Additive Interaction Between Potentially Modifiable Risk Factors And Ethnicity In The Han, Tujia and Miao Populations With First-Ever Ischemic Stroke

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Abstract

Background: As a country with one-fifth of the global population, China has had explosive growth in ischemic stroke burden with significant ethnic and geographic disparities. The aim of this study was to examine the relative risk of potentially modifiable risk factors for ischemic stroke among the Han population and two ethnic minorities (Tujia and Miao).

Methods: A case-control study was conducted: 324 cases of first-ever IS from the hospitals of the Xiangxi Tujia and Miao Autonomous Prefecture and 394 controls were surveyed using structured questionnaires from communities covering the same area. Univariate and multivariate logistic regression analyses with adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were used to examine the association between risk factors and ischemic stroke. The additive model was used to study the interaction between the modifiable risk factor and ethnicity in the R software.

Results: Higher high-sensitivity C-reactive protein level (OR 50.54, 95% CI 29.76-85.85), higher monthly family income (4.18, 2.40-7.28), increased frequency of hot pot consumption (2.90, 1.21-6.93), diabetes mellitus (2.62, 1.48-4.62), higher apolipoprotein (Apo)(B)/ApoA1 ratio (2.60, 1.39-4.85), hypertension (2.52, 1.45-4.40) and moderate-intensity physical activity (0.50, 0.28-0.89) were associated with ischemic stroke. There is an additive interaction between ApoB/ApoA1 ratio and ethnicity in Tujia and Miao populations with first-ever ischemic stroke (the relative excess risk due to interaction was 5.75, 95% CI 0.58–10.92; the attributable proportion due to interaction was 0.65, 95% CI 0.38–0.91; the synergy was 3.66, 95% CI 1.35–9.93).

Conclusions: It is the first case-control study examining modifiable risk factors for ischemic stroke among the Han population and two ethnic minorities (Tujia and Miao) in China, some differences were observed in the impact of risk factors among these ethnic groups. Our results may help interpret health-related data, including surveillance and research, when developing strategies for stroke prevention.

Background

With the acceleration of social aging and urbanization, the popularity of unhealthy lifestyles among residents, and the widespread exposure to cerebrovascular risk factors, the stroke burden in China has shown explosive growth over the past 30 years. It is characterized by rapid growth in low-income populations, distinct sex- and region-related differences, and a younger trend of incidence[1–2]. The Global Burden of Disease 2017 Study (GBD2017) reported that stroke is the leading cause of death and disability-adjusted life-years at the national level in China and the third cause of global years of life lost[3–4]. Ischemic stroke (IS) occurs when a vessel supplying blood to the brain is obstructed, and constitutes 69.6% and 77.8% of total stroke incidence and prevalence, respectively[1]. Hence, IS has become one of the most important disease burdens and a major public health problem in China. Ten modifiable risk factors for IS, in descending order of importance, include hypertension (HT), apolipoprotein (Apo)B/ApoA1 ratio, physical activity, diet, waist-to-hip ratio (WHR), psychosocial factors, smoking, cardiac causes, diabetes mellitus (DM), and alcohol consumption, all of which accounted for 91.5% and 95.2% of the population attributable risk (PAR) of IS worldwide and in China, respectively, as quantified by the INTERSTROKE investigators[5]. In this regard, it is suggested that a large proportion of IS burden may be preventable through control of the above 10 risk factors, with population-level primary interventions.

