assessments. Cox proportional hazard models were employed to analyze the longitudinal associations of DI-GM with stroke and its subtypes. Restricted cubic spline (RCS) and subgroup analyses were also performed. Additionally, mediation analyses were conducted to explore the potential mediating role of inflammatory biomarkers between DI-GM and stroke risk. *Results*: During a median follow-up of 11.08 years, 3741 participants experienced a stroke, including 1626 ischemic strokes and 536 hemorrhagic strokes. After adjusting for covariates in the main model, higher DI-GM was significantly associated with reduced risks of stroke (HR = 0.97, 95% CI, 0.95–0.99, $P < 0.001$) and ischemic stroke (HR = 0.96, 95% CI, 0.94–0.99, $P = 0.008$), but not hemorrhagic stroke. No significant non-linear association was observed in the RCS analysis. Mediation analyses indicated that inflammatory biomarkers, including C-reactive protein, neutrophils, monocytes, leukocytes, neutrophil-to-lymphocyte ratio, and INFLA-score, partially mediated the association, accounting for 2.82% to 10.40% of the total effect. *Conclusions*: Higher DI-GM was associated with a reduced risk of stroke, particularly ischemic stroke. This protective association may be partially mediated by reductions in serum inflammatory biomarkers.

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Background

Stroke is the second leading cause of death globally, responsible for 7.3 million deaths in 2021, and ranks as the third leading cause of disability, with 160.5 million disability-adjusted life years (DALYs) lost during the same year.[1] The burden of stroke is rising due to population aging and lifestyle changes,[1] with stroke-related deaths expected to rise from 6.6 million to 9.7 million by 2050, and DALYs from 144.8 million to 189.3 million.[2] However, there is currently no effective method to eradicate this disease. Therefore, identifying modifiable protective factors and implementing early preventive interventions to decrease the risk of stroke is crucial.

The gut microbiota, often described as a "virtual organ",[3,4] is essential for human health by influencing neural, hormonal, and immunological pathways.[5,6] Growing evidence indicates that the gut microbiota is vital for regulating the central nervous system (CNS), forming the foundation of the "microbiota-gut-brain axis",[7,8] with imbalances in this axis associated with the pathophysiology of stroke.[9] Research has shown a significant reduction in gut microbiota diversity in patients who have had a stroke.[10] Diet, a key modifiable lifestyle factor, has been found to significantly influence the composition of the gut microbiota.[11,12] For instance, a high-fermenting diet has been shown to increase the diversity of the gut microbiota, whereas diets with a higher fat-to-carbohydrate ratio are associated with reduced diversity.[13] There has been a growing focus on using dietary interventions to modulate the gut microbiome, with evidence that dietary changes can induce

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substantial changes in gut microbial diversity.[14,15] Recently, Kase *et al.* conducted an analysis of 106 studies investigating the relationship between diet and gut microbiota in adults, identifying 14 dietary factors that positively or negatively influence on the composition of gut microbiota. They proposed a new dietary index for gut microbiota (DI-GM) to assess the quality of diet associated with maintaining a healthy gut microbiome. DI-GM was positively correlated with biomarkers of gut microbial diversity, including urinary enterodiol and enterolactone, suggesting its potential ability in identifying dietary patterns conducive to gut health.[16] However, there has been a shortage of study on the relation between DI-GM and stroke and its subtypes.

Research has shown that the levels of inflammatory biomarkers increase progressively with aging,[17] a process strongly linked to stroke, an age-related disease closely associated with inflammation.[18] Diet, as a modifiable factor, plays an essential role in regulating inflammation within the body.[19] Additionally, the gut microbiota, influenced by dietary patterns, can modulate systemic inflammation through immune pathways.[13,20] Given this evidence, we hypothesize that dietary patterns supporting gut microbiota diversity may lower stroke risk by reducing systemic inflammation.

To date, only one study based on the NHANES database has investigated the association between DI-GM and stroke.[21] However, this study was cross-sectional, and did not explore potential mechanisms. Therefore, the relationship between DI-GM and stroke warrants further investigation. To provide a more comprehensive evaluation of the relationship between DI-GM and stroke, we utilized data from the UK Biobank, a large population-based cohort. This study aimed to investigate the longitudinal relation between DI-GM and stroke, including its subtypes (ischemic and hemorrhagic stroke), and to examine whether chronic inflammatory biomarkers mediate this association.

Methods

Study cohort

Data from the UKB, a large and ongoing cohort involving more than 500 000 participants ranging from 37–73 years old at recruitment, were used in this study. Participants were recruited through the UK National Health Service and enrolled from 22 assessment centers throughout the UK between 2006 and 2010. The recruitment process involved public recruitment and voluntary participation, and participants were not selected through traditional random sampling. Comprehensive baseline information was collected using self-reported questionnaires, physical evaluations, biological samples, and linked medical records. Follow-up visits were carried out periodically to monitor participants' health and update their medical details. Ethical approval for the study was granted by the North West Multicenter Research Ethics Committee, and all participants provided written informed consent.

From the 502 292 participants initially recruited by UKB, we excluded 375 503 individuals who completed fewer than two valid 24-hour dietary assessments. We also excluded 1800 participants diagnosed with stroke at the time of completing their last 24-hour dietary assessment and 46 participants with inconsistent or unreliable dietary questionnaire dates. Finally, 124 943 participants were eligible to participate this study (Fig. 1). For the mediation analysis, participants with missing inflammatory biomarker data or extreme outlier values (beyond 4 standard deviations (SD)) were excluded, leaving a final sample of 109 422 participants.

Dietary assessment

Dietary intake was evaluated through the Oxford WebQ, a 24-hour online dietary questionnaire implemented as part of the UKB study. Detailed information about the Oxford WebQ has been comprehensively described in previous publications.[22] During the final phase of UKB recruitment from 2009 to 2010, the Oxford WebQ was introduced as part of the baseline survey and completed by approximately 70 000 participants. Between February 2011 and April 2012, those who had given a valid email address during recruitment were invited to fill out the Oxford WebQ online up to four times. The follow-up 24-hour dietary assessments had a response rate varying between 26.15% and 32.83%. Overall, compared to respondents, non-respondents were younger, had a higher proportion of males, a higher smoking rate, a lower drinking rate, and a higher proportion of overweight individuals. The detailed demographic characteristics of responders and non-responders were provided in ESI Table 1.† Validated in earlier studies, the Oxford WebQ assesses the consumption of over 200 different foods and beverages, while estimating energy and nutrient intake.[22,23] The reliability of the Oxford WebQ has been supported by a validation study using blood and urine biomarkers.[24] To better reflect habitual dietary intake, nutrient and food intake data were averaged from at least two assessments, and only participants with a minimum of two valid dietary assessments were included in the analyses.

