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Synergistic effects of elevated homocysteine level and abnormal blood lipids on the onset of stroke

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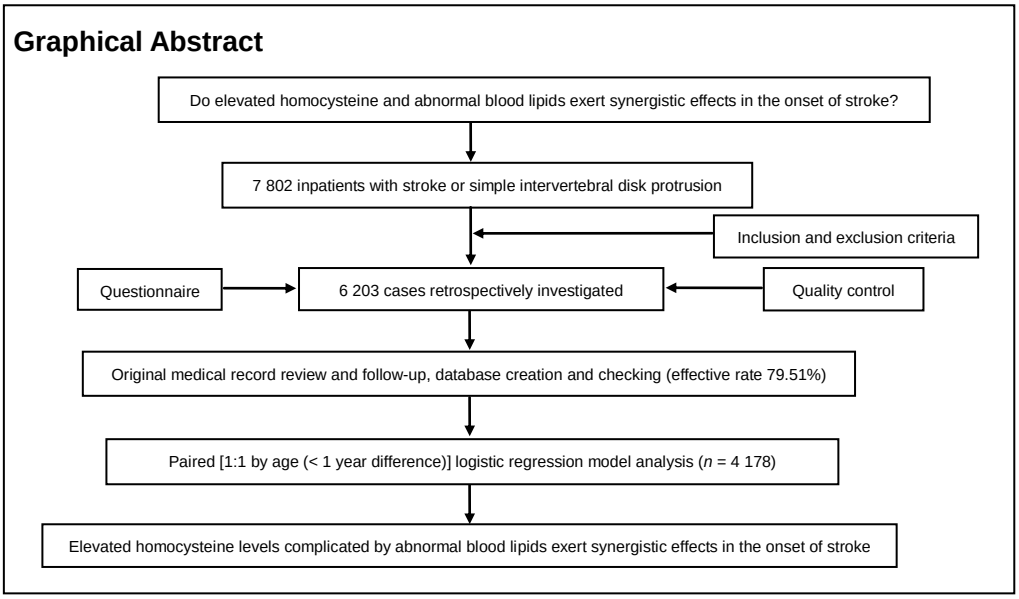

Abstract

Hyperhomocysteinemia and abnormal blood lipids are independent risk factors for stroke. However, whether both factors exert a synergistic effect in the onset of stroke remains unclear. The present study is a retrospective analysis of 2 089 cases of stroke and 2 089 control cases of simple intervertebral disk protrusion using a paired multivariate logistic regression method. Adjusting for known confounding variables including the patients' age, gender, smoking status, alcohol consumption status, patient and family medical history, and clinical biochemical indices, elevated homocysteine level was related to the onset of stroke. Patients with elevated homocysteine levels and abnormal blood lipids showed a 40.9 % increase in the risk for stroke compared to patients with normal homocysteine levels and blood lipids (odds ratio 1.409; 95% confidence interval 1.127–1.761). These results indicate that elevated homocysteine and abnormal blood lipids exert synergistic effects in the onset of stroke. Patients with elevated homocysteine levels and abnormal blood lipids are predisposed to stroke.

Key Words

neural regeneration; stroke; cysteine; risk factor; case-control study; abnormal blood lipids; medication; inpatients; cardiovascular disease; paired analysis; grants-supported paper; neuroregeneration

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INTRODUCTION

Hyperhomocysteinemia and abnormal blood lipids are independent risk factors for stroke. However, whether they exert a synergistic effect in the onset of stroke remains poorly understood. There is evidence that a family history of abnormal blood pressure and blood lipids increases the risk for ischemic stroke in stroke patients compared to those without stroke, and the pathological mechanisms underlying the different subtypes of ischemic stroke are varied[1-3]. Elevated blood pressure/blood lipids is correlated with ischemic stroke risk[4-5]. Large artery atherosclerotic ischemic stroke is particularly closely related to blood lipids[6-8].

Hyperhomocysteinemia is an independent risk factor for atherosclerosis. Ten percent of coronary heart disease patients have hyperhomocysteinemia, and slightly or moderately elevated homocysteine levels can increase the risk of cardiovascular disease four to sixfold[9-12].

Many studies have investigated risk factors for stroke, but there is a lack of studies addressing the association between homocysteine, blood lipids, and stroke risk. The present study is a retrospective analysis of inpatients across a 5 year period from the Chinese PLA General Hospital, based on a matched pairs case control design.