The INTERSTROKE investigators also found regional and ethnic variations in the effect of risk factors that were related to differences in risk factor prevalence among regions; this may contribute to worldwide variations in the frequency of IS, and thus, support the development of population-specific measures to prevent IS[5]. According to the Framingham Heart Study, stroke incidence has declined over time. However, the cohort used was predominantly Caucasian[6], and the racial and geographic disparities are significant, with African-Americans and residents of southeastern United States experiencing the greatest disease burden[7]. There is a north-to-south gradient in stroke burden in China, with the greatest stroke burden observed in the northern and central regions[1, 8]. China is also a unified multi-ethnic country with a total of 56 ethnic groups, of which the Han is the largest group, and the other 55 ethnic groups are referred to as ethnic minorities. Many of the Chinese ethnic minorities are quite similar to the Han in language and culture, but others are quite different both from the Han and from one another in some very important features, such as diet, attire, marriage, customs and lifestyle. The preserved large numbers of unique features in ethnic minorities may have had an impact on the prevalence of common stroke risk factors for IS. According to the sixth national population census in 2010, the Han (9.43 million) and Tujia (8.35 million) minorities were ranked the fifth and seventh largest minority groups, respectively, but there is little reliable data available to identify the difference in risk factors for IS among the Tujia, Miao, and Han populations. In China, people of Tujia are mainly distributed in the Hunan and Hubei Provinces, whereas people of Miao are mainly distributed in the Guizhou and Hunan Provinces. Xiangxi Tujia and Miao Autonomous Prefecture, located in western Hunan Province and adjacent to Hubei and Guizhou Provinces, is the only autonomous prefecture for minorities in Hunan, where people of Tujia and Miao constitute 80% of the total population of 2.98 million.

Statistically, an interaction is defined as a departure from the underlying disease risk model, which depends on the selection of proper scale for measuring the presence of interactions[9]. And additive interaction has been shown to be more relevant for evaluating prevention or intervention strategies in public health decision-making[10–11]. Nevertheless, there is little data to study the additive interaction between common risk predictors of IS and ethnicity. This study aimed to study the differences between the Tujia, Miao, and Han populations in the prevalence of IS risk factors, and their interaction with ethnicity in the Xiangxi Tujia and Miao Autonomous Prefecture, and provide new insights into the risk factors, prevention and management strategies of IS among the Tujia, Miao, and Han ethnicities.

Methods

This study was a case-control study. Participants were recruited between May 1, 2018 and April 30, 2019 from all 8 counties of the Xiangxi Tujia and Miao Autonomous Prefecture (Jishou, Baojing, Fenghuang, Guzhang, Huayuan, Longshan, Luxi, and Yongshun). All participants were residents who had lived in Xiangxi for more than 5 years.
Case Selection

The case group included all IS patients who were admitted to the First Affiliated Hospital of Jishou University and all 8 County People's Hospitals of the Xiangxi Tujia and Miao Autonomous Prefecture within 5 days of symptom onset and 72 h of hospital admission and with a discharge diagnosis of first-ever IS. IS was diagnosed according to the World Health Organization (WHO) clinical criteria[12]. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain was completed within 1 week of presentation. All patients also underwent a range of blood tests, chest radiography, and electrocardiography at admission. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[13], IS was divided into 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology. Disease severity was estimated by the National Institutes of Health Stroke Scale (NIHSS) score on admission by the physician. For patients unable to communicate adequately, proxy respondents were used. We defined a valid proxy respondent as a spouse or first-degree relative who was living in the same home or was aware of the participant's previous medical history and current treatments. The exclusion criteria included those who: (1) were unable to communicate and without a valid surrogate respondent; (2) had subdural hemorrhage, tumor, or brain abscess (i.e., non-vascular causes); (3) were under current hospitalization for acute coronary syndrome or myocardial infarction; and (4) an inability to obtain consent from the patient or surrogate.

Control Selection

Controls were community-based from all 8 counties and had no history of stroke. Each control was matched for age (± 5 years) with the case. Exclusion criteria for controls were identical to those described for cases.