Assessment of dietary index for gut microbiota

The DI-GM is a literature-based tool designed to quantify the dietary impact on gut microbiota. Based on Kase *et al.*'s scoring criteria, the DI-GM incorporates 14 key dietary components, with their intake closely linked to the diversity and health status of microbiota.[16] Beneficial components included avocado, broccoli, coffee, fermented milk products, fiber, green tea, soy and whole grains, chickpeas, cranberries (data for chickpeas and cranberries were unavailable as the UKB did not record specific type of legume and berry consumption), while unfavorable components were red meat, processed meat, refined grains and a high-fat diet (≥40% energy from fat). The DI-GM was calculated using the 24-hour dietary assessment, with its components and detailed scoring criteria provided in ESI Table 2.† DI-GM scores (range: 0–12) reflect the dietary impact on gut microbiota, comprising a beneficial to gut microbiota score (BGMS: 0–8) and an unfavorable to gut microbiota score (UGMS: 0–4). Higher DI-GM scores indicate a diet more favorable to gut microbiota diversity. The

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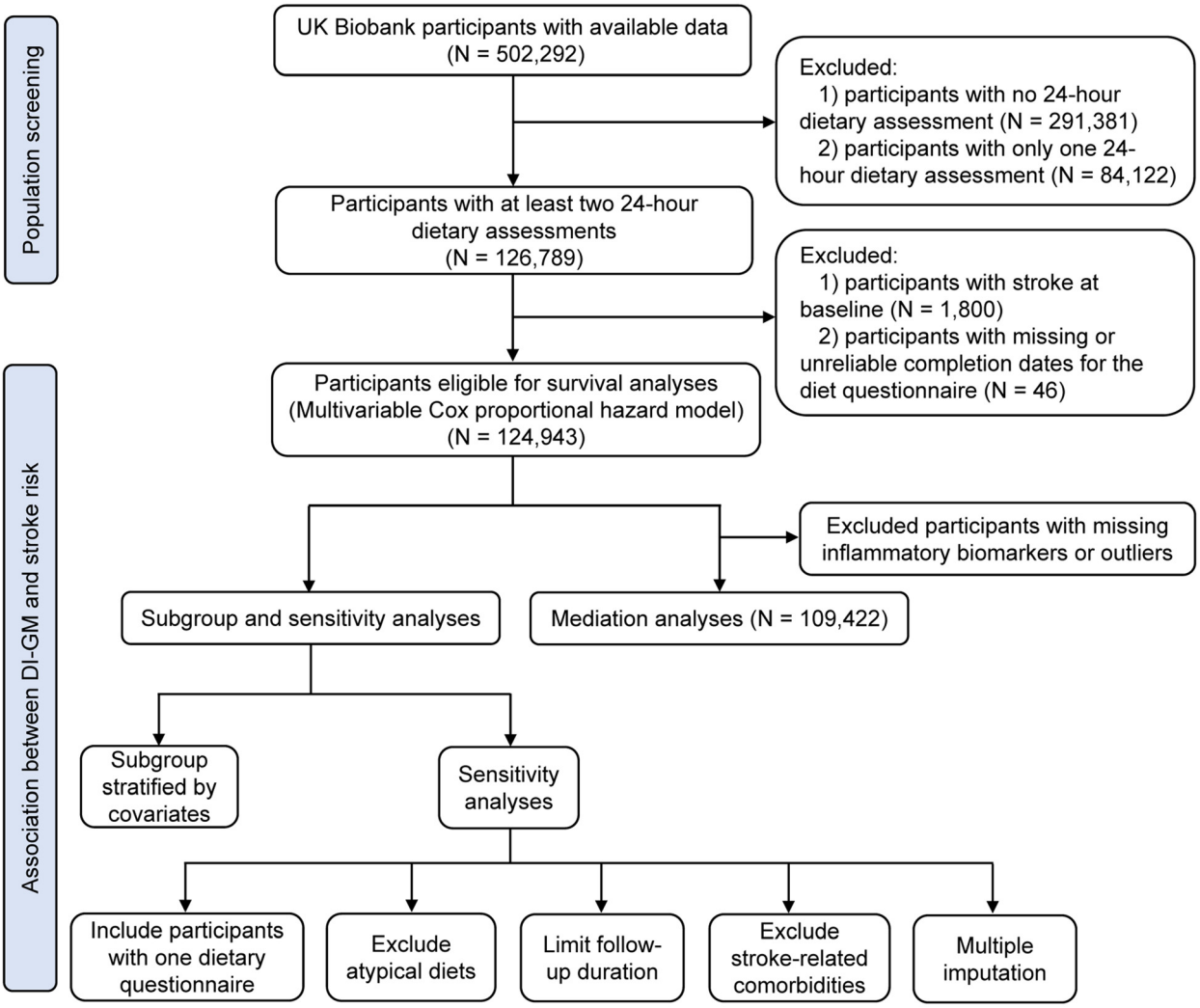

Fig. 1 Flow chart of the design. *Abbreviations*: UK, the United Kingdom; DI-GM, dietary index for gut microbiota; N, number of participants.

distribution of these scores was presented in ESI Fig. 1.† Additionally, the DI-GM was categorized into groups: 0–3, 4, 5, ≥6 for further analysis.[25]

Assessment of stroke

Stroke diagnoses were determined using data from first occurrence reports, algorithmic definitions, death certificates, and hospital inpatient records. Stroke was defined as any cerebrovascular disease (I_{60}–I_{69}), with ischemic stroke (I_{63}) and hemorrhagic stroke (I_{60}–I_{61}) distinguished separately, based on the International Classification of Diseases 10th revision (ICD-10) codes. Follow-up started from the last 24-hour dietary assessment and continued until the earliest occurrence of stroke diagnosis, loss to follow-up, death, or the most recent hospital inpatient data update (September 2023).

Inflammatory biomarkers

Peripheral inflammatory biomarkers were collected from blood count and biochemistry data, obtained from approximately 480 000 participants during the baseline assessment. To explore the impact of inflammation in the relationship between DI-GM and stroke, we selected inflammatory biomarkers that have been identified as key indicators of inflammatory processes, including C-reactive protein (CRP), neutrophil, monocyte, white blood cell (WBC), lymphocytes, platelet and the neutrophil-to-lymphocyte ratio (NLR). To ensure the reliability of the data, we excluded outlier values for these inflammatory biomarkers, defined as those exceeding 4 SD above or below the mean.