RESULTS

Quantitative analysis of subjects

A total of 7 802 questionnaires were handed out and 6 203 were completed, with an effective rate of 79.51%. 2 089 stroke patients (case group) and 2 089 simple intervertebral disk protrusion patients (control group) were paired, and their data were analyzed. All 4 179 cases were included in the final analysis, without loss.

Baseline subject characteristics

Number of patients presenting with known risk factors and mean values of biochemical indices are provided in Table 1.

Multivariate analysis of stroke-related risk factor

With the exception of age, triglycerides, and history of coronary heart disease and diabetes mellitus, all other variables differed significantly between the case and control groups ($P < 0.05$).

Adjusting for age, gender, smoking status, alcohol consumption, family medical history (coronary heart disease, hypertension, stroke and diabetes mellitus), patient history (coronary heart disease, hypertension, stroke, diabetes mellitus, and hyperlipidemia), body mass index, systolic pressure, total cholesterol, triglycerides, low- and high-density lipoprotein cholesterols, and fasting blood glucose, we found that homocysteine levels were related to the onset of stroke.

The risk for stroke was 1.297 times higher in females than males, and 2.739 times higher in smokers than non-smokers; compared with cases with no family history of cardiovascular events, stroke risk was 10.515, 2.830 and 5.145 times higher in cases who had a family history of coronary heart disease, hypertension or stroke, respectively; 2.161 times higher in cases who had a previous history of hypertension than those who did not. Risk was 1.220 and 2.335 times higher in cases in the low body weight or obese groups, respectively, than those in the normal body mass index (BMI) group. Compared with the normal blood pressure group, the risk for stroke was increased by 2.7% for each increase of 1 mmHg (0.133 kPa) in systolic pressure. The risk for stroke was 3.082 times higher in the elevated total cholesterol group than in the normal cholesterol level group, and lower in the elevated triglycerides group than in the normal triglycerides, although this may be a result of interaction between risk factors.

The risk for stroke was 1.539 times higher in the elevated high-density lipoprotein cholesterol group than the normal high-density lipoprotein cholesterol group, increased by

14.6% for each increase of 1 mmol/L fasting blood glucose compared with the normal fasting blood glucose group, and increased by 1.8% for each increase of 1 μmol/L homocysteine compared with the normal homocysteine level group. These data are summarized in Table 2.

Synergistic effect of homocysteine level and abnormal blood lipids on the onset of stroke

Taking into account age, gender, smoking status, alcohol consumption, body mass index, systolic pressure, family history of hypertension, stroke or coronary heart disease, and patient history of hypertension or coronary heart disease, odds ratio (*OR*) was 1.409 with a 95% confidence interval (*CI*) of 1.127 to 1.761 in the group with combined abnormal homocysteine and blood lipid levels compared to patients with normal levels.

This means that the risk for stroke in the group with elevated homocysteine levels complicated by abnormal blood lipids was increased by 40.9% (P = 0.003) compared with the group in which both factors were normal, indicating that elevated homocysteine level and abnormal blood lipid promote the onset of stroke.

DISCUSSION

The present study correlated stroke with two important risk factors, elevated homocysteine and abnormal blood lipids. Both factors were significantly correlated with stroke onset. Further analysis revealed that stroke risk was higher in the group in which both factors were present together than in the groups presenting with elevated homocysteine or abnormal blood lipids alone. These findings indicate that the combined effect of elevated homocysteine and abnormal blood lipids should be taken into consideration in the clinical treatment of stroke.

Evidence for the effect of abnormal blood lipids and elevated homocysteine levels on the onset of stroke has previously been inconclusive, highlighting the need for further analysis of the pathological mechanisms and the prevention and treatment strategy of stroke. In the present study, the conventional risk factors of stroke were further evaluated.