Assessment Of Risk Factors

Data on occupation, education, fertility, monthly family income, smoking status, frequency of fast food consumption, frequency of hot pot consumption, moderate-intensity physical activity (MIPA), and history of HT, DM and hyperlipidemia were collected by the study physicians using structured questionnaires. Occupation was classified as either mental or manual work. Education was classified as either 9 years of school education or ≥ 9 years (senior high school or above). The history of fertility was classified as having given birth to ≤ 2 children or to ≥ 3 children. Smoking status was classified as never smoked and current smoking (smoking ≥ 1 cigarette per day within the year prior to the interview and included those who had quit smoking less than a year). MIPA was defined as 4 h or more per week, including brisk walking, dancing, gardening, housework and domestic chores, traditional hunting and gathering, general building tasks (e.g., roofing, thatching, painting), carrying/moving moderate loads (< 20 kg), and so on[14]. HT was defined as under treatment with antihypertensive medication, a previous HT diagnosis, or current HT according to the 2003 WHO criteria (blood pressure of 140/90 mmHg or higher). For those with a history of DM or treated diabetes preceding IS, diabetes was defined according to the 1999 WHO criteria as fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dl), a 2-h oral glucose tolerance test of ≥ 11.1 mmol/L (200 mg/dl), or glycated hemoglobin (HbA1c) ≥ 6.5%. We defined dichotomous components of hyperlipidemia as total cholesterol (TC) ≥ 6.2 mmol/L (240 mg/dl), triglyceride (TG) ≥ 2.3 mmol/L (200 mg/dl), low-density lipoprotein cholesterol (LDL-C) ≥ 4.1 mmol/L (160 mg/dl), or high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L (40 mg/dl)[15].

Wrist and hip circumferences were measured in the standing and supine positions. If patients were unable to stand because of disability, these measurements were completed only in the supine position[16]. Fasting blood samples (10 mL) were taken from cases and controls within 72 h of recruitment, separated by centrifugation, and frozen at -70 °C immediately after processing. Samples were shipped in packaging incorporating dry ice cooling agents by courier from every site to a blood storage site, where they were stored at -70 °C. FPG, HbA1c, TP, TC, TG, LDL-C, HDL-C, ApoA1, ApoB and high-sensitivity C-reactive protein (hs-CRP) concentrations were measured at Dian Diagnostics Group with a Beckman Coulter (Brea, CA) AU680 Clinical Chemistry Analyzer and Beckman Coulter reagents. Detailed cutoffs for WHR[17], HDL-C[18], ApoB/ApoA1 ratio[18] and hs-CRP[19] appear in Additional file 1: Table S1.

Statistical analysis

Statistical analyses were produced with IBM SPSS Statistics for Windows (version 23.0; Armonk, NY) and R for Windows (Version 4.0.3). All statistical tests were two-sided.

First, we performed a comparison between case and control groups using the Chi-squared tests and calculated univariate odds ratios (ORs) and 95% confidence intervals (CIs) for all dichotomized or multinomial risk factors. Second, binary multivariable logistic regression was applied, with backward (likelihood ratio) variable removal at the level of P < 0.10, and adjusted ORs and 95% confidence intervals (CIs) were calculated. The Breslow-Day test was used for the homogeneity of the association between modifiable risk factors and IS by ethnicity[20], if P < 0.05, we will detect the biological interaction between the modifiable risk factor and ethnicity. Three measures of biological interaction: RERI, the relative excess risk due to interaction; AP, the attributable proportion due to interaction; and S, the synergy[21]; index with corresponding 95% confidence intervals were calculated in R[22]. RERI and AP equal to 0 and S equal to 1 were defined as no interaction[21]. The names and values of variables in univariate and multivariate logistic regression analyses also appear in Additional file 1: Table S1.

Results

Basic information

The study included 324 patients and 394 controls, with ages ranging from 22 to 80 years. Descriptive characteristics of patients, including age, sex, TOAST classification, and NIHSS score, are reported in Table 1. One hundred and seventy (50.1%) patients had minor stroke and 115 (33.9%) had moderate stroke.
Table 1