Additionally, a composite low-grade chronic inflammation (INFLA) score was calculated using CRP, WBC, platelet, and NLR. The INFLA-score was calculated by assigning values to biomarkers based on their distribution in deciles. Biomarker levels in the top deciles (7th to 10th) were assigned values ranging from +1 to +4, while those in the bottom deciles (1st to 4th) received values from −4 to −1. The resulting INFLA-score can range from −16 to +16, with higher scores indicating greater levels of low-grade inflammation.[26] The distribution of

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INFLA-score among the participants was presented in ESI Fig. 2.† The specific field IDs of inflammatory biomarkers were provided in ESI Table 3.†

Assessment of covariates

Covariates included age, gender (male *vs.* female), education level, ethnicity (white *vs.* other), the Townsend deprivation index (TDI), smoking status (never *vs.* previous/current), drinking status (never *vs.* previous/current), body mass index (BMI), family history of stroke, blood pressure, diabetes, atrial fibrillation (AF), atherosclerosis, dementia, depression, energy intake and physical activity (whether an individual met the UK physical activity guidelines, which recommend either 150 minutes of moderate-intensity walking or physical activity per week, or 75 minutes of vigorous-intensity activity).

Statistical analysis

Baseline characteristics were compared based on stroke status, with categorical variables shown as percentages and continuous variables as mean (SD). Cox proportional hazard models were used to examine the longitudinal associations between DI-GM, DI-GM groups, BGMS and UGMS with the risk of stroke. Three models were constructed. Model 1 adjusted for age, sex, ethnicity, education level, and TDI. Model 2 (main model) further adjusted for smoking status, drinking status, BMI, blood pressure, family history of stroke, diabetes and energy intake. Model 3 additionally adjusted for AF, atherosclerosis, dementia, depression and physical activity. The proportional hazard assumption was tested using Schoenfeld residuals. Restricted cubic spline (RCS) analyses were performed within Cox proportional hazard models to assess potential non-linear associations between DI-GM (as well as BGMS and UGMS) and incident stroke.

Stratified analyses were conducted based on the following factors: age (<65 *vs.* ≥65 years), sex (male *vs.* female), education level (higher education (college/university degree or other professional qualification) *vs.* others), TDI (below *vs.* above median), smoking status (never *vs.* previous/current smoker), drinking status (never *vs.* previous/current drinker), BMI (<25 *vs.* ≥25 kg m^{-2}), energy intake (below *vs.* above median), blood pressure (normal *vs.* hypertension), family history of stroke (yes *vs.* no), and diabetes status (yes *vs.* no) to assess the vulnerability of different populations. Interaction terms between DI-GM and each stratification factor were included in the models, and Wald tests were used to assess statistical significance of interaction (*P* for interaction).

We further explored the association between DI-GM and inflammatory biomarkers. First, multiple linear regression (MLR) was used to examine the relationship between baseline DI-GM and baseline inflammatory biomarkers. Longitudinal changes in inflammatory biomarkers were then assessed by calculating the rate of change using linear mixed-effects models, followed by MLR to evaluate the association between DI-GM and the inflammatory biomarkers trajectories. Due to the limited availability of biomarker data during follow-up, this longitudinal analysis included only 9336 participants.

Mediation analyses were performed using the 'mediation' package in R to assess whether inflammatory biomarkers mediated the association between DI-GM and stroke. Based on the above analysis of the association between baseline DI-GM and inflammatory biomarkers, we conducted survival analysis to examine the association between inflammatory biomarkers and stroke. Only biomarkers significantly associated with both DI-GM and stroke risk were included in the mediation models. To address the limitations of using Cox proportional hazard models in mediation, we employed accelerated failure time (AFT) models with 'Weibull' distributions for survival analysis.[27] This approach was supported by recent studies.[28,29] In the mediate analyses, the regression coefficients were interpreted as indicators of the relative rate of outcome progression, where a positive coefficient corresponded to a slower progression, indicating a lower risk. Mediation effects were estimated using 10 000 bootstrap iterations, with adjustments for the covariates included in model 2 for each pathway. In addition, structural equation modeling (SEM) was used to estimate relationships between DI-GM, inflammation, and stroke risk. Confirmatory factor analysis (CFA) was performed to evaluate the latent variable representing inflammation. Before incorporating the variables into the model, DI-GM and each individual component of the latent variables were independently standardized to ensure uniform scaling across measures.

Furthermore, sensitivity analyses were conducted to test the robustness of the findings: (1) including participants with only one 24-hour dietary assessment. (2) Excluding participants with extreme energy intakes (females: outside 600–3500 kcal day^{-1}; males: outside 800–4200 kcal day^{-1}) and those self-reported atypical diets.[30] (3) Excluding participants diagnosed with stroke within the first two years of follow-up to minimize reverse causation. (4) Excluding participants with baseline AF, atherosclerosis, dementia, or depression. (5) Using multiple imputation by chained equations (MICE) for missing covariates, generating five imputed datasets to minimize the impact of missing covariates. Missing data proportions for covariates were provided in ESI Table 4.† Covariates were adjusted based on model 2 for all sensitivity analyses, except for multiple imputation, which was adjusted based on model 3.

All analyses were conducted using R (version 4.4.2), with statistical significance defined as $P < 0.05$.

Results

Characteristics of study participants

This study included 124 943 participants. During a median follow-up period of 11.08 years, 3741 participants developed stroke, including 1626 ischemic strokes and 536 hemorrhagic strokes. Table 1 summarized the baseline characteristics of participants according to their stroke status. Overall, the mean age was 59.44 years, 56.0% were female, and 96.5% were of White ancestry. The average DI-GM score was 5.02. Compared with participants without stroke, those who developed stroke (either ischemic or hemorrhagic) were older, more likely to be

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Table 1 Baseline characteristics of participants