Table 1 Baseline subject characteristics

Variable	Case group (n = 2 089)	Control group (n = 2 089)	P	t	X^2
Age (year)	46.29±12.95	45.68±13.59	0.144	–26.40	
Male	1 358(65.0)	1 228(58.8)	0.000		23.14
Smoking	585(28.0)	242(11.6)	0.000		180.95
Drinking	470(22.5)	201(9.6)	0.000		129.15
Family history					
Coronary heart disease	61(2.9)	8(0.4)	0.000		43.02
Hypertension	211(10.1)	56(2.7)	0.000		99.59
Stroke	194(9.3)	38(1.8)	0.000		117.25
Diabetes mellitus	58(2.8)	33(1.6)	0.006		7.71
Previous history					
Coronary heart disease	31(1.5)	40(1.9)	0.398		0.71
Hypertension	568(27.2)	297(14.2)	0.000		115.65
Stroke	77(3.7)	33(1.6)	0.000		18.28
Hyperlipidemia	38(1.8)	13(0.6)	0.000		12.23
Diabetes mellitus	111(5.3)	115(5.5)	0.953		0.00
Body mass index (kg/m^2)	25.02±3.54	25.31±3.68	0.009	2.598	
Systolic pressure (mmHg)	132.49±17.94	128.03±16.16	0.000	–0.830	
Diastolic pressure (mmHg)	82.57±12.40	80.77±10.56	0.000	–4.962	
Total cholesterol (mmol/L)	4.47±12.95	4.70±0.99	0.000	7.172	
Triglyceride (mmol/L)	1.71±1.19	1.67±1.15	0.253	–1.143	
Low-density lipoprotein cholesterol (mmol/L)	2.59±0.86	2.76±0.80	0.000	6.730	
High-density lipoprotein cholesterol (mmol/L)	1.12±0.30	1.19±0.30	0.000	7.192	
Fasting blood glucose (mmol/L)	5.50±1.77	5.22±1.20	0.000	–5.974	
Homocysteine (μmol/L)	17.39±11.27	15.12±9.45	0.000	–6.209	

With the exception of age, history of coronary heart disease and diabetes mellitus and triglyceride, the other variables differed significantly between the case and control groups (P < 0.05). Chi-square test was used for comparison of numeration data expressed as n (%) between two groups and independent sample t-test or Mann-Whitney U test for comparison of measurement data (mean ± SD). Smoking: According to World Health Organization criteria (1984), at least one cigarette per day for 1 year or longer. Drinking: Alcohol consumption once a week for 1 year or longer. Body mass index was divided into four groups: (1) normal: 18.50–23.99 kg/m^2; (2) low: < 18.50 kg/m^2; (3) overweight: 24.00–27.99 kg/m^2; (4) obese: ≥ 28.00 kg/m^2. Normal and high fasting levels of total serum homocysteine were 5–15 and > 15 μmol/L, respectively. Abnormal blood lipids refers to total cholesterol level < 3.1 or > 5.7 mmol/L and/or triglyceride < 0.44 or > 1.70 mmol/L and/or high density lipoprotein cholesterol < 1.0 or > 1.6 mmol/L and/or low density lipoprotein cholesterol > 3.4 mmol/L. 1 mmHg = 0.133 kPa.

Table 2 Stroke risk factors

Item	*B*	*SE*	*OR*	95%*CI*	*P*
Age (year)					
< 60		1.000			
60–69	–0.071	0.578	0.932	0.300–2.895	0.903
70–79	–0.054	0.585	0.947	0.301–2.978	0.926
≥ 80	–0.212	0.599	0.809	0.250–2.616	0.703
Gender (female *vs*. male)	0.260	0.115	1.297	1.035–1.625	0.024
Smoking (smoking *vs*. non-smoking)	1.007	0.195	2.739	1.870–4.012	0.000
Drinking (drinking *vs*. non-drinking)	0.680	0.213	1.974	1.299–2.999	0.001
Family history (with *vs*. without)					
Coronary heart disease	2.353	0.648	10.515	2.953–37.446	0.000
Hypertension	1.040	0.297	2.830	1.581–5.067	0.000
Stroke	1.638	0.305	5.145	2.829–9.359	0.000
Diabetes mellitus	–0.007	0.429	0.993	0.429–2.302	0.988
Patient history (with *vs*. without)					
Hypertension	0.771	0.157	2.161	1.589–2.939	0.000
Stroke	0.415	0.352	1.515	0.760–3.018	0.238
Coronary heart disease	–0.509	0.384	0.601	0.283–1.275	0.185
Hyperlipidemia	0.347	0.597	1.415	0.439–4.555	0.561
Diabetes mellitus	–0.516	0.279	0.597	0.346–1.031	0.064
Body mass index (kg/m^2)					
18.5–23.99			1.000		
< 18.5	0.199	0.092	1.220	1.019–1.462	0.031
24–27.99	0.848	0.239	2.335	1.462–3.730	0.000
≥ 28	0.158	0.087	1.172	0.988–1.390	0.069
Systolic pressure		0.004	1.027	1.019–1.034	0.000
Total cholesterol (mmol/L)					
3.1–5.7			1.000		
< 3.1	0.156	0.102	1.169	0.957–1.427	0 .125
> 5.7	1.125	0.185	3.082	2.145–4.427	0 .000
Triglyceride (mmol/L)					
0.44–1.7			1.000		
< 0.44	–0.002	0.074	0.998	0.864–1.154	0.981
> 1.7	–0.930	0.413	0.395	0.176–0.887	0.024
Low-density lipoprotein cholesterol (mmol/L)	–0.149	0.232	0.861	0.547–1.357	0.520
High-density lipoprotein cholesterol (mmol/L)					
1.0–1.6			1.000		
< 1.0	0.106	0.119	1.112	0.881–1.403	0.372
> 1.6	0.431	0.131	1.539	1.192–1.988	0.001
Fasting blood glucose	0.136	0.043	1.146	1.053–1.247	0.002
Homocysteine	0.018	0.005	1.018	1.007–1.673	0.001