Demographic and Clinical Characteristics of Cases by Ethnic Group

| Age (years)       | All (N = 324) | Tujia (N = 178) | Miao (N = 95) | Han (N = 51) |
|-------------------|---------------|-----------------|---------------|--------------|
|                   | mean (SD)     | mean (SD)       | mean (SD)     | mean (SD)    |
|                   | 61.6 (11.4)   | 62.4 (11.2)     | 60.9 (12.3)   | 60.3 (10.2)  |
| Women             | 98 (30.2)     | 62 (34.8)       | 26 (27.4)     | 10 (19.6)    |
| TOAST classification |               |                 |               |              |
| Large-artery atherosclerosis | 134 (41.4) | 71 (39.9)       | 41 (43.2)     | 22 (43.1)    |
| Cardioembolism    | 15 (4.6)      | 13 (7.3)        | 2 (2.1)       | -            |
| Small-vessel occlusion | 168 (51.9) | 90 (50.6)       | 50 (52.6)     | 28 (54.9)    |
| Stroke of other determined etiology | 4 (1.2) | 2 (1.1)       | 1 (1.1)       | 1 (2.0)      |
| Stroke of undetermined etiology | 3 (0.9) | 2 (1.1)       | 1 (1.1)       | -            |
| NIHSS score       |               |                 |               |              |
| 0 (no stroke symptoms) | 45 (13.3) | 26 (14.6)       | 10 (10.5)     | 6 (11.8)     |
| 1–4 (minor stroke) | 170 (50.1) | 81 (45.5)       | 58 (61.1)     | 25 (49.0)    |
| 5–15 (moderate stroke) | 115 (33.9) | 66 (37.1)       | 27 (28.4)     | 18 (35.3)    |
| 16–20 (moderate to severe stroke) | 9 (2.7) | 5 (2.8)       | -             | 2 (3.9)      |
| CT or MRI of brain | 324 (100.0) | 178 (100.0)     | 95 (100.0)    | 51 (100.0)   |
| ECG               | 324 (100.0)   | 178 (100.0)     | 95 (100.0)    | 51 (100.0)   |

Date are mean (SD) or number (%).

Abbreviation: TOAST indicates Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; CT, Computed tomography; MRI, magnetic resonance imaging; ECG, electrocardiography.

Univariate Analysis Of Risk Factors For First-ever Ischemic Stroke

Table 2 provides the univariate analysis results for the entire population, we found all 15 risk factors to be statistically associated with first-ever IS. Higher hs-CRP level, higher ApoB/ApoA1 ratio, DM, higher monthly family income, HT, increased frequency of fast food consumption, lower HDL-C level, increased frequency of hot pot consumption, hyperlipidemia, higher education level, higher WHR, current smoking, higher fertility number of women were all associated with an increased risk of IS, and manual work and moderate-intensity physical activity were both associated with a reduced risk of IS.
### Table 2
Univariate Analysis of Risk Factors for First-Ever Ischemic Stroke in entire population

| Risk factor                                      | Case(N = 324) | Control(N = 394) | Crude OR(95%CI) |
|-------------------------------------------------|---------------|------------------|-----------------|
| Manual Worker                                   | 257(79.3%)    | 342(86.8%)       | 0.58(0.39–0.87) |
| Education ≥ 9 years                             | 98(30.2%)     | 86(21.8%)        | 1.55(1.11–2.18) |
| Given birth to 3 or more children               | 160(49.4%)    | 163(41.4%)       | 1.38(1.03–1.86) |
| Monthly family income≥5000                      | 148(45.7%)    | 71(18.0%)        | 3.83(2.73–5.36) |
| Current Smoking                                 | 155(47.8%)    | 155(39.3%)       | 1.41(1.05–1.90) |
| Eating fast food frequency ≥ once per week      | 41(12.7%)     | 16(4.1%)         | 3.42(1.88–6.22) |
| Eating hot Pot frequency ≥ once per week        | 40(12.3%)     | 24(6.1%)         | 2.17(1.28–3.69) |
| MIPA                                            | 228(70.4%)    | 318(80.7%)       | 0.57(0.40–0.80) |
| Hypertension                                    | 268(82.7%)    | 226(57.4%)       | 3.56(2.51–5.05) |
| Diabetes mellitus                               | 148(45.7%)    | 63(16.0%)        | 4.42(3.12–6.25) |
| Hyperlipidemia                                  | 152(46.9%)    | 135(34.3%)       | 1.70(1.25–2.29) |
| WHR(female:>0.8, male:>1.0)                     | 150(46.3%)    | 144(36.5%)       | 1.50(1.11–2.02) |
| HDL-C < 1.0 mmol/L                              | 86(26.5%)     | 55(14.0%)        | 2.23(1.53–3.25) |
| Apo B/Apo A1 > 0.9                              | 133(41.0%)    | 47(11.9%)        | 5.14(3.53–7.49) |
| Hs-CRP ≥ 5.0 mg/L                               | 277(85.5%)    | 40(10.2%)        | 52.16(33.26–81.80) |