Characteristics	Overall $N = 124\,943$	Control $N = 121\,202$	Incident stroke		Incident ischemic stroke		Incident hemorrhage stroke	
			$N = 3741$	P	$N = 1626$	P	$N = 536$	P
Age (mean (SD))	59.44 (7.84)	59.28 (7.83)	64.58 (6.37)	<0.001	64.56 (6.44)	<0.001	63.22 (6.69)	<0.001
Sex (%)				<0.001		<0.001		0.062
Female	69 911 (56.0)	68 287 (56.3)	1624 (43.4)		662 (40.7)		280 (52.2)	
Male	55 032 (44.0)	52 915 (43.7)	2117 (56.6)		964 (59.3)		256 (47.8)	
Ethnic (%)				0.039		0.647		0.115
White	120 593 (96.5)	116 959 (96.5)	3634 (97.1)		1573 (96.7)		510 (95.1)	
Others	4350 (3.5)	4243 (3.5)	107 (2.9)		53 (3.3)		26 (4.9)	
Education levels[a] (%)				<0.001		<0.001		0.095
College degree	58 740 (47.2)	57 223 (47.4)	1517 (40.7)		641 (39.5)		225 (42.2)	
A level	16 784 (13.5)	16 318 (13.5)	466 (12.5)		201 (12.4)		68 (12.8)	
O level	24 444 (19.6)	23 655 (19.6)	789 (21.2)		355 (21.9)		126 (23.6)	
CSE	4373 (3.5)	4260 (3.5)	113 (3.0)		53 (3.3)		15 (2.8)	
NVQ	6088 (4.9)	5837 (4.8)	251 (6.7)		115 (7.1)		31 (5.8)	
Professional qualification	6100 (4.9)	5867 (4.9)	233 (6.2)		95 (5.9)		28 (5.3)	
Others	8027 (6.4)	7667 (6.3)	360 (9.7)		161 (9.9)		40 (7.5)	
TDI (mean (SD))	−1.64 (2.84)	−1.64 (2.83)	−1.57 (2.90)	0.157	−1.72 (2.76)	0.278	−1.59 (2.87)	0.700
Energy intake (mean (SD))	2065.90 (518.28)	2065.12 (517.80)	2091.46 (533.24)	0.002	2101.20 (542.46)	0.005	2057.60 (534.74)	0.737
Smoking status				<0.001		<0.001		0.028
Never	71 530 (57.4)	69 760 (57.7)	1770 (47.4)		775 (47.7)		283 (52.9)	
Previous or current	53 147 (42.6)	51 182 (42.3)	1965 (52.6)		850 (52.3)		252 (47.1)	
Drinking status (%)				0.238		0.624		0.397
Never	3561 (2.9)	3442 (2.8)	119 (3.2)		50 (3.1)		19 (3.5)	
Previous or current	121 293 (97.1)	117 672 (97.2)	3621 (96.8)		1575 (96.9)		517 (96.5)	
BMI (%)				<0.001		<0.001		0.683
Health weight	49 559 (39.8)	48 321 (40.0)	1238 (33.2)		492 (30.4)		208 (39.0)	
Overweight	50 850 (40.8)	49 237 (40.7)	1613 (43.3)		722 (44.5)		214 (40.2)	
Obesity	24 266 (19.5)	23 390 (19.3)	876 (23.5)		407 (25.1)		111 (20.8)	
Physical activity[b] (%)				0.007		0.033		0.182
No	10 012 (10.1)	9763 (10.2)	249 (8.6)		105 (8.3)		34 (8.1)	
Yes	88 935 (89.9)	86 295 (89.8)	2640 (91.4)		1160 (91.7)		387 (91.9)	
Blood pressure status (%)				<0.001		<0.001		<0.001
Normal	17 354 (14.5)	17 091 (14.8)	263 (7.3)		118 (7.6)		35 (6.7)	
Elevated	14 686 (12.3)	14 367 (12.4)	319 (8.9)		127 (8.2)		47 (9.0)	
Hypertension stage 1	53 818 (45.1)	52 173 (45.1)	1645 (45.8)		686 (44.2)		253 (48.6)	
Hypertension stage 2	33 429 (28.0)	32 066 (27.7)	1363 (38.0)		621 (40.0)		186 (35.7)	
Family history of stroke (yes, %)	32 809 (26.7)	31 562 (26.5)	1247 (33.9)	<0.001	545 (34.1)	<0.001	189 (35.7)	<0.001
Diabetes (yes, %)	3232 (2.6)	2999 (2.5)	233 (6.2)	<0.001	92 (5.7)	<0.001	26 (4.9)	0.001
Atrial fibrillation (yes, %)	2533 (2.0)	2293 (1.9)	240 (6.4)	<0.001	117 (7.2)	<0.001	34 (6.3)	<0.001
Atherosclerosis (yes, %)	143 (0.1)	118 (0.1)	25 (0.7)	<0.001	3 (0.2)	0.475	3 (0.6)	0.007
Dementia (yes, %)	47 (0.0)	41 (0.0)	6 (0.2)	<0.001	2 (0.1)	0.214	0 (0.0)	1.000
Depression (yes, %)	9999 (8.0)	9683 (8.0)	316 (8.4)	0.324	130 (8.0)	1.000	41 (7.6)	0.834
DI-GM (mean (SD))	5.02 (1.82)	5.02 (1.82)	5.01 (1.82)	0.700	4.98 (1.78)	0.347	4.98 (1.78)	0.592
DI-GM group (%)				0.422		0.849		0.437
0–3	26 328 (21.1)	25 510 (21.0)	818 (21.9)		345 (21.2)		122 (22.8)	
4	23 658 (18.9)	22 976 (19.0)	682 (18.2)		321 (19.7)		88 (16.4)	
5	26 350 (21.1)	25 580 (21.1)	770 (20.6)		336 (20.7)		112 (20.9)	
≥6	48 607 (38.9)	47 136 (38.9)	1471 (39.3)		624 (38.4)		214 (39.9)	
BGMS (mean (SD))	2.64 (1.44)	2.64 (1.44)	2.59 (1.45)	0.048	2.57 (1.43)	0.050	2.55 (1.40)	0.148
UGMS (mean (SD))	2.38 (0.94)	2.38 (0.94)	2.42 (0.94)	0.022	2.41 (0.94)	0.233	2.43 (0.95)	0.236

P-values are derived using either Student's *t*-test or Mann–Whitney *U* test (for continuous variables) and chi-square test (for categorical variables). *Abbreviations*: N, number of participants; TDI, Townsend deprivation index; BMI, body mass index; DI-GM, dietary index for gut microbiota; BGMS, beneficial to gut microbiota score; UGMS, unfavorable to gut microbiota score; SD, standard deviation. [a] Classification of education level is defined according to UKB Field ID 6138. [b] Physical activity is defined as meeting the UK physical activity guidelines, which recommend at least 150 minutes of walking or moderate activity, or 75 minutes of vigorous activity per week.

male, and had a higher prevalence of hypertension, overweight or obesity, diabetes, AF, atherosclerosis, family history of stroke, and smoking. Additionally, these participants exhibited lower DI-GM and BGMS, and higher UGMS; however, these differences were not statistically significant.