OR was calculated using logistic regression analysis for 1:1 matched pairs and adjusted for age, gender, smoking, drinking, family history (coronary heart disease, hypertension, stroke, and diabetes mellitus), patient history (coronary heart disease, hypertension, stroke, diabetes mellitus, and hyperlipidemia), body mass index, systolic pressure, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose. Homocysteine level was related to the onset of stroke.

Smoking: According to World Health Organization criteria (1984), at least one cigarette per day for 1 year or longer. Drinking: Alcohol consumption once a week for 1 year or longer.

Body mass index was divided into four groups: (1) normal: 18.50–23.99 kg/m^2; (2) low: < 18.50 kg/m^2; (3) overweight: 24.00–27.99 kg/m^2; (4) obese: ≥ 28.00 kg/m^2. Normal and high fasting levels of total serum homocysteine were 5–15 and > 15 μmol/L, respectively. Abnormal blood lipids refers to total cholesterol level < 3.1 or > 5.7 mmol/L and/or triglyceride < 0.44 or > 1.70 mmol/L and/or high-density lipoprotein cholesterol < 1.0 or > 1.6 mmol/L and/or low-density lipoprotein cholesterol > 3.4 mmol/L. 1 mmHg = 0.133 kPa.

The results show that total cholesterol, low- and high-density lipoprotein cholesterols, and triglycerides are related to the onset of stroke; smoking correlates positively with stroke; and systolic pressure is an independent stroke risk factor. Results from this study also showed that BMI is related to stroke; further study is required to elucidate the pathological mechanism behind this. Surprisingly, we found no correlation between family or patient history of diabetes mellitus and stroke. To our knowledge, the present study is the first to examine the relationship between stroke risk and elevated homocysteine levels complicated by abnormal blood lipids. To our knowledge, the present study is the first to examine the relationship between stroke risk and elevated homocysteine levels complicated by abnormal blood lipids[13-40]. Total cholesterol, low- and high-density lipo-

protein cholesterols, and triglycerides are known risk factors for ischemic stroke[40-43].

Table 3 Synergistic effect of elevated homocysteine level and abnormal blood lipid on the onset of stroke

Item	*B*	*SE*	*OR*	95%*CI*	*P*
Age	0.000	0.003	1.000	0.995–1.006	0.945
Gender (female *vs*. male)	0.065	0.085	1.067	0.903–1.260	0.445
Smoking (smoking *vs*. non-smoking)	1.057	0.146	2.877	2.161–3.829	0.000
Drinking (drinking *vs*. non-drinking)	0.088	0.153	1.092	0.809–1.475	0.563
Family history (with *vs*. without)					
Hypertension	0.525	0.191	1.690	1.162–2.457	0.006
Stroke	1.164	0.214	3.202	2.105–4.870	0.000
Coronary heart disease	1.483	0.427	4.405	1.908–10.173	0.001
Previous history (with vs. without)					
Hypertension	0.593	0.104	1.809	1.589–2.939	0.000
Coronary heart disease	–0.752	0.295	0.471	0.760–3.018	0.011
Body mass index (kg/m^2)					
18.5–23.99			1.000		
< 18.5	0.677	0.256	1.967	1.192–3.248	0.008
24–27.99	–0.179	0.087	0.836	0.705–0.991	0.039
≥ 28	–0.374	0.110	0.688	0.554–0.853	0.001
Systolic pressure	0.222	0.089	1.248	1.048–1.487	0.013
Blood lipid and homocysteine					
Both normal			1.000		
Abnormal blood lipid or elevated homocysteine level	0.034	0.099	1.034	0.852–1.255	0.733
Both abnormal	0.343	0.114	1.409	1.127–1.761	0.003

OR was calculated using logistic regression analysis for 1:1 matched pairs and adjusted for age, gender, smoking, drinking, family history (coronary heart disease, hypertension, stroke), patient history (coronary heart disease, hypertension), body mass index, and systolic pressure. Compared to patients with normal homocysteine level and blood lipids, the risk of stroke was increased in patients with both abnormal blood lipids and elevated homocysteine levels.