Abbreviation: MIPA, moderate-intensity physical activity; WHR, waist-to-hip ratio; HDL-C, high-density lipoprotein cholesterol; Apo B, apolipoprotein B; Apo A1, apolipoprotein A1; Hs-CRP, high-sensitivity C-reactive protein.

We analyzed the association between all the modifiable risk factors and IS and tested the homogeneity in different ethnic group with the Breslow-Day test, the results showed that only the difference of the association between higher ApoB/ApoA1 ratio and first-ever IS in Tujia and Miao population had a statistical significance($P < 0.05$)(Table 3).
### Table 3
The Homogeneity of the Association Between Risk Factors and Ischemic Stroke by Ethnicity

| Risk factor                          | Tujia | Miao | Han |    |     |     |
|--------------------------------------|-------|------|-----|----|-----|-----|
|                                      | Case  | Control | Crude OR (95%CI) | Case  | Control | Crude OR (95%CI) | Case  | Control | Crude OR (95%CI) | P_1 | P_2 | P_3 |
| Case (N = 178)                       | 144   | 158   | 0.80(0.47–1.38)  | 76    | 127   | 0.32(0.14–0.71)  | 37    | 57     | 0.56(0.23–1.34)  | 0.482 | 0.351 | 0.058 |
| Control (N = 188)                    |       |       |                |       |       |                |       |         |                |       |       |      |
| Education ≥ 9 years                  | 53    | 51    | 1.14(0.72–1.79) | 27    | 21    | 2.19(1.15–4.18) | 18    | 14     | 2.14(0.94–4.87) | 0.185 | 0.965 | 0.102 |
| Given birth to 3 or more children   | 98    | 77    | 1.77(1.17–2.67) | 48    | 65    | 1.13(0.67–1.91) | 14    | 21     | 0.87(0.39–1.93) | 0.119 | 0.582 | 0.191 |
| Monthly family income≥5000          | 80    | 39    | 3.12(1.97–4.94) | 42    | 14    | 6.96(3.51–13.82)| 26    | 18     | 2.95(1.37–6.35)| 0.901 | 0.101 | 0.055 |
| Current smoking                     | 84    | 61    | 1.86(1.22–2.84) | 48    | 61    | 1.27(0.75–2.15) | 23    | 33     | 0.90(0.43–1.85) | 0.088 | 0.443 | 0.269 |
| Eating fast food frequency ≥ once per week | 20    | 5     | 4.63(1.70–12.63)| 15    | 9     | 2.67(1.12–6.38) | 6     | 2      | 4.47(0.86–23.13)| 0.970 | 0.585 | 0.412 |
| Eating hot Pot frequency ≥ once per week | 24    | 16    | 1.68(0.86–3.27) | 12    | 6     | 3.16(1.14–8.74) | 4     | 2      | 2.85(0.50–16.21)| 0.573 | 0.921 | 0.306 |
| MIIPA                                | 133   | 158   | 0.56(0.34–0.94) | 61    | 105   | 0.55(0.31–0.97) | 34    | 55     | 0.51(0.22–1.16) | 0.845 | 0.890 | 0.948 |
| Hypertension                         | 149   | 110   | 3.64(2.23–5.96) | 77    | 81    | 2.96(1.60–5.48) | 42    | 35     | 4.53(1.92–10.72)| 0.666 | 0.428 | 0.604 |
| Diabetes mellitus                    | 84    | 33    | 4.18(2.60–6.77) | 42    | 21    | 4.38(2.36–8.11) | 22    | 9      | 5.06(2.07–12.36)| 0.718 | 0.794 | 0.916 |
| Hyperlipidemia                       | 86    | 62    | 1.90(1.25–2.90) | 44    | 43    | 1.89(1.10–3.24) | 22    | 30     | 0.99(0.48–2.05) | 0.127 | 0.162 | 0.983 |
| WHR(female:>0.8, male:>1.0)          | 87    | 82    | 1.24(0.82–1.87) | 41    | 43    | 1.66(0.96–2.86) | 22    | 19     | 2.00(0.93–4.29) | 0.279 | 0.700 | 0.396 |
| HDL-C<1.0 mmol/L                     | 50    | 32    | 1.90(1.15–3.14) | 23    | 13    | 3.05(1.46–6.38) | 13    | 10     | 2.02(0.81–5.06) | 0.913 | 0.166 | 0.302 |
| Apo B/Apo A1 > 0.9                   | 79    | 17    | 8.03(4.50–14.33)| 35    | 22    | 3.05(1.64–5.66) | 19    | 8      | 4.53(1.79–11.48)| 0.304 | 0.487 | 0.024 |
| HS-CRP ≥ 5.0 mg/L                    | 159   | 26    | 52.14(27.75–97.97)| 75    | 11    | 42.96(19.51–94.58)| 43    | 3       | 118.25(29.71–470.68)| 0.287 | 0.208 | 0.707 |