Associations between DI-GM and stroke risk

The associations of DI-GM, DI-GM groups, BGMS, and UGMS with the risk of stroke and its subtypes were examined using multivariable Cox proportional hazards models, with results

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shown in Fig. 2. After adjustment for covariates in model 2, higher DI-GM was significantly associated with a lower risk of stroke (HR = 0.97, 95% CI, 0.95–0.99, $P < 0.001$) and ischemic stroke (HR = 0.96, 95% CI, 0.94–0.99, $P = 0.008$), but not with hemorrhagic stroke (HR = 0.96, 95% CI, 0.92–1.01, $P = 0.137$). After grouping DI-GM, participants with scores of 4, 5, and ≥6 groups had significantly reduced risks of stroke compared to those in the 0–3 group (HR = 0.85, 95% CI, 0.77–0.95, $P = 0.003$; HR = 0.84, 95% CI, 0.76–0.93, $P < 0.001$; HR = 0.84, 95% CI, 0.77–0.92, $P < 0.001$, respectively). A similar trend was observed for ischemic stroke, with a significantly reduced risk in the ≥6 group (HR = 0.86, 95% CI, 0.75–0.99, $P = 0.037$). No significant associations were observed between DI-GM groups and hemorrhagic stroke. In the trend test, when the DI-GM groups were treated as a continuous variable, a significant linear association was observed with both stroke (P for trend < 0.001) and ischemic stroke (P for trend = 0.020). Additionally, higher BGMS was significantly associated with a reduced risk of stroke and both subtypes (stroke: HR = 0.94, 95% CI, 0.92–0.97, $P < 0.001$; ischemic stroke: HR = 0.94, 95% CI, 0.90–0.97, $P < 0.001$; and hemorrhagic stroke: HR = 0.93, 95% CI, 0.87–0.99, $P = 0.024$). In contrast, UGMS was not significantly associated with stroke or its subtypes. Similar associations were observed in model 1 and model 3. However, for hemorrhagic stroke, when stratified by DI-GM score, a significant association was observed only in the group with a DI-GM score of 4, while no similar associations were found in the two higher DI-GM groups. The number of hemorrhagic stroke cases in each DI-GM group, both in the total study population and across the three models excluding participants with missing covariates, was presented in ESI Fig. 3.†

Additionally, no significant non-linear association between DI-GM and stroke or its subtypes was observed in the RCS analysis (stroke: P for non-linearity = 0.410; ischemic stroke: $P = 0.970$; hemorrhagic stroke: $P = 0.269$). Similar results were found in BGMS (stroke: $P = 0.092$; ischemic stroke: $P = 0.336$; hemorrhagic stroke: $P = 0.431$) and UGMS (stroke: $P = 0.229$; ischemic stroke: $P = 0.074$; hemorrhagic stroke: $P = 0.560$) (ESI Fig. 4†).

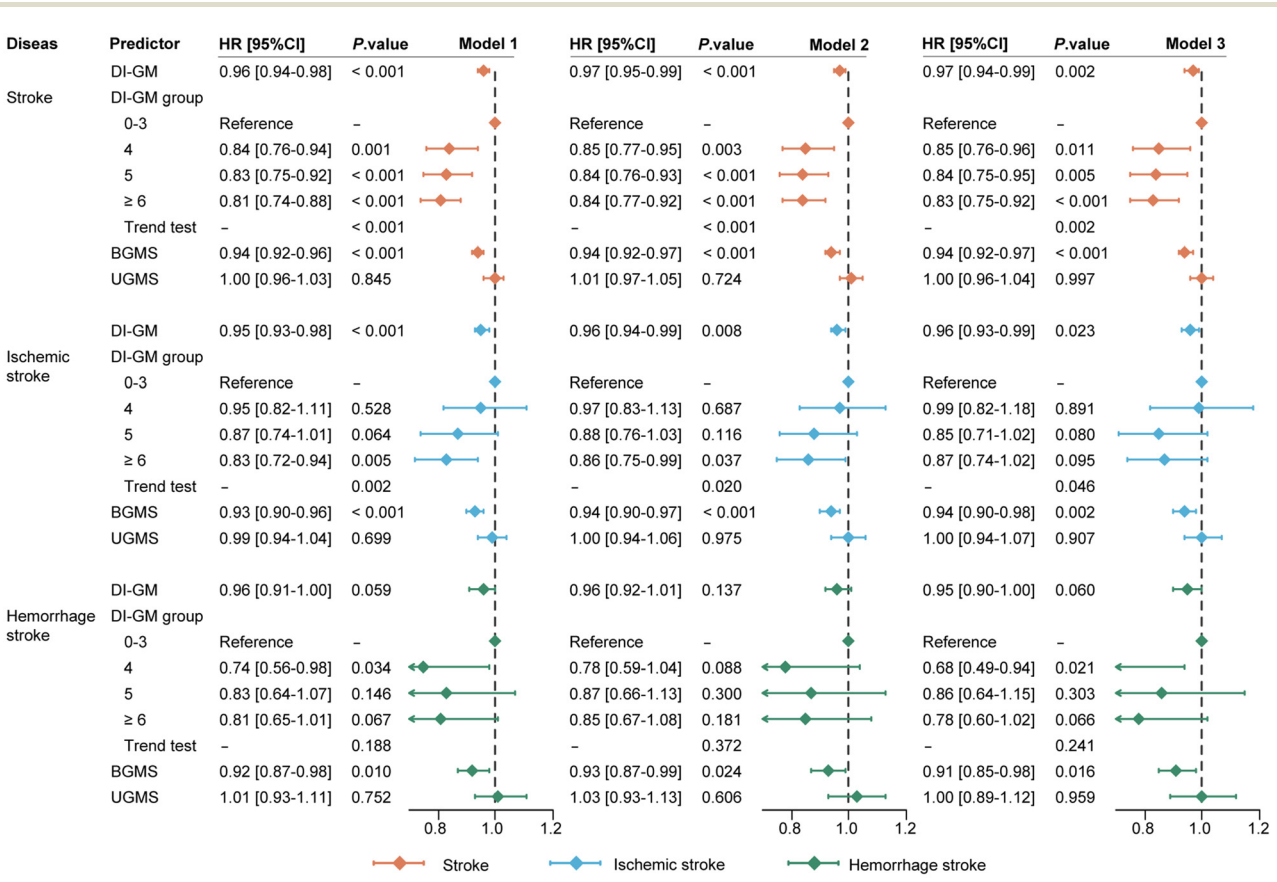

Fig. 2 Associations of DI-GM, DI-GM groups, BGMS, and UGMS with stroke risk. A total of 124 943 participants from the UK Biobank were included to investigate the associations of DI-GM, DI-GM groups, BGMS and UGMS with stroke risk, using Cox proportional hazard models. Model 1 was adjusted for age, sex, ethnicity, education level, and TDI. Model 2 further adjusted for smoking status, drinking status, BMI, blood pressure, family history of stroke, diabetes and energy intake (main model). Model 3 additionally adjusted for AF, atherosclerosis, dementia, depression and physical activity. The results are presented as HR [95% CI]. The error bars represent the 95% CI of the HR. Two-sided P values from multivariate Cox proportional hazard models are also provided to reflect the associations. *Abbreviations*: DI-GM, dietary index for gut microbiota; BGMS, beneficial to gut microbiota score; UGMS, unfavorable to gut microbiota score; TDI, Townsend deprivation index; BMI, body mass index; AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval.