Smoking: According to World Health Organization criteria (1984), at least one cigarette per day for 1 year or longer. Drinking: Alcohol consumption once a week for 1 year or longer.

Body mass index was divided into four groups: (1) normal: 18.50–23.99 kg/m^2; (2) low: < 18.50 kg/m^2; (3) overweight: 24.00–27.99 kg/m^2; (4) obese: ≥ 28.00 kg/m^2. Normal and high fasting levels of total serum homocysteine were 5–15 and > 15 μmol/L, respectively. Abnormal blood lipids refers to total cholesterol level < 3.1 or > 5.7 mmol/L and/or triglyceride < 0.44 or > 1.70 mmol/L and/or high density lipoprotein cholesterol < 1.0 or > 1.6 mmol/L and/or low density lipoprotein cholesterol > 3.4 mmol/L. 1 mmHg = 0.133 kPa.

The correlation between triglycerides and stroke remains disputed[43-46]. Chyou and Eaker[47] reported that total cholesterol is a risk factor for all-cause mortality in patients aged > 65 years. Wells *et al* [48] concluded that low-density lipoprotein cholesterol is an important predictor of cardiovascular disease. Similarly, the effects of blood lipid components are also affected by many other factors; for example, the effects of total serum cholesterol on all-cause mortality are correlated with smoking, drinking and hypertension[49]. The correlation between each factor and stroke has yet to be fully evaluated.

Shinton and Beevers[50] performed a meta-analysis on smoking and stroke and found that the risk for stroke in smokers was 1.2 times higher than that in non-smokers. Wolf *et al* [51] concluded that heavy smokers had very high risk of stroke. Another study revealed that *OR* (95% *CI*) for stroke was 2.10 (1.33–3.32) and 1.66 (1.07–2.57) in male and female passive smokers, respectively[52], which further implicates the effect of smoking.

Hypertension has been shown by many studies to be the most important risk factor for stroke; several multi-center, large-sample clinical trials have investigated the treatment of isolated systolic hypertension in the elderly [53-55]. Lida *et al* [56] performed a 14 year study confirming that hypertension is an important risk factor not only for stroke but also for all-cause mortality. The unavoidable risk factors for stroke include age, family history, gender and race[57-61]. Recent evidence also implicates elevated homocysteine level[62], inflammatory markers such as C reactive protein[63], and blood clotting factors such as fibrinogen[64].

The present study investigates a large, representative sample with a high response rate and good subject cooperation. However, the fact that it is a single-center study may have introduced selection bias. Moreover, patients suffered from various diseases and thereby many risk factors coexist, which likely has certain effects on the assessment of results. This case-controlled study provides level 3 evidence and as such the conclusions

require further validation by large, prospective studies. The study was designed to investigate the synergistic effect of elevated homocysteine levels and abnormal blood lipids in stroke patients, an approach that differs from previous studies that examined the effect of a single risk factor in elderly stroke patients or from a selection of community populations[65-66]. Nevertheless, the results from this study suggest that elevated homocysteine and abnormal blood lipids likely have a synergic effect on the onset of stroke, and provide evidence to inform the prevention and treatment of stroke.

SUBJECTS AND METHODS

Design

A single-center, 1:1 matched, case-control study.

Time and setting

This study was performed in the Institute of Geriatrics, Chinese PLA General Hospital, Beijing, China, between January 2007 and December 2012.

Subjects

2 089 stroke patients (case group) and 2 089 patients with simple intervertebral disk protrusion (control group) who received treatment between January 2007 and December 2012 in the Chinese PLA General Hospital were included in this study. These subjects were 1:1 matched by age (difference < 1 year). After 1 month of medical records checks, 2 089 pairs of cases and controls were included in the final analysis. To ensure representative sampling, subjects were selected consecutively over the same time period.