P_1 value for Tujia vs Han, P_2 value for Miao vs Han, P_3 value for Tujia vs Miao.

### Multivariate Logistic Regression Analysis of Risk Factors for First-Ever Ischemic Stroke

Sex, age, ethnicity and all 15 risk factors showed statistical association with IS in the univariate comparisons were included in binary multivariate logistic regression analysis. In the entire population, six significant risk factors for the first-ever IS included (in decreasing order of risk): higher hs-CRP level, higher monthly family income, increased frequency of hot pot consumption, DM, higher ApoB/ApoA1 ratio, HT. Moderate-intensity physical activity was significantly associated with a reduced risk of IS (Table 4).

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Table 4

Multivariate Logistic Regression Analysis of Risk Factors for First-Ever Ischemic Stroke

| Risk factor                        | b    | Sb   | Wald χ² | Adjusted OR(95%CI) | P     |
|------------------------------------|------|------|---------|--------------------|-------|
| Monthly family income ≥5000        | 1.43 | 0.28 | 25.65   | 4.18(2.40–7.28)    | 0.000 |
| Eating hot pot frequency ≥ once per week | 1.06 | 0.45 | 5.71    | 2.90(1.21–6.93)    | 0.017 |
| MIPA                               | -0.70| 0.30 | 5.48    | 0.50(0.28–0.89)    | 0.019 |
| Hypertension                       | 0.93 | 0.28 | 10.69   | 2.52(1.45–4.40)    | 0.001 |
| Diabetes mellitus                  | 0.96 | 0.29 | 10.99   | 2.62(1.48–4.62)    | 0.001 |
| Apo B/Apo A1 > 0.9                 | 0.96 | 0.32 | 9.03    | 2.60(1.39–4.85)    | 0.003 |
| Hs-CRP ≥ 5.0 mg/L                  | 3.92 | 0.27 | 210.63  | 50.54(29.76–85.85) | 0.000 |

Abbreviation: MIPA, moderate-intensity physical activity; Apo B, apolipoprotein B; Apo A1, apolipoprotein A1; Hs-CRP, high-sensitivity C-reactive protein.

Additive interaction analysis between Risk Factors and Ethnicity for first-ever ischemic stroke

For the interaction analysis, let Tujia = 1 and Miao = 0, ApoB/ApoA1 > 0.9 = 1 and ApoB/ApoA1 ≤ 0.9 = 0, OR_{00} = 1. In program R the function used a general linear model to estimate ORs with 95% CIs from a logistic regression model. And then we used the epi.interaction function for calculating additive interaction by means of RERI, AP and SI with 95% CIs. The results of interaction analysis showed that there is a biological interaction between ApoB/ApoA1 ratio and ethnicity in Tujia and Miao populations. The risk of IS related to the ApoB/ApoA1 ratio was significantly higher in Tujia population (OR 8.91, 95% CI 4.84–16.39) than in Miao population (3.05, 1.64–5.66) (Table 5).