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Subgroup and sensitivity analyses

In the subgroup analyses (Fig. 3), significant effect modifications were observed for stroke when stratified by age and drinking status (P for interaction < 0.05). For ischemic stroke, significant effect modifications were observed when stratified by age and smoking status (P for interaction < 0.05). For hemorrhagic stroke, significant effect modifications were observed when stratified by family history of stroke and diabetes status (P for interaction < 0.05). No significant effect modifications were observed in the remaining subgroup analyses (P for interaction > 0.05).

Sensitivity analyses were conducted to assess the robustness of the results, and the findings were largely consistent with those from the main analyses. Detailed results were available in ESI Tables 5–9.†

Association between DI-GM and inflammatory biomarkers at baseline and follow-up

In our study, baseline DI-GM was significantly and inversely associated with the inflammatory biomarkers used in our study, including CRP, neutrophils, monocytes, WBC, lymphocytes, platelets, NLR, and INFLA-score (β ranging from −0.258 to −0.013, all P < 0.0001; ESI Table 10†).

Furthermore, baseline DI-GM was significantly associated with the longitudinal changes in these inflammatory biomarkers (β ranging from −0.031 to −0.016, all P < 0.05), except for platelets (β = −0.011, P = 0.057) and NLR (β = −0.006, P = 0.265) (ESI Table 11†).

The mediating role of blood inflammatory biomarkers

As described above, DI-GM was significantly associated with inflammatory biomarkers, including CRP, neutrophils, monocytes, WBC, lymphocytes, platelets, NLR, and INFLA-score. And most of these biomarkers were also longitudinally associated with stroke risk, except for lymphocytes and platelets (ESI Table 12†). Mediation analyses revealed that CRP, neutrophil, monocyte, WBC, NLR, and INFLA-score acted as mediators in the relationship between DI-GM and stroke risk. Among these, CRP had the highest mediation proportion (10.40%, P = 0.009), followed by INFLA score (9.81%, P = 0.011), neutrophil (5.49%, P = 0.022), WBC (4.87%, P = 0.042), monocyte (4.48%, P = 0.010), and NLR (2.82%, P = 0.012) (Fig. 4A).

SEM was conducted to further evaluate the interrelationships between DI-GM, inflammation, and stroke. CFA was first performed to define the latent variable representing systemic inflammation, with INFLA-score, neutrophil, and monocyte identified as significant indicators (β = 0.955, 0.823, 0.323,

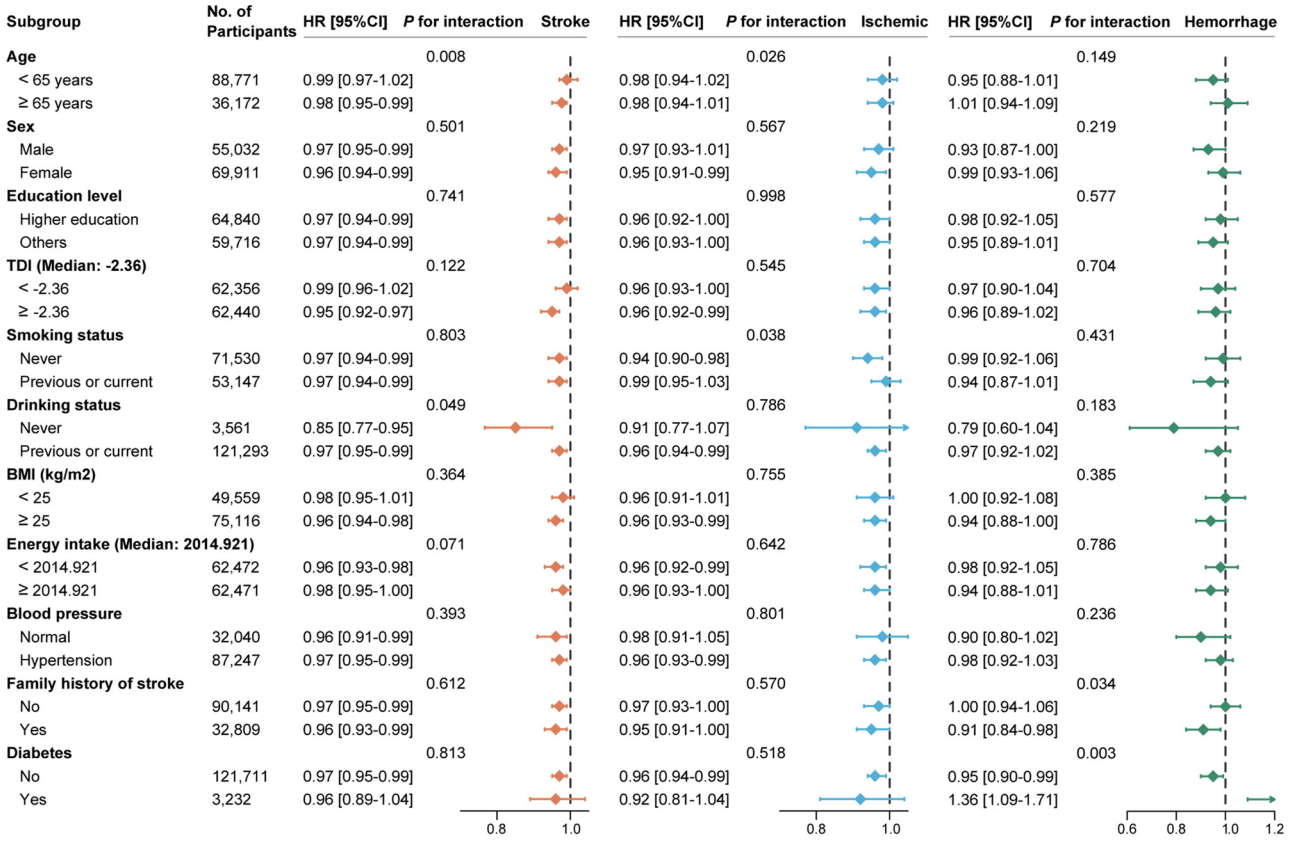

Fig. 3 Associations between DI-GM and stroke in subgroups. Subgroup analyses were conducted using Cox proportional hazards models, adjusting for age, sex, ethnicity, education level, TDI, smoking status, drinking status, BMI, blood pressure, family history of stroke, diabetes and energy intake. *Abbreviations*: DI-GM, dietary index for gut microbiota; TDI, Townsend deprivation index; BMI, body mass index.