Diagnostic criteria of stroke

Cerebrovascular diseases were categorized and diagnosed according to The International Classification of Diseases, Edition 9 (ICD-9.0; CVD430-438) and Classification of Cardiovascular Disease issued by the Second National Cerebrovascular Disease Chinese Physician Association[67]. A diagnosis of cerebrovascular disease was confirmed by CT examination and by the provincial (municipal) hospital (both necessary for final diagnosis) and in some cases by an experienced neurologist.

Inclusion criteria of case group: (1) stroke inpatients at the Chinese PLA General Hospital who met the diagnostic criteria for stroke; (2) full medical record information and related examination data.

Exclusion criteria of case group: (1) incomplete medical records or examination data; (2) clinical examination that did not correspond to the medical record; (3) patients who were not willing to participate.

Inclusion criteria of control group: (1) inpatients with simple intervertebral disk protrusion at the Chinese PLA General Hospital; (2) complete medical record information and related examination data.

Exclusion criteria of control group: (1) other medical conditions; (2) incomplete medical record or examination data; (3) clinical examination that did not correspond to the medical record; (4) subjects not willing to participate.

Related indices

Smoking: According to World Health Organization criteria (1984), at least one cigarette per day for a period of 1 year or longer.

Drinking: Consumption of alcohol once a week for 1 year or longer.

BMI: body weight (kg)/body height $(m)^2$. According to the normal distribution of Chinese adults, BMI was divided into four groups: (1) normal: 18.50–23.99 kg/m^2; (2) low: < 18.50 kg/m^2; (3) overweight: 24.00–27.99 kg/m^2; (4) obese: ≥ 28.00 kg/m^2.

Normal and high fasting levels of total serum homocysteine were 5–15 and > 15 μmol/L, respectively. Abnormal blood lipids refers to total cholesterol level < 3.1 or > 5.7 mmol/L and/or triglyceride < 0.44 or > 1.70 mmol/L and/or high density lipoprotein cholesterol < 1.0 or > 1.6 mmol/L and/or low density lipoprotein cholesterol > 3.4 mmol/L.

Methods

Retrospective analysis of medical records of included cases

Investigation was performed by neurology and epidemiology experts. Patient characteristics for analysis were obtained from the medical records as follows: age, gender, medical history, family medical history, body height, body weight, blood pressure, total serum cholesterol, triglyceride level, low density lipoprotein cholesterol level, high density lipoprotein cholesterol level, and fasting blood glucose.

Investigation was performed by 15 clinical physicians and postgraduates from the Chinese PLA General Hospital between January 2007 and December 2012. Prior to the study, all investigators were trained by the Institute of

Gerontology, Chinese PLA General Hospital, to ensure consistent assessment methods and procedures. Twelve investigators were responsible for data quality control, medical checks, questionnaire management, and index standardization. The questionnaire was carefully designed and modified several times before use.

Statistical analysis

The subject database was created using Epidata 3.0 (The EpiData Association; http://www.epidata.dk/; Odense, Denmark). Statistical analysis was performed using SPSS 13.0 software (SPSS, Chicago, IL, USA). Ten percent of cases were randomly selected from the entire sample for double checking. The proportion of case numbers included for the final analysis in total number of hospitalized cases > 85% qualified for inclusion. Continuous data are presented as mean ± SD, and categorical data as constituent ratio (%). An independent samples *t*-test was used to compare normally-distributed data, and the Mann-Whitney *U* test was used for non-parametric data. The chi-square test was used for one-way analysis of categorical data, and 1:1 paired logistic regression for multivariate analysis of continuous data. A level of $P < 0.05$ was considered statistically significant.

Research background: Despite many studies evaluating risk factors for stroke, the association between elevated homocysteine, abnormal blood lipids, and stroke onset has not yet been investigated.

Research frontiers: Hyperhomocysteinemia is an independent risk factor for atherosclerosis and stroke. Abnormal blood lipids also increase the risk of ischemic stroke. However, whether abnormal blood lipids are associated with the onset of stroke remains unclear.

Clinical significance: This study investigated the impact of elevated homocysteine complicated by abnormal blood lipids on stroke risk and provides evidence to inform the prevention and treatment of stroke.

Academic terminology: Hyperhomocysteinemia refers to a condition in which the homocysteine level in the blood is abnormally elevated.

Peer review: This study investigates a large sample with complete record information and is scientifically designed and performed. Results of this investigation into the effects of elevated homocysteine levels and abnormal blood lipids on stroke onset are of significance in guiding further clinical studies and in stroke diagnosis and treatment.

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