Table 5

Additive interaction analysis between ApoB/ApoA1 ratio and ethnicity for first-ever ischemic stroke

| Ethnicity | OR(95%CI) ApoB/ApoA1 ≤ 0.9 | OR(95%CI) ApoB/ApoA1 > 0.9 | RERI(95%CI) | AP(95%CI) | S(95%CI) |
|-----------|----------------------------|-----------------------------|-------------|-----------|---------|
| Miao      | 1.00(Ref.)                 | 3.05(1.65–5.72)             | 5.75(0.58 ~ 10.92) | 0.65(0.38 ~ 0.91) | 3.66(1.35 ~ 9.93) |
| Tujia     | 1.11(0.75–1.66)            | 8.91(4.94–16.82)            |             |           |         |

Abbreviation: Apo B, apolipoprotein B; Apo A1, apolipoprotein A1; RERI, the relative excess risk due to interaction; AP, the attributable proportion due to interaction; and S, the synergy.

Discussion

In this case-control study, we found marked differences in IS risk profiles among the Han, Tujia, and Miao populations, which may help clinicians to establish population-specific IS prevention programs and aid in future research.

Ischemic stroke is mainly caused by atherosclerosis and thrombotic obstruction of cerebral blood flow [23–26]; therefore, the identification of biomarkers for atherosclerosis–artery stenosis or occlusion is essential for the early prevention of stroke. Considerable clinical observational studies of different populations have demonstrated that serum hs-CRP is a useful and powerful inflammatory marker in predicting future cardiovascular and cerebrovascular events [19, 27–31]. Our findings are in accordance with those of previous studies. Higher hs-CRP level was first demonstrated as an independent predictor for IS in all ethnic groups of the Xiangxi Tujia and Miao Autonomous Prefecture. Although CRP should be considered only as a surrogate biomarker of upstream cytokines (IL-6 and IL-1β) [32], the classical acute-phase reactant that can be measured with high-sensitivity assays seems to be relevant for risk prediction. Specifically, higher hs-CRP levels appeared to increase the risk of recurrent stroke and vascular events in a hs-CRP sub-study in J-STARTS [33], and hs-CRP level may be useful in individuals classified as “intermediate risk for IS by traditional risk factors” in the Atherosclerosis Risk in Communities (ARIC) study [34]. The ARIC study suggested that determination of plasma hs-CRP concentration could be used as an adjunct for risk assessment in primary and secondary prevention of IS, especially in different ethnic populations. However, in our study we didn’t find higher hs-CRP concentration and ethnicity had a significant additive interaction effect on first-ever IS in the Han, Tujia and Miao populations.

Consistent with previous studies, our findings showed that HT and DM were significant risk factors for IS [5, 35]. HT and DM are global epidemic and have been recognized as common modifiable risk factors for both cardiovascular disease and stroke. Some studies have found marked ethnic differences in association between BP parameters and stroke [36–38]. A 10-mm Hg difference in SBP was associated with an 8%(95CI, 0%-16%) increase in stroke risk for Caucasians, but a 24%(95CI, 14%-35%) increase for African-Americans (P_{interaction}=0.02) [38]. Limited data exists on understanding ethnic differences in association between HT and stroke in China, and in our study there was not any additive interaction effect on first-ever IS between HT and ethnicity in the Han, Tujia and Miao populations.