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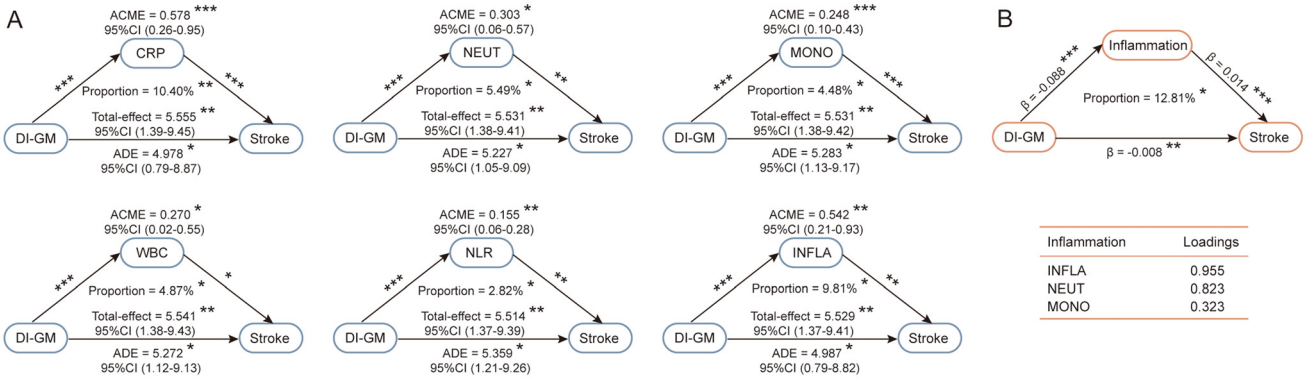

Fig. 4 Mediation analysis of inflammatory biomarkers in the association between DI-GM and stroke. The role of each inflammatory biomarker in mediating the association between DI-GM and stroke (A), and the structural equation model evaluating the mechanisms by which DI-GM influences stroke risk through inflammatory pathways (B). Adjusted for age, sex, ethnicity, education level, TDI, smoking status, drinking status, BMI, blood pressure, family history of stroke, diabetes and energy intake for each pathway. Asterisks denoted the significance of each path, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. *Abbreviations*: DI-GM, dietary index for gut microbiota; TDI, Townsend deprivation index; BMI, body mass index; CRP, C-reaction protein; NEUT, neutrophil; MONO, monocyte; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; INFLA-score, low-grade chronic inflammation score; ACME, average causal mediation effect; average direct effect; CI, confidence interval.

respectively, $P < 0.001$). The latent variable was then incorporated into the SEM to estimate the path coefficients. The SEM analysis revealed that DI-GM significantly predicted both inflammation ($\beta = -0.088$, $P < 0.001$) and stroke risk ($\beta = -0.008$, $P = 0.010$), and inflammation was also a significant predictor of stroke ($\beta = 0.014$, $P < 0.001$). These inflammatory biomarkers collectively mediated 12.81% of the relation between DI-GM and stroke (Fig. 4B).

Discussion

This study provided a comprehensive assessment of the correlation between DI-GM and stroke risk in a large prospective cohort. Our findings indicated that higher DI-GM and BGMS were associated with a reduced risk of stroke. When examining stroke subtypes, our analysis demonstrated that DI-GM, DI-GM ≥ 6, and BGMS were significantly associated with a reduced risk of ischemic stroke. For hemorrhagic stroke, BGMS was significantly associated with a decreased risk. Notably, when stratified by DI-GM score, only the group with a score of 4 was significantly associated with hemorrhagic stroke in models 1 and 3, while the association in model 2 approached statistical significance. No similar associations were observed in the two higher DI-GM groups across any of the models. This finding appears to be somewhat anomalous. We speculated that this finding might be due to the relatively small number of hemorrhagic stroke events in this group, which could have resulted in limited statistical power and an increased likelihood of a false-positive result. No significant non-linear association between DI-GM and stroke or its subtypes was observed in the RCS analysis. Furthermore, we identified a mediating role of inflammatory biomarkers in the association between DI-GM and stroke risk.

Up to 90% of strokes are preventable by managing modifiable risk factors, with diet being one of the most accessible and cost-effective lifestyle interventions.[31] Accumulating evidence has highlighted close links between dietary patterns and stroke risk.[32,33] For instance, excessive sodium intake has been strongly associated with an increased risk of stroke.[32,34] Similarly, the dietary inflammatory index (DII), which measures the inflammatory potential of diet, has been shown to increase stroke risk.[35] In contrast, certain dietary patterns have demonstrated protective effects against stroke. The Mediterranean diet, widely studied in this area, has been demonstrated to significantly lower stroke risk due to its anti-inflammatory and cardiovascular benefits.[32,36] Likewise, the Dietary Approaches to Stop Hypertension (DASH) diet, has been found to slow the progression of cognitive impairment and dementia in stroke survivors.[37] A recent cross-sectional study based on the NHANES database also found an inverse association between DI-GM and stroke.[21] Our longitudinal findings not only confirm but also extend this observation by demonstrating a stronger association with ischemic stroke. Furthermore, we found that this protective effect may be partially mediated by reduced inflammatory biomarkers, reinforcing the potential value of DI-GM as a modifiable dietary index in stroke prevention.

Notably, our current fundings showed that DI-GM was significantly associated with reduced risk of ischemic stroke, but not with hemorrhagic stroke. Previous studies have reported that the pathogenesis and pathophysiology of ischemic and hemorrhagic stroke differ,[34,38] and that the classic risk factors for stroke have different influences on different stroke subtypes.[39] Therefore, we hypothesize that DI-GM may exert different effects on stroke subtypes. One potential mechanism is that foods like avocados, coffee, green tea, and dietary fiber have been shown to enhance endothelial function,[40–43] which is considered a key pathogenic factor in ischemic stroke.[44] Moreover, these foods are rich in bioactive compounds such as catechins and antioxidants that reduce oxidative stress, which

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may help reduce ischemic stroke risk.[42,45] Conversely, risk factors for hemorrhagic stroke such as severe small vessel diseases and use of antithrombotic medications, are more closely related to vascular fragility and rupture.[31] Although these mechanisms are biologically plausible, further studies are required to validate their relevance and to clarify the exact role and mechanisms of DI-GM in ischemia stroke.

Our study also demonstrated that DI-GM could decrease the risk of stroke through reducing the levels of inflammatory biomarkers. On the one hand, beneficial dietary components within DI-GM, such as fiber, green tea, and fermented foods, possess intrinsic anti-inflammatory properties. On the other hand, these foods may modulate the gut microbiota composition, thereby reducing systemic inflammation.[13] Specifically, short-chain fatty acids (SCFAs) produced by gut microbiota can enhance intestinal barrier integrity, reduce translocation of pro-inflammatory factors such as lipopolysaccharides (LPS),[46–48] and inhibit NF-κB signaling, a key regulator of inflammation.[49] Experimental study further supported this mechanism, showing that transplanting SCFA-producing microbiota into aged stroke mice increased SCFA levels, reduced inflammation, and improved neurological outcomes.[50] These results emphasize the complex interactions between diet, gut microbiota, and stroke risk. A healthy diet may not only help reduce systemic inflammation through its intrinsic anti-inflammatory properties but also enhance the diversity of beneficial gut microbiota, whose metabolic products may further reduce systemic inflammation and potentially lower the risk of stroke.