In multivariate analyses of our study, the ApoB/ApoA1 ratio was a stronger risk predictor of IS than hyperlipidemia, WHR and HDL-C level. An elevated ApoB/ApoA1 ratio mirrors an adverse imbalance between proatherogenic and antiatherogenic lipoprotein particles, which may result in enhanced atherosclerotic burden [39–40]. There are still controversies regarding lipid profile results as risk markers of IS events [41–43], and recent evidence from various large studies suggested that the ApoB/ApoA1 ratio was better than the lipid profile and in detecting IS risk [44–45], which is in agreement with our results. A study demonstrated that increased ApoB/ApoA1 ratio was independently associated with occurrence of IS in young patients [46]. Furthermore, in our
study we found that ApoB/ApoA1 ratio and ethnicity have an additive interaction effect on first-ever ischemic stroke (RERI 5.75, 95%CI 0.58 ~ 10.92). The ethnic difference in the impact of the ApoB/ApoA1 ratio on stroke risk may be related to genetics or metabolism. Further studies are needed to clarify this mechanism. Overall, there is a clear need to focus on the ApoB/ApoA1 ratio to improve the prevention and treatment of IS in patients of different ethnicities.

In our study, we also found that higher monthly family income and increased frequency of hot pot consumption were significantly associated with IS. Hot pot is a local cuisine in the Tujia and Miao ethnic populations, and it has been appearing on tables all year round in the Xiangxi Tujia and Miao Autonomous Prefecture. There are always chock-full of Sichuan peppercorns, chili pepper, and sour pickles in broth of the Tujia and Miao-style hot pot. And most of the ingredient are salted or pickled food, such as pickled fish, pork and chicken, in the Tujia and Miao-style hot pot. Hot pot was first identified as the important risk factor for IS, and further research is needed for clarification of the mechanism. Recent study demonstrated that moderate-to-vigorous physical activity doses equivalent to meeting the current recommendations attenuate or effectively eliminate the association between sitting and all-cause and CVD mortality risk among the least physically active adults[47], similar to the findings reported by the current study. This study suggested that targeted interventions that promote physical activity and a healthy diet for different ethnic populations could substantially reduce the burden of IS.

Limitations And Strengths

Our study has several potential limitations. First, there may be some potential confounding factors that may not have been taken into account. Second, our sample size may be inadequate to provide reliable information about the importance of each risk factor in different ethnic groups.

This study also has some strengths. Our study included the unique ethnic customs of Tujia and Miao populations as risk factors, such as local cuisine, which may add substantial information to other commonly modifiable risk factors.

Conclusions

In conclusion, we provide the first evidence of ethnic variations among the Han, Tujia, and Miao populations in the effect of risk factors of IS in the Xiangxi Tujia and Miao Autonomous Prefecture. Therefore, we propose multidimensional IS prevention approaches among diverse populations, encompassing the population, community, health system, and individual levels. Racial and ethnic categories may help interpret health-related data, including surveillance and research, and are important in ensuring that IS prevention programs remain generalizable to diverse populations.

Abbreviations

TOAST: Trial of Org 10172 in Acute Stroke Treatment; NIHSS: National Institutes of Health Stroke Scale; CT: Computed tomography; MRI: magnetic resonance imaging; ECG: electrocardiography; MIPA: moderate-intensity physical activity; WHR: waist-to-hip ratio; HDL-C: high-density lipoprotein cholesterol; Apo B: apolipoprotein B; Apo A1: apolipoprotein A1; Hs-CRP: high-sensitivity C-reactive protein; RERI: the relative excess risk due to interaction; AP: the attributable proportion due to interaction; S: the synergy

Declarations

Ethics approval and consent to participate

The research was approved by the ethics committees of the Xiangya School of Public Health Central South University(XYGW-2018-26). Every participant, or their proxy respondent, provided informed written consent before participating in the study.

Consent of publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

Hongzhuan Tan and Na Zhang designed the study. Na Zhang, Mengyuan Tian, Xiaolei Wang, Yong Tian, Chengcai Liang, Zhi Zeng and Hua Xiang recruited participants, collected basic data and samples. Na Zhang and Xinrui Wu analyzed the data. Hongzhuan Tan, Jian Ding, and Hua Xiang contributed to discussion and reviewed/edit the manuscript. Na Zhang wrote the manuscript. Hongzhuan Tan and Hua Xiang supervised the study and the guarantor of this work. All authors read and approved the final manuscript.
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