The relationship observed between DI-GM and stroke risk is in accordance with evidence highlighting the significance of the "microbiota-gut-brain axis" in stroke pathology. Studies have revealed significant variations in gut microbiota diversity when comparing stroke patients to healthy individuals.[9,51] For instance, an increased abundance of Enterobacteriaceae has been identified in ischemic stroke patients, potentially serving as an isolated risk indicator during early recovery.[52] Animal models have also demonstrated that the gut microbiota composition changes significantly within hours of stroke onset, with reduced alpha diversity and changes in the Actinomycetota, Bacteroidota and Firmicutes phyla.[52,53] Fecal microbiota transplantation experiments show that microbiota from stroke models or patients can worsen brain injury,[54,55] while transplantation from young donors improves recovery and reduces infarct volume.[56] Consistent with these results, our study demonstrated that DI-GM, a metric quantifying the dietary impact on gut microbiota, was correlated with a decreased stroke risk. This supports the growing evidence that dietary interventions influencing microbiota composition and related metabolic pathways may serve as a potential strategy to reduce stroke risk and improve recovery outcomes. By promoting gut microbiota diversity and reducing systemic inflammation, targeted dietary approaches could provide the basis for microbiome-focused therapies in stroke prevention and treatment.

Although our findings indicated that higher DI-GM is associated with reduced stroke risk after adjusting for confounders, it remains unclear whether such benefits can be achieved through dietary changes alone. Previous research examining the relationship between various dietary patterns and healthy aging indicated that different diets may influence distinct aspects of health.[57] Therefore, we hypothesized that different dietary patterns might have varying effects on stroke risk reduction. While different dietary patterns shared some common features, such as increasing fruit and vegetable intake while reducing processed meat consumption, each pattern also emphasized specific components. For example, the Mediterranean diet highlighted olive oil and fish, while the DASH diet focused on restricting sodium intake. In addition, the DI-GM lacked some health-promoting foods like fish, seafood, and eggs. Thus, we hypothesized that combining the DI-GM with other beneficial dietary patterns might more effectively prevent stroke and promote overall health. However, more research is needed to confirm these hypotheses.

This study has several strengths. Firstly, this is the first longitudinal study to examine the relationship between DI-GM and stroke using a large prospective cohort. Secondly, this study not only explored the relation between DI-GM and stroke risk but examined its relationship with different stroke subtypes, including ischemic stroke and hemorrhagic stroke, offering a more comprehensive perspective for stroke prevention. However, several limitations should be acknowledged. Firstly, the UKB study assessed nutrient intake through 24-hour dietary assessment, which introduces the possibility of inaccuracies due to memory recall bias. Secondly, the original DI-GM was constructed based on 14 foods, but data on specific legumes and berries, including chickpeas and cranberries, were not available in the UKB 24-hour dietary assessment, resulting in missing food parameters for these items. Previous studies have shown that these two foods are beneficial for cardiovascular health,[58,59] and stroke is closely linked to cardiovascular health. Therefore, the absence of these data may lead to an underestimation of the DI-GM total score. In our analysis, where the DI-GM was based on 12 foods, higher scores were associated with a stronger negative correlation between DI-GM and stroke. Thus, we hypothesize that if these data were available, the DI-GM would likely be higher, further enhancing the negative correlation between DI-GM and stroke. Future studies should validate these findings in cohorts that include the full range of these 14 foods to minimize potential bias. Thirdly, participants who completed the Oxford WebQ were more likely to be older, female, white, more educated, and less deprived than other UKB participants,[60] potentially introducing selection bias. Finally, as the UK Biobank primarily consists of individuals of European ancestry, the applicability of these findings to other ethnic populations should be interpreted with caution. Further studies involving diverse ethnic groups are essential to validate these results.

Conclusion

In conclusion, this study demonstrated that higher DI-GM was related to a reduced risk of stroke, particularly ischemic stroke.

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Mediation analyses revealed the role of inflammation in this association, suggesting that dietary interventions targeting gut microbiota may help reduce inflammation and, consequently, lower stroke risk. These results offer novel insights into the "microbiota-gut-brain axis" and emphasize the potential of microbiota-targeted dietary strategies in stroke prevention and recovery.

Abbreviations

DI-GM	Dietary index for gut microbiota
BGMS	Beneficial to gut microbiota score
UGMS	Unfavorable to gut microbiota score
INFLA-score	Low-grade chronic inflammation
DALYs	Disability-adjusted life years
CNS	Central nervous system
CRP	C-reactive protein
WBC	White blood cell
NLR	Neutrophil-to-lymphocyte ratio
SD	Standard deviations
ICD-10	International Classification of Diseases 10th revision
TDI	Townsend deprivation index
BMI	Body mass index
AF	Atrial fibrillation
RCS	Restricted cubic spline
MLR	Multiple linear regression
AFT	Accelerated failure time
SEM	Structural equation modeling
CFA	Confirmatory factor analysis
MICE	Multiple imputation by chained equations
DASH	Dietary approaches to stop hypertension
DII	Dietary inflammatory index
SCFAs	Short-chain fatty acids
LPS	Lipopolysaccharides
HR	Hazard ratio
CI	Confidence interval

Ethics approval and consent to participate

All research procedures involving human participants were performed in accordance with the ethical guidelines of the UK Biobank and approved by the NHS National Research Ethics Service (16/NW/0274). All participants provided written informed consent prior to data collection. The research conducted in this study was performed in compliance with these ethical standards, the guidelines set forth by the UK Biobank, and the relevant UK laws and regulations concerning the use of human data in medical research, including the General Data Protection Regulation and the Declaration of Helsinki.

Author contributions

L. T. concepted and designed the study, analyzed the data, and drafted the manuscript. M. L., M. H., and Y. F. extracted, analyzed, and interpreted the data, and drafted the manuscript. D. D. Z., Y. L. Z., and Q. Y. L. analyzed the data and drafted the manuscript. H. H., H. H. G. and L. Y. H. extracted, analyzed the data and drafted the manuscript. C. C. T. and W. X. drafted the manuscript. All authors have contributed to the manuscript writing and revision. All authors read and give final approval of the version.

Data availability

Researchers can request the data used for the analysis from the UK Biobank (**https://www.ukbiobank.ac.uk/**).

Conflicts of interest

The authors declare that they have no competing interests.